Sundhedsudvalget (2. samling)
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København den 23. juni 2008

Kære Sundhedsudvalg

Hermed fremsender Kræftens Bekæmpelse forskelligt baggrundsmateriale vedrørende solariers skadelige virkning.

Baggrundsmaterialet dokumenter sammenhængen mellem brug af solarier og øget risiko for kræft i huden (modermærkekræft og alm. hudkræft). Baggrundsmaterialet består af Kræftens Bekæmpelses anbefalinger, internationale anbefalinger, relevante videnskabelige artikler og den nyligt vedtaget skotske lov, der forbyder unge under 18 år at benytte solarier.

- Kræftens Bekæmpelses anbefalinger
- Faktaark fra Miljøministeriet, DMI, Dansk Dermatologisk Selskab, Sundhedsstyrelsen og Kræftens Bekæmpelse
- Det Amerikanske "National Toxicology Program" UV stråling er carcinogent
- Relevante videnskabelige artikler
- EU's videnskabelige komites konklusioner om solarier
- IARCs konklusioner (The International Agency for Research on Cancer) på solarieområdet
- WHO's konklusion på solarieområdet

Venlig hilsen
Anja Philip, projektchef – Solkampagnen

København, 23. juni 2008

Anbefalinger til, hvordan man kan arbejde for at begrænse effekten af solariernes skadelige UV-stråling. Afsender: Kræftens Bekæmpelse.

VIDEN

Kræft i huden:

- Kræft i huden er forårsaget af for megen UV-stråling fra solen og solariet og for mange skoldninger.
- 1 ud af 12 danskere får kræft i huden – 22 personer får dagligt stillet diagnosen "kræft i huden".
- Næsten dagligt dør en dansker af kræft i huden (300 personer årligt).
- Personer under 30 år, øger deres risiko for modermærkekræft 3 gange, hvis de går i solarium én gang om måneden eller oftere.
- På verdensplan ligger Danmark på 7. pladsen, når det gælder antal tilfælde af modermærkekræft.

Baggrund, udvikling i hudkræft – den hyppigste kræftform i Danmark

De danske tilfælde af kræft i huden (modermærke– og almindelig hudkræft) er tredoblet på 30 år, og kræft i huden er nu den hyppigste kræftform herhjemme. 80.300 danskere har sygdommen i dag, og der registreres ca. 8.000 nye tilfælde om året. Da sygdommen ofte kommer igen er det årlige antal tilfælde anslået til 12-15.000. Mindst 85 % af tilfældene kan føres tilbage til for megen UV-stråling – enten fra solen eller solariet.

I modsætning til andre kræftformer rammer, særligt modermærkekræft, også unge. Forskning har vist, at børn og unge er særligt følsomme overfor UV-stråling og at skoldninger tidligt i livet øger risikoen for at udvikle modermærkekræft.

Danmark ligger på en syvende plads på verdensplan, når det gælder kræft i huden. Og faktisk er det én af de få typer kræft, vi stort set kan forebygge. Det kræver bedre solvaner med en lavere livstids dosis af UV-stråling, og at vi helt undgår solskoldninger om sommeren, når solen står højt på himlen. Og at vi skal undgår at bruge solarium.

Baggrund, danske undersøgelser:

To store danske undersøgelser viser et bekymrende stort forbrug af solarium – især blandt unge

Danskernes solvaner, forår 2007

En rapport fra en stor, repræsentativ interviewundersøgelse af danskernes solvaner fra foråret 2007[1] gennemført af Kræftens Bekæmpelse og TrygFonden viser, at alt for mange opsøger det lokale solarium: Hver 4. dansker går i solarium – og 52 % af de helt unge mellem 15 og 17 år har brugt solarium inden for det sidste år.
Samtidig viser undersøgelsen, at netop den unge aldersgruppe solbader hyppigst og mest i tidsrummet mellem kl. 12 & 15, hvor UV-strålingen i sommerperioden er på sit højeste.

Til Nyhedsavisens journalist Pernille Mainz siger Projektchef fra Kræftens Bekæmpelse Anja Philip, tirsdag den 11. september 2007:
"*Vores nye solvaneundersøgelse viser, at hele 52 % af de helt unge mellem 15 og 17 år har været i solarium inden for de sidste 12 måneder. Det er bekymrende, for jo yngre man er, når man får hudskader, jo flere år har hudskaderne til at udvikle sig til kræft i huden. I Kræftens Bekæmpelse mener vi, at der skal lovgivning til for at beskytte børn og unge. Vi mener, at det bør forbydes for unge under 18 år at bruge solarium. Og for at det realistisk set skal kunne lade sig gøre, bør der også stilles krav om, at solarierne skal bemandes.*"

Undersøgelsen viser desuden at hele 94 % af de unge godt ved, at det kan give kræft i huden at bruge solarium. Men det ændrer altså ikke på deres brug af solarium. Derfor mener Kræftens Bekæmpelse, at et forbud mod at bruge solarium for unge under 18 år er helt nødvendigt.

"Unges solariebrug", januar 2007
Kræftens Bekæmpelses og TrygFondens undersøgelse af "Unges solariebrug" i januar 2007[2] gav et lignende billede – godt 59% af de unge mellem 15 og 17 år har brugt solarium inden for det seneste år. Samtidig viser denne undersøgelse, at en tredjedel af de unge besøger solariet én eller flere gange om måneden – og at mange har deres debut som 13-årige eller derunder. Undersøgelsen afslører også, at 54 % af de unge, der har brugt solariet, oplever skoldninger eller blærer på huden efter solarie-besøget. En bekymrende tendens, da mange videnskabelige undersøgelser har fastslået den direkte sammenhæng mellem skoldninger og risikoen for at udvikle modermærkekræft.[3]

<u>Baggrund, sammenhæng mellem solarier og kræft:</u>

Et besøg i solarium om måneden øger risikoen for modermærkekræft med 55 %
En stor svensk-norsk undersøgelse fra 2003[3] viser med signifikans, hvad mange tidligere studier indtil da havde antydet, at solarier giver øget risiko for melanom. Over 100.000 kvinder er fulgt i en årrække – i gennemsnit 8 år.

Undersøgelsen viser, at de kvinder, der tog solarium en eller flere gange om måneden, da de var i 20-29 års alderen, havde 2-3 gange større risiko for at udvikle modermærkekræft, end de kvinder som aldrig brugte solarium.
Så man på kvinder i alle aldre, havde de, der brugte solarium mere end en gang om måneden, 55 % større risiko for at udvikle modermærkekræft end de kvinder, der aldrig gik i solarium.

I undersøgelsen tog man højde for nogle af de andre faktorer, som øger risikoen for modermærkekræft - som f.eks. hårfarve, antal forbrændinger og større modermærker - og antallet af solbadeferier.

Et canadisk team har foretaget et systematisk review af al litteratur på området. Konklusionen er klar: Besøg i solarium giver en 25 % signifikant øget risiko for modermærkekræft. Og jo længere man opholder sig i solarium - og jo tidligere debut - jo højere risiko [18]. En analyse af over 1000 kræftdiagnoser viser, at solarium også giver øget risiko for almindelig hudkræft: 2,5 gang for pladecellekræft og 0,5 gang for basalcellekræft [19].

Baggrund IARC og WHO anbefaler et forbud mod solarium:

IARC fastslår, at brug af solarier før 35 års alderen giver 75 % øget risiko for melanom
I en forskningsrapport fra "The International Agency for Research on Cancer " har man gennemført et systematisk review af væsentlige epidemiologiske og biologiske videnskabelige studier vedr. solarier indtil 2006 for WHO [4]. Det viste, at brug af solarium af personer under 35 år signifikant øger risikoen for den livsfarlige modermærkekræft med hele 75 %. Ja, overhovedet at have besøgt solariet – uanset alder - giver 15 % øget risiko for modermærkekræft (grænse signifikant). IARC peger på betydningen af politisk at sætte ind over for helt unges markante brug af solarier.

Det er professor Peter Boyle, som står bag forskningsrapporten. Han udtaler bl.a:
"Solariums can produce UV-radiation up to five times stronger than the midday summer sun and, when used before the age of 35, increase melanoma risk up to 75 percent".

Anbefalinger fra WHO
WHO anbefaler på denne baggrund, at de forskellige landes regeringer vedtager lovgivningsmæssige restriktioner, som forbyder unge under 18 år at bruge solarium, samt at det skal være lovpligtigt for solarierne at placere advarselsskilte synligt for brugerne i deres lokaler.[5] WHO fremhæver nødvendigheden af at bemande solarier og af en skrap lovgivning for at opretholde forbuddet (sanktionsmuligheder). [7]

The Australasian College of Dermatologists, The Cancer Council Australia og deres affilierede medlemsorganisationer samt The Cancer Society of New Zealand er gået ud med følgende position statement:

- Befolkningen skal undgå enhver kosmetisk brug af kunstig UV-stråling
- Befolkningen skal informeres om solariernes øgede kræftrisiko
- Nationale og regionale forbud mod al brug af solarier for unge under 18, forbud mod ubemandede solarier, uddannet personale i solarierne samt information til kunder.

Den 6. marts 2006 skriver Sara Hiom, Head of Health Information, Cancer Research UK at Cancer Research UK går ind for et forbud mod ubemandede solarier samt forbud mod solarier for alle under 16 år. Organisationen foreslår, at solarier kan reguleres gennem licensaftaler.

Sundhedsstyrelsen, Forbrugerrådet, Euroskin og det videnskabelige forebyggelsesudvalg i Kræftens Bekæmpelse bakker op om restriktioner

The European Society of Skin Cancer Prevention (Euroskin) har i oktober 2007 afholdt en videnskabelig konference om solarium, kræft og D-vitamin. De har ultimo 2007 sendt en anbefaling til EU med følgende væsentlige pointer:

- Brug af kunstige UV-kilder bør frarådes alle. Nedre aldersgrænser bør fastsættes.

- Anbefalinger er ikke tilstrækkeligt - der må lovgivning og kontrol til.
- En standardisering bør gennemføres både mht. stråling, kontrol, mærkning, hygiejne og bemanding.
- Kunstig UV-stråling anbefales ikke som kilde til D-vitamin.
- Terapeutisk brug af kunstig UV-stråling bør varetages af læger.[20]

Sundhedsstyrelsen udtaler "*at brug af solarier til andet end medicinsk brug ikke er tilrådelig, og fraråder særligt personer under 18 år og personer med særlig lys hud at gå i solarium*".

Forbrugerrådet mener, på baggrund af de overbevisende videnskabelige data, at, et forbud for al brug af solarium under 18 år er nødvendigt. Forbrugerrådet argumenterer også for et forbud samt en tvungen bemanding af solarierne, fordi børn og unge er mere udsatte for carcinogener end voksne, fordi de unge er mere underlagt sociale normer og modeidealer og bl.a. derfor er de hyppigste brugere af solarium. Forbrugerrådet går ind for bemandede solarier til at sikre den fastsatte aldersgrænse. Forbrugerrådet hæfter sig ligesom Kræftens Bekæmpelse også ved de utilstrækkelige sikkerhedskrav til solarier, og at solarier kan give en alt for høj stråling.

Andre lande, som regulerer eller har planer om at regulere solarieindustrien

- I Australien har følgende guidelines for solarieindustrien: Information om den øgede kræftrisiko, skriftlig samtykke fra forældre til unge mellem 15-18 år, forbud for unge med hudtype 1 og alle under 15 år. Der må ikke reklameres med ikke-kosmetiske sundhedsfordele. Desværre forvaltes disse guidelines utilfredsstillende viser et studie gennemført i Melbourne, Australien. [8]
  Den seneste udmelding fra premierminister John Howard viser, at der er politisk vilje til at pålægge solarieindustrien restriktioner, så specielt de helt unge beskyttes. Sundhedsminister Daniel Andrews i staten Victoria har annonceret, at han vil have indført restriktioner for solarieindustrien.

- I flere stater i USA er det ulovligt at for unge under 18 år at bruge solarium uden forældres tilladelse. I nogle stater er det helt forbudt.[6]

- I Belgien, Sverige og Frankrig er det lovbestemt at andelen af UV-B stråling fra solarierør maksimalt må være 1,5 %. Det svarer til den sammensætning, vi får fra solen. [7]

- I Frankrig er det forbudt for unge under 18 år, at bruge solarium og solarierne skal være bemandet med uddannet personale. Desuden må solarieindustrien ikke markedsføre sundhedsfordele ved anvendelsen.[7]

- I Sverige er der krav om standardiserede solarierør samt opsat information om risici, anbefalet brugsfrekvens og information om at unge under 18 frarådes al brug af solarier. [8]

- I Skotland er der netop vedtaget et lovforbud mod at unge under 18 år må bruge solarium, solarieejerne modtager en bøde hvis de lader unge under 18 år bruge deres solarium. Skotterne har også forbudt mønt-solarier, hvor der ikke er personale der kan kontrollere gæsternes alder.

Konklusion:

- kosmetisk brug af solarier bør være forbudt for alle under 18 år
- al kosmetisk brug af solarium og højfjeldssole bør frarådes alle danskere
- lovgivning bør sikre en regelmæssigt tilsyn og kontrol
- alle solarier bør bemandes med uddannet personale
- der bør være forbud mod solarier i alle offentlige bygninger
- befolkningen skal informeres om den kræftrisiko, solarier udgør med tydelig mærkning/skiltning
- sanktionsmuligheder bør pålægges ejer (bøder) – ved overtrædelse af forbud

Referencer

[1] Solundersøgelsen, forår 2007 - en baseline undersøgelse af danskernes solvaner inden kampagnen "skru ned for solen". Kræftens Bekæmpelse og TrygFonden, forår 2007

[2] Unges brug af solarium, Kræftens Bekæmpelse og TrygFonden, januar 2007

[3] Veierød, M.B. et al (2003) "A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women." *Journal of National Cancer Institute* 95 (20):1530-1538.

[4] The International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer (2006) "The association of use of sunbeds with with cutaneous malignant melanoma and other skin cancers: A systematic review" *International Journal of Cancer* 120: 116-1122

[5] Exposure to Artificial UV Radiation and Skin Cancer. IARC- International Agency for Research on Cancer; 2006. Report No.: 1.

[6] Jody A. et al (2005) "The indoor UV tanning industry: A review of skin cancer rsik, health benefit claims, nd regulation" *Journal of American Academy of Dermatology* 53 (6) 1038-1044

[7] WHO (17/03/2005) "The World Health Organisation recommends that no person under 18 should use a sunbed. http://www.who.int/mediacentre/news/notes/2005/np07/en/index.html

[8] Dobbinson S. Wakefield M. and Sambell N. (2006) "Acess to commercial indoor tanning facilities by adults with highly sensitive skin and by under-age youth: Compliance tests at solarium centers in Melbourne, Australia" *European Journal of Cancer Prevention* 15:424-430

[9] Position Statement: Solariums march 2007, www.sunsmart.org.nz/skin-cancer-control-in-nz/position-statements/solariums

[12] Autier P (2004) Perspecitives in melanoma prevention: The case of sunbeds. European Journal of Cancer, 40:2367-2376)

[13] Weinstock MA, Colditz GA and Willett WC, Nonfamilial cutaneous melanoma incidence in woman associated with sun exposure before 20 years of age. Paediatrics 1989.84: p 199-204

[14] Gilchrest BA, Eller MS, and Baker SG, The pathogenesis of melanoma induces by ultraviolet radiation. N. Engl J Med, 1999. 340: p 1341-8

[15] Autier, OP. & Dore, J. Influence of sunexposure as a risk factor for melanoma: A systematic review of epidemiologic studies. Cancer Causes Control 12, 69-82 (2001)

[16] Elwood, J.&Jopson, J. Melanoma and sun exposure: an overview of ublished studies. Int J Cancer 73, 198-203 (1997)

[17] Heffernan, A. & O'Sullivan, A. Pediatric sun exposure. Nurse Pract 23, 67-86 (1998)

[18] Gallagher, R.P., Spinelli J.J., Lee T.K. Tanning beds, sunlamps and risk of cutaneous malignant melanoma. Cancer Epidemiol Biomarkers Prev 2005; 14:562-6

[19] Karagas MR, Stannard VA, Mott LA, Slattery MJ, Spencer SK, Weinstock MA. Use of tanning devices and risk of basal cell and squarmous cell skin cancers. J Natl Cancer Inst 2002, 94: 224-6

FAKTAARK SOLARIUM

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Brug af solarium frarådes

Den ultraviolette stråling (UV-stråling) fra solarier og højfjeldssol øger risikoen for at udvikle kræft i huden og risikoen for tidlig ældet hud (1). Derfor fraråder vi brug af solarium.

UV-stråling i solarium

Solarier udsender en koncentreret UV-stråling, der indeholder mere UVA-stråling end middagssolen, men mindre UVB-stråling (1;2).

Tidligere troede man, at det kun var UVB-stråling, som forårsager kræft i huden. Nu ved man, at *både* UVA- *og* UVB-stråling er skadelig. UVA-stråling kan give for tidlig ældning af huden (rynker), øjenskader og kan desuden bidrage til kræft i huden (1;3;4). UVB-stråling giver især anledning til solskoldninger og på lang sigt hudskader i form af ru pletter, pigmentpletter og kræft i huden.

Skru ned for solen mellem kl. 12 & 15

Når UV-indexet er 3 eller mere, anbefaler vi, at man beskytter sig i solen. I Danmark er det typisk i tidsrummet mellem kl. 12 & 15 fra april til september, når der er skyfrit eller kun få skyer på himlen. Man kan beskytte sig ved at følge de fire solråd: Siesta, Solhat, Solcreme, Sluk Solariet. Læs mere på www.skrunedforsolen.dk

Solarium

Ultraviolet (UV-)stråling fra solarium udgør en væsentlig risiko for solskoldninger, rynker og tidlig ældning af huden og forøger risikoen for kræft i huden. Derfor frarådes al kosmetisk brug af solarier.

Sammenhængen mellem kræft i huden og UV-stråling er enkel – jo mere UV-stråling fra sol og solarium og jo flere forbrændinger, des større risiko for kræft i huden og tidlig ældning af huden.

Sundhedsrisici ved solariebrug

En svensk-norsk undersøgelse har fulgt over 100.000 kvinder i en årrække og viser, at de kvinder, der tog solarium en eller flere gange om måneden, da de var i 20-29 års alderen, havde 2-3 gange større risiko for at udvikle modermærkekræft, end de kvinder som aldrig brugte solarium.
Så man på kvinder i alle aldre, viste denne undersøgelse, at de, der brugte solarium mere end en gang om måneden, halvanden gang større risiko for at udvikle modermærkekræft end hos de kvinder, der aldrig gik i solarium (5).

Op mod halvdelen af solariebrugerne udvikler irritation, rødme, kløe og udtørring af huden. Solarielys kan undertiden fremkalde og forværre soleksem. På sigt ældes huden tidligere end normalt. UV-stråling fra solarier forårsager også ændringer i hudens immunforsvar, der har betydning for den øgede risiko for kræft i huden (1).

Hvis man alligevel vælger at lægge sig under de kunstige stråler, bør man altid bruge beskyttelsesbriller.

Solariernes standard

I Danmark har vi ingen formelle krav til uddannelse af personale i solarierne. Solarier skal følge EU-standarder for type, styrke og UV-stråling, men der stilles ikke krav til inspektion og regulering af UV-strålingen. Derfor kan man ikke vide, hvilken intensitet og hvilke bølgelænger det enkelte solarium udsender eller være sikker på, at man får den korrekte vejledning af eventuelt personale.

Solarium og solskoldning

Solarielys anvendes undertiden til at "forbrune" huden, inden man går ud i sommersolen eller rejser på solferie. Det er vigtigt at vide, at forbruningens beskyttende effekt mod solskoldning er lille (6). Vi anbefaler derfor, at man beskytter sig, når man er ude i solen - også, hvis man har været i solarium inden.

Solarium og D-vitamin

Der er stor variation i, hvilken UV-stråling der er i solarier. Derfor ved man ikke præcist, hvor meget solariet kan bidrage med at danne D-vitamin. Det frarådes at bruge solarium som kilde til D-vitamin.

MILJØMINISTERIET
Miljøstyrelsen
DMI Vejr, klima og hav
Dansk Dermatologisk Selskab
Sundhedsstyrelsen
Kræftens Bekæmpelse

Selvbrunende cremer

Hvis man ønsker en brun kulør, kan selvbrunende cremer være et alternativ. Selvbrunere danner den brune farve i huden ved en kemisk proces og har ingen kendte bivirkninger. Huden får en 'brunhed', som ligner almindelig solbrændthed. Selvbrunere yder nogen beskyttelse i solen (7). Vi anbefaler, at man beskytter sig, når man er ude i solen - også, hvis man har brugt selvbruner.

Læs mere

En ekspertgruppe under WHO har gennemgået de videnskabelige undersøgelser, der har belyst sammenhængen mellem anvendelse af solarium og risiko for kræft i huden (8). Ekspertgruppen anbefaler et forbud mod solarier for alle under 18 år. Læs mere på http://www.sst.dk/upload/forebyggelse/cff/miljoemedicin/solarier/iarc_rap_om_solarier.pdf og http://www.who.int/mediacentre/news/notes/2005/np07/en/index.html

Referencer

(1) Autier P. Perspectives in melanoma prevention: The case of sunbeds. Eur J Cancer 2004 Nov;40(16):2367-76

(2) Exposure to Artificial UV Radiation and Skin Cancer. IARC- International Agency for Research on Cancer; 2006. Report No.: 1.

(3) Guidelines on Limits of Exposure to Ultraviolet Radiation of Wavelengths Between 180 nm and 400 nm (Incoherent Optical Radiation). The International Non-Ionizing Radiation Committee of the International Radiation Protection Association. Health Phys 1985 Aug;49(2):331-40

(4) The International Agency for Research on Cancer Working Group on Artificial Ultraviolet (UV) Light and Skin Cancer (2006) "The Association of Use of Sunbeds with Cutaneous Malignant Melanoma and Other Skin Cancers: A Systematic Review" International Journal of Cancer 120: 116-1122.

(5) Veierød, M.B. et al (2003) A prospective Study of Pigmentation, Sun Exposure, and Risk of Cutaneous Malignant Melanoma in Women. Journal of National Cancer Institute 95 (20):1530-1538.

(6) Farschou A, Wulf H.C., Durability of the Sun Protection Factor Provided by Dihydroxyacetone. Photodermatol. Photoimmunol, Pthotomed 2004; 20: 239-242

(7) Exposure to Artificial UV Radiation and Skin Cancer. IARC- International Agency for Research on Cancer; 2006. Report No.: 1.

(8) WHO (17/03/2005) "The World Health Organisation recommends that no person under 18 should use a sunbed. http://www.who.int/mediacentre/news/notes/2005/np07/en/index.html

FAKTAARK KRÆFT I HUDEN

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Betegnelsen kræft i huden dækker over to typer kræft: Almindelig hudkræft og modermærkekræft.
Almindelig hudkræft er den hyppigste, og er sjældent dødelig. *Modermærkekræft* er den farligste og mest aggressive. Begge typer kræft i huden skal under behandling. Jo tidligere kræft i huden opdages og behandles, des større chancer er der for at blive helbredt, og det kosmetiske resultat bliver bedst.

Kræft i huden skyldes i langt de fleste tilfælde for megen UV-stråling fra solen eller solarium. Kræft i huden kan forebygges.

Skru ned for solen mellem kl. 12 & 15
Når UV-indexet er 3 eller mere, anbefaler vi, at man beskytter sig i solen. I Danmark er det typisk i tidsrummet mellem kl. 12 & 15 fra april til september, når der er skyfrit eller kun få skyer på himlen. Man kan beskytte sig ved at følge de fire solråd: Siesta, Solhat, Solcreme, Sluk Solariet. Læs mere på www.skrunedforsolen.dk

Kræft i huden
Kræft i huden kan forebygges. Man bør jævnligt undersøge sin hud for tegn på kræft og følge de fire solråd.

Den hyppigste kræftform i Danmark
Danmark har en af de højeste forekomster af både hudkræft og modermærkekræft i verden. Gennem de seneste 30 år er antal tilfælde af hudkræft og modermærkekræft tredoblet (1).

Almindelig hudkræft
I dag er almindelig hudkræft den hyppigste kræftform blandt danskere (2). Omkring 80.000 danskere har været i behandling for almindelig hudkræft. Kun få dør af sygdommen.

Almindelig hudkræft kan behandles kirurgisk. Disse indgreb giver undertiden grimme ar, og man anvender derfor mere og mere cremebehandlinger evt. sammen med lys, der giver et pænere resultat. Andre behandlinger kan bestå i frysning eller røntgenstråling. Hvis man en gang har haft hudkræft, skønnes cirka 30% risiko for, at få sygdommen igen et nyt sted.

Modermærkekræft
Omkring 13.000 danskere har været i behandling for modermærkekræft. Mere end 80% overlever sygdommen (2).

Modermærkekræft behandles med operation, hvis det sidder som en samlet knude og ikke har spredt sig. Er der sket spredning, afhænger behandlingen af spredningsgraden. Det kan gå fra yderligere operation og evt. stråling til forskellige behandlinger med immunterapi. Ved spredning kan kemoterapi også være en mulighed. Chancen for at overleve modermærkekræft afhænger af, hvor tidligt sygdommen bliver opdaget og behandlet.

Hold øje med din hud
Man kan undersøge sin hud ved at se efter nye eller eksisterende pletter eller knuder, der ændrer farve, størrelse eller form. Det kan også være sår, der ikke heler. Kræft i huden kan også være et mærke, der bløder let, ikke heler eller klør. Undersøg hele kroppen, da kræft i huden også kan forekomme, hvor man normalt ikke er udsat for sol. Man bør opsøge læge, hvis man opdager forandringer.

Læs mere
Om modermærkekræft: http://www.cancer.dk/Alt+om+kraeft/kraeftsygdomme/modermaerke/
Om almindelig hudkræft: http://www.cancer.dk/Alt+om+kraeft/kraeftsygdomme/huden/hudkraeft.htm

Referencer

(1) www.cancer.dk/nordcan

(2) Clemmensen IH, Nedergaard KH, Storm HH. Kræft i Danmark- En opslagsbog. 2006. Kræftens Bekæmpelse, Fadl's Forlag.

MILJØMINISTERIET Miljøstyrelsen · dmi Vejr, klima og hav · Dansk Dermatologisk Selskab · Sundhedsstyrelsen · Kræftens Bekæmpelse

FAKTAARK D-VITAMIN

-del af en serie på i alt ni faktaark

Når kroppen udsættes for sollys (UVB-stråling), dannes der D-vitamin i kroppen. D-vitamin hjælper kroppen til at optage kalk, og er nødvendig for knogler og muskler. Mangel på D-vitamin øger risikoen for knogleskørhed og kan give muskelsmerter og svage muskler.

Kilder til D-vitamin

Solens UVB-stråling er en effektiv kilde til D-vitamin. Fødevarer som fisk, kød, æg og mælkeprodukter indeholder også D-vitamin. Især fede fisk som sild og laks er gode kilder til D-vitamin. Men det er vanskeligt at dække hele sit behov for D-vitamin udelukkende gennem maden (1).

Skru ned for solen mellem kl. 12 & 15

Når UV-indexet er 3 eller mere, anbefaler vi, at man beskytter sig i solen. I Danmark er det typisk i tidsrummet mellem kl. 12 & 15 fra april til september, når der er skyfrit eller kun få skyer på himlen. Man kan beskytte sig ved at følge de fire solråd: Siesta, Solhat, Solcreme, Sluk Solariet. Læs mere på www.skrunedforsolen.dk

D-vitamin

Når huden udsættes for sollys (UVB-stråling), dannes der D-vitamin. Mange danskere opholder sig så meget udendørs i sommerhalvåret, at de får tilstrækkeligt D-vitamin, men nogle mennesker har behov for et tilskud.

Ophold i solen får kroppen til at danne D-vitamin. Hvor meget D-vitamin, der dannes i kroppen, afhænger af hvor stærk solens UVB-stråling er og hvor lang tid, man opholder sig i solen (2).

I sommerhalvåret – fra maj til september – er solens lys i Danmark så kraftigt, at udendørs ophold før kl. 12 og efter kl. 15 giver tilstrækkelig mulighed for at danne D-vitamin. Mange danskere opholder sig nok udendørs i sommerhalvåret til, at de får tilstrækkeligt D-vitamin, men nogle mennesker har behov for et tilskud.

I vinterhalvåret - fra oktober til april – er solens stråling i Danmark ikke stærk nok til, at der dannes D-vitamin, når man opholder sig i solen (3).

For lidt D-vitamin?

Børn og voksne der ikke er ret meget udendørs kan have svært ved at danne tilstrækkelig D-vitamin. Det samme gælder børn og voksne, som er tildækket, når de er udendørs - fx med lange ærmer og lange bukser eller kjoler. Derfor anbefales, at disse grupper tager et dagligt D-vitamintilskud på 10 ug (400 IU). Personer over 65 år anbefales under alle omstændigheder at tage dette D-vitamintilskud.

Børn og voksne med mørk hud kan danne ligeså meget D-vitamin som børn og voksne med lys hud (2). Men det tager længere tid, så derfor kan det være svært at få dækket behovet for D-vitamin i det danske klima. Denne gruppe bør derfor også tage et dagligt tilskud af D-vitamin på 10 ug (400 IU).

Gravide har et større behov for D-vitamin, derfor anbefales det at gravide tager et D-vitamin tilskud på 10 ug (400 IU). Spædbørn skal have D-vitamin, fordi de ikke må opholde sig i solen og ikke kan få dækket behovet gennem kosten.

Solcreme og D-vitamin

Undersøgelser tyder på, at solcreme hæmmer dannelsen af D-vitamin (2). Når brug af solcreme ikke fører til D-vitaminmangel, skyldes det formentlig, at solcreme ikke bruges systematisk (4). Vi anbefaler, at man beskytter sig mod solen i tidsrummet ml. 12 og 15. Men efter dette tidsrum er det ikke altid nødvendigt at bruge solcreme.

Pas på med UV-stråling fra solarium

Der er stor variation i, hvilken UV-stråling der er i solarier. Derfor ved man ikke præcist, hvor meget solariet kan bidrage med at danne D-vitamin. Det frarådes at bruge solarium som kilde til D-vitamin.

MILJØMINISTERIET
Miljøstyrelsen
DMI Vejr, klima og hav
Dansk Dermatologisk Selskab
Sundhedsstyrelsen
Kræftens Bekæmpelse

Referencer

(1) Danskernes kostvaner 2000-2002. Danmarks Fødevareforskning 2005. www.food.dtu.dk

(2) Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80(6 suppl): 1678S-88S.

(3) Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80(6 suppl): 1678S-88S

(4) Marks R, Foley PA, Jolley D, Knight KR, Harrison J, Thompson SC, The effect of regular sunscreen use on vitamin D levels in an Australian population. Arch Dermatol 1995;131:415-21

Report on Carcinogens (RoC)

The RoC is an informational scientific and public health document first ordered by Congress in 1978 that identifies and discusses agents, substances, mixtures, or exposure circumstances that may pose a hazard to human health by virtue of their carcinogenicity. The RoC is published biennially and serves as a meaningful and useful compilation of data on:

1. The carcinogenicity (ability to cause cancer), genotoxicity (ability to damage genes), and biologic mechanisms (modes of action in the body) of the listed substance in humans and/or animals.
2. The potential for human exposure to these substances.
3. Federal regulations to limit exposures.

For more background information please select Questions & Answers about the RoC.

View the most recent edition of the RoC (11^{th}) on-line or download a copy as a zipped file (30 mb).

View the review process for the 12^{th} RoC.

The National Toxicology Program announces the availability of draft background documents: Aristolochic Acid Related Exposures and Riddelliine. View the Federal Register Notice.

Ultraviolet Radiation Related Exposures

Introduction

Ultraviolet radiation (UVR) is electromagnetic radiation found between X-rays and light in the electromagnetic spectrum. It is emitted by the sun and artificial devices, including sunbeds or sunlamps. UVR can be divided into UVA, UVB, and UVC components.

Solar radiation and exposure to sunlamps or sunbeds were first listed in the *Ninth Report on Carcinogens* (2000) and broad-spectrum UVR and its components ultraviolet A radiation (UVA), ultraviolet B radiation (UVB), and ultraviolet C radiation (UVC) were first listing in the *Tenth Report on Carcinogens* (2002). Much of the evidence for listing the various UVR related-exposures applies to more than one type of UVR, thus the profiles for these listings are discussed together. Evidence for the carcinogenicity of broad-spectrum UVR comes from studies on solar radiation and exposure to sunlamps or sunbeds. Similarly, studies to evaluate the carcinogenicity of solar radiation in animals and to determine the mechanism(s) by which it causes cancer (mechanistic studies) involve exposure to broad-spectrum UVR or its UVA, UVB, or UVC components. Use of sunlamps or sunbeds entails exposure to ultraviolet radiation. Evidence for the carcinogenicity of the UVR-related exposures is discussed separately and follows this introduction. However, most of the information on additional information relevant to carcinogenicity, properties, use, production, exposure, and regulations is common to all listings for exposures related to UVR and therefore has been combined into one section following the carcinogenicity discussions. The listings for exposures related to UVR are as follows:

- Solar radiation is *known to be a human carcinogen*
- Exposure to sunlamps or sunbeds is *known to be a human carcinogen*
- Broad-spectrum UVR is *known to be a human carcinogen*
- Ultraviolet A radiation is *reasonably anticipated to be a human carcinogen*
- Ultraviolet B radiation is *reasonably anticipated to be a human carcinogen*
- Ultraviolet C radiation is *reasonably anticipated to be a human carcinogen*

Solar Radiation

Known to be a human carcinogen
First Listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Solar radiation is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, which indicate a causal relationship between exposure to solar radiation and skin cancer (both cutaneous malignant melanoma and non-melanocytic skin cancer). Some studies suggest that solar radiation also may be associated with melanoma of the eye and non-Hodgkin's lymphoma (IARC 1992).

Exposure to Sunlamps or Sunbeds

Known to be a human carcinogen
First Listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Exposure to sunlamps or sunbeds is *known to be a human carcinogen,* based on sufficient evidence of carcinogenicity from studies in humans, which indicate a causal relationship between exposure to sunlamps or sunbeds and human cancer. Sunlamps and sunbeds emit primarily UVA and UVB radiation. Epidemiological studies have shown that exposure to sunlamps or sunbeds increases the risk of malignant melanoma (Swerdlow *et al.* 1988, Walter *et al.* 1990, Autier *et al.* 1994, Westerdahl *et al.* 1994, Chen *et al.* 1998, Walter *et al.* 1999, Westerdahl *et al.* 2000). The longer the exposure, the greater the risk, especially in people exposed before the age of 30 or people who have been sunburned. Malignant melanoma of the eye also is associated with use of sunlamps (IARC 1992).

Broad-Spectrum UVR

Known to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Broad-spectrum UVR is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans that show a causal relationship between exposure and human cancer. Epidemiology studies have shown that exposure to broad-spectrum UVR (solar radiation) causes skin cancer (both melanocytic and non-melanocytic). Studies of humans exposed to solar radiation, artificial devices emitting broad-spectrum UVR, or devices emitting predominantly UVA or UVB all contribute to these conclusions. Evidence that the broad-spectrum UVR component of solar radiation is carcinogenic comes from (1) studies of human cancer associated with exposure to devices that emit artificial broad-spectrum UVR, (2) the fact that tumors develop at the same sites both in humans exposed to sunlight and in animals exposed to broad-spectrum UVR from artificial sources, and (3) mechanistic studies in which human tissue was exposed to artificial sources of broad-spectrum UVR.

Broad-spectrum UVR is absorbed by DNA and causes direct and indirect DNA damage with the potential to result in mutations, as demonstrated by mechanistic studies using human tissue. Mutations found in the *p53* tumor suppressor gene of human skin cancer are specific for broad spectrum UVR-induced damage.

The findings in humans are supported by evidence in experimental animals. Exposure to broad-spectrum UVR caused skin tumors (papilloma and squamous cell carcinoma) and eye tumors (spindle-cell sarcoma) in albino rats and skin tumors (fibrosarcoma and/or squamous-cell carcinoma) in mice, hamsters, and opossums (IARC 1992).

UVA

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVA is *reasonably anticipated to be a human carcinogen* based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals. Epidemiological studies on the effects of sunlight or artificial broad-spectrum UVR cannot identify effects due specifically to UVA, UVB, or UVC exposure. However, information about the specific effects of UVA, UVB, and UVC exposure can be inferred by comparing the results of human epidemiology studies of broad-spectrum UVR exposure with the results of studies on the effects of specific broad-spectrum UVR components in experimental animals and human tissues.

In studies where most of the UVR exposure was to UVA (i.e., exposure to solar radiation or UVA-emitting sunbeds), there was an increased risk of skin cancer. Westerdahl *et al.* (2000) studied exposure to sunbeds emitting mainly UVA (with 0.1% to 2.1% UVB) and found an increased risk of melanoma. The available data from experimental animals show that exposure to UVA caused skin tumors in mice (squamous-cell carcinoma and papilloma) and fish (melanoma) (IARC 1992).

UVB

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVB is *reasonably anticipated to be a human carcinogen* based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals. Mechanistic studies with human tissue have demonstrated that the UVB component in solar radiation is absorbed by DNA, resulting in DNA damage that leads to the characteristic *p53* gene mutations observed in human skin cancer. However, epidemiologic studies linking these exposures to skin cancer are limited because they lack information on the specific wavelengths of UVR to which the individuals were exposed. Although increased skin cancer is clearly associated with exposure to UVB (as a component of solar radiation or from sunlamps used before the early 1970s), the people in these studies also were exposed to other components of broad-spectrum UVR. Therefore, the studies could not distinguish between the effects of UVB and other components of UVR. Sunlamps used in the early 1970s produced significant amounts of UVB (22 to 40%); one study found that exposure to UVB-emitting sunlamps increased the risk of malignant melanoma of the skin (Chen *et al.* 1998). In experimental animals, prolonged exposure to devices emitting primarily UVB caused skin tumors in rats (papilloma), mice (squamous-cell carcinoma, fibrosarcoma, papilloma, and keratoacanthoma), guinea pigs (fibroma and trichofolliculoma), and opossums (melanocytic hyperplasia and melanoma) (IARC 1992).

UVC

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVC is *reasonably anticipated to be a human carcinogen* based on limited evidence from mechanistic studies with human tissue and sufficient evidence from studies in experimental animals. Human studies, including those with cultured human cells, have shown that exposure to UVC causes DNA damage. UVC is absorbed by DNA and causes damage similar to that caused by UVB. However, no epidemiological studies have adequately evaluated UVC carcinogenicity in humans. UVC is absorbed by the ozone layer and does not contribute to solar exposure. In studies of exposure to artificial devices emitting UVC, the devices also emitted other components of UVR. Exposure to high doses of radiation from devices emitting primarily UVC caused skin tumors in rats (keratoacanthoma-like tumors) and mice (squamous-cell carcinoma and fibrosarcoma) (IARC 1992).

Ultraviolet Radiation Related Exposures

Additional Information Relevant to Carcinogenicity

Broad-spectrum UVR causes skin cancer via DNA damage, suppression of the immune system, tumor promotion, and mutations in the *p53* tumor suppressor gene. Broad-spectrum UVR causes mutations in cultured human cells; the type of damage depends on the specific wavelength of UVR and whether the affected cells can repair the damage without error. DNA absorbs broad-spectrum UVR (mainly UVB and UVC), and this reaction yields products that can cause mutations (discussed below under "Properties"). UVB causes the following four major DNA base modifications (changes to DNA's structure) in people: cyclobutane-type pyrimidine dimers, (6-4) photoproducts, the corresponding Dewar isomers, and thymine glycols. Both UVA and UVB induce 8-hydroxydeoxyguanosine production from guanosine by the action of singlet oxygen (Griffiths *et al.* 1998).

UVA, UVB, and UVC as individual components of broad-spectrum UVR cause genotoxic damage in several *in vitro* test systems, including bacteria, yeast, rodent cells, and human cells. Moreover, exposure to each of the three components of broad-spectrum UVR causes DNA damage in humans. UVA's biological effects are indirect and largely the result of energy transferred through reactive oxygen intermediates (free radicals), whereas UVB and UVC are absorbed by DNA and directly damage DNA through base modifications. Based on the number of studies showing genetic damage, UVC is the strongest genotoxin of the three components of broad-spectrum UVR, and UVA is the weakest.

More than 90% of human squamous-cell carcinomas contain mutations of the *p53* tumor suppressor gene. These mutations were found in 74% of sun-exposed normal human skin and only 5% of unexposed skin, indicating a strong association with sun exposure. Observed *p53* gene mutations were most frequently C to T or CC to TT transitions at pyrimidine–pyrimidine sequences. These specific *p53* mutations now are considered a signature of broad-spectrum UVR carcinogenesis (Brash *et al.* 1991, Ziegler *et al.* 1993, Griffiths *et al.* 1998, Wikonkal and Brash 1999).

Exposure to solar radiation and broad-spectrum UVR alters immune function in humans and experimental animals (IARC 1992). Evidence that immunosuppression is related to skin cancer comes from the following observations: (1) immunosuppressed organ transplant recipients showed a marked increase in skin cancer, particularly squamous-cell carcinoma, (2) broad-spectrum UVR decreased the ability to mount a delayed-type hypersensitivity response, and (3) mice exposed to low levels of broad-spectrum UVR failed to reject highly immunogenic tumor cell lines (Quinn 1997).

Exposure of human skin grafts on mice to UVB radiation after pretreatment with the carcinogen dimethylbenz(*a*)anthracene causes human skin tumors (squamous-cell carcinoma, actinic keratoses, melanocytic hyperplasia, and melanoma) (Atillasoy *et al.* 1997). Exposure of human skin grafts on mice to UVB alone causes precancerous lesions (melanocytic hyperplasia).

Properties

Solar radiation includes most of the electromagnetic spectrum. Of the bands within the optical radiation spectrum, UVR is the strongest and most damaging to living things (IARC 1992). Broad-spectrum UVR includes wavelengths of light ranging from 100 to 400 nm. UVR is divided into wavelength ranges identified as UVA (315 to 400 nm), UVB (280 to 315 nm), and UVC (100 to 280 nm). Of the solar UV energy reaching the equator, 95% is UVA and 5% is UVB. No measurable UVC from solar radiation reaches the earth's surface, because the shortest UV wavelengths are completely absorbed by

ozone, molecular oxygen, and water vapor in the upper atmosphere (Farmer and Naylor 1996).

Molecules that absorb UVR and visible light (photoreactive molecules) contain segments that react with light (called chromophores), in which photons of light excite electrons from the ground state to higher-energy states. These molecules then generally re-emit light on returning to lower-energy or ground states (Dyer 1965). The various molecules sensitive to UVR differ in the wavelengths of UVR that they absorb and the light that they emit.

Photochemical and photobiological interactions occur when photons react with a photoreactive molecule, forming either an altered molecule or two separate molecules (Phillips 1983, Smith 1989). For such a reaction to occur, the photons must have enough energy to alter a photoreactive chemical bond (i.e., to break the original bond or form new bonds).

The photobiological reactions related to skin cancer risk due to UVR exposure are the reactions with the main chromophores of the skin's outer layer—urocanic acid, DNA, tryptophan, tyrosine, and the melanins. The products resulting from UVR's reaction with DNA (DNA photoproducts) include pyrimidine dimers, pyrimidine-pyrimidone (6-4) photoproducts, thymine glycols, and DNA exhibiting cytosine and purine damage and other damage, such as DNA strand breaks and cross-links and DNA-protein cross-links. The various DNA photoproducts differ in their mutagenic potential (IARC 1992).

UVR-induced DNA photoproducts cause a variety of cellular responses that contribute to skin cancer. Unrepaired DNA photoproducts may result in the release of cytokines that contribute to tumor promotion, tumor progression, immunosuppression, and the induction of latent viruses (IARC 1992, Yarosh and Kripke 1996).

UVB is considered to be the major cause of skin cancer, despite the fact that it does not penetrate the skin as deeply as UVA or react with the outer skin layer as vigorously as UVC. Its high reactivity with macromolecules, coupled with the depth to which it penetrates skin, makes UVB the most potent portion of the UV spectrum for both short-term and long-term biological effects. UVA, while possibly not as dangerous, also causes biological damage (Farmer and Naylor 1996).

Use

Broad-spectrum UVR has many uses as a natural source of energy and is important in various biological processes. Solar radiation is required for life. Plants must have sunlight to grow and to produce carbohydrates and oxygen. Broad-spectrum UVR from solar radiation helps produce vitamin D in human skin cells. Vitamin D metabolites promote the absorption of calcium by the intestinal tract; therefore, it is essential for the growth and development of healthy bones. Brief exposure to sunlight on a regular basis is sufficient to produce all of the vitamin D most people need. This vitamin also can be obtained from dietary sources. Artificial sources of broad-spectrum UVR have many uses, including tanning, medical diagnosis and treatment, and promotion of polymerization reactions (e.g., curing of protective coatings). Sunbeds use artificially produced UVR to enable individuals to develop a suntan for cosmetic reasons. Originally, sunbeds were built with mercury arc lamps, which emitted large quantities of UVB and UVC. Now, sunbeds and solaria emit mostly UVA (IARC 1992).

Broad-spectrum UVR has both diagnostic and therapeutic uses in medicine and dentistry. More than 30 disorders now can be treated through UVA exposure combined with compounds called psoralens (PUVA therapy). Psoriasis and eczema are the skin diseases most frequently treated with PUVA therapy. PUVA can also be used with UVB exposure to treat psoriasis patients who are not good candidates for systemic therapy with methotrexate or etretinate (Morrison 1992). In addition, broad-spectrum UVR and, more commonly, UVB are used with coal-tar creams to treat psoriasis (Reid 1996). UVB also may be used to convert 7-dehydrocholesterol (provitamin D) to vitamin D in the skin of vitamin D-deficient patients.

UVA may be a component of the phototherapy to treat neonatal jaundice or hyperbilirubinemia. Typically an infant is irradiated with visible light for several hours a day, for up to one week; however, the lamps also may emit UVR, and one commercial neonatal phototherapy unit was found to emit UVA and shorter wavelengths of UVR (IARC 1992). UVA has been found to react with melatonin, a hormone that helps to regulate sleep-wake cycles. Although the photoproducts of melatonin have not been identified, melatonin has been predicted to be moderately phototoxic (Kim *et al.* 1999).

Broad-spectrum UVR has many industrial applications. One of its major industrial uses is in photopolymerization, including curing of protective coatings and inks. Broad-spectrum UVR is used to simulate weathering of various materials, such as polymers. UVR (usually UVC at 260 to 265 nm) is used to sterilize and disinfect tools and materials. Other uses include UV photography, UV lasers, and in dental examinations to detect early dental caries, dental plaque, and calculus (IARC 1992).

Sources

In the broadest sense, broad-spectrum UVR is formed when something is heated or when electrons that have been raised to an excited state return to a lower energy level. Broad-spectrum UVR is naturally emitted by the sun. An estimated two-thirds of the energy emitted by the sun penetrates the atmosphere. Broad-spectrum UVR constitutes approximately 5% of the solar radiation that reaches the earth's surface (IARC 1992).

Six artificial sources of broad-spectrum UVR have been identified: incandescent lights, gas discharge lamps, arc lamps, fluorescent lamps, metal halide lamps, and electrodeless lamps. Incandescent sources provide visible radiation in a continuous spectrum. Gas discharge lamps produce visible radiation when an electrical current is passed through a gas. The type of gas present in the lamp determines the emission wavelengths; low gas pressures produce narrow bands, whereas higher pressures produce broad bands. Arc lamps are intense sources of broad-spectrum UVR and often are used to simulate solar radiation. Fluorescent lamps emit radiation from a low-pressure mercury discharge, which produces a strong emission at 254 nm; this radiation excites the phosphor-coated lamp to produce fluorescence. Various emission spectra can be obtained by altering the makeup and thickness of the phosphor and the glass envelope. In metal halide lamps, metal halide salts are added to a mercury-vapor discharge lamp, thus creating extra emission lines. Electrodeless lamps use magnetrons to generate microwave energy, which then is absorbed by the discharge tube (IARC 1992).

Low-pressure mercury vapor lamps, sunlamps, and black-light lamps are considered to be low-intensity UVR sources. High-intensity UVR sources include high-pressure mercury vapor lamps, high-pressure xenon arc lamps, xenon-mercury arc lamps, plasma torches, and welding arcs.

Sunlamps and sunbeds emit broad-spectrum UVR. Sunbeds now chiefly emit UVA; however, before the mid 1970s, they more commonly emitted UVB and UVC (IARC 1992). Three different UVA phosphors have been used in sunlamps sold in the United States since the late 1970s, producing emission spectra that peak at 340, 350, or 366 nm. Two modern sunlamps evaluated by the U.S. Food and Drug Administration emitted 99.0% and 95.7% UVA; the remaining radiation was UVB. A new high-pressure UVA sunbed with eighteen 1600-watt filtered arc lamps emitted 99.9% UVA. An older type of sunlamp, used prior to the late 1970s (UVB/FS type), emitted 48.7% UVA (Miller *et al.* 1998).

Exposure

The greatest source of human exposure to broad-spectrum UVR is solar radiation; however, the exposure varies with geographical location. Information on global broad-spectrum UVR levels has been compiled from data gathered for epidemiological studies of skin cancer

and other health effects, such as premature aging of the skin, cataracts, and suppression of the immune response. Despite the large number of measurements, estimating human exposure is complex. The UVR wavelengths to which an individual is exposed vary considerably with latitude, altitude, time of day, and season. People also vary in their length of outdoor exposure, the parts of the body they expose, and the shapes of their bodies. Nevertheless, many studies have estimated exposure to broad-spectrum UVR. Few studies, however, were able to distinguish between UVA, UVB, and UVC exposure (IARC 1992).

Various factors influence terrestrial levels of UVA (i.e., levels found at the earth's surface). UVA levels decrease with increasing distance from the equator and increase with increasing altitude. Terrestrial UVA levels also are decreased by stratospheric ozone, which varies with latitude and season. When there is less ozone, more UVA reaches the earth's surface. Time of day also influences UVA levels. Clouds reduce the amount of UVA reaching ground level. Air pollution, including tropospheric ozone, can decrease UVA exposure, especially in urban areas. Surface reflection also contributes to personal exposures to UVA and can result in exposure to body parts that otherwise would be shaded from the sun (IARC 1992).

Terrestrial UVB levels are affected by the same factors as terrestrial UVA levels; however, since UVB is absorbed more by stratospheric ozone than is UVA, differences in latitude and altitude affect UVB exposure more than UVA exposure. Seasonal changes affect UVB levels, mostly in temperate regions. Generally, cloud cover scatters less than 10% of the UVB under a clear sky; however, very heavy cloud cover virtually eliminates UVB, even in the summer. Surface reflection also contributes to human UVB exposure (IARC 1992).

Commonly used fluorescent sunlamps deliver 0.3 to 1.2 times the annual UVA dose from the sun to a typical tanner exposed for 20 sessions at 2 minimal erythemal doses (MED) per session (Miller *et al.* 1998). (The MED is the lowest UVR exposure sufficient to produce well-defined reddening of the skin within 24 hours of exposure.) A frequent tanner (100 sessions at 4 MED/session) receives 1.2 to 4.7 times the annual solar UVA dose, while the newer high-pressure sunlamps deliver 12 times the annual solar UVA dose to the frequent tanner.

Approximately 25 million people in the United States use sunbeds each year, and one to two million people visit tanning facilities as often as 100 times per year (Sikes 1998, Swerdlow and Weinstock 1998). Teenagers and young adults are prominent among users. A 1995 U.S. survey found that of commercial tanning salon patrons, 8% were 16 to 19 years old, 42% were 20 to 29 years old, and 71% were female (Swerdlow and Weinstock 1998).

Anyone working outside (such as agricultural, construction, and road work laborers) is exposed to solar radiation on the job. For a group of more than 800 outdoor workers in the United States at 39° N latitude (the latitude of Philadelphia), personal annual exposure of the face was estimated at 30 to 200 MED (Rosenthal *et al.* 1991). However, this estimate may be low because Rosenthal and colleagues assumed facial exposure to be only 5% to 10% of ambient exposure, whereas other data suggested that it could be as high as 20%. Based on this higher estimate, the annual facial exposure doses for these outdoor workers would be 80 to 500 MED (IARC 1992).

Occupational exposure to artificial broad-spectrum UVR occurs in industrial photo processes, principally UV curing of polymer inks, coatings, and circuit board photoresists; sterilization and disinfection; quality assurance in the food industry; medical and dental practices; and welding (IARC 1992). UV lasers, such as those used in cornea shaping and coronary angioplasty, are another potential source of occupational exposure, with relative risks that could be comparable to risks for individuals in outdoor professions (Sterenborg *et al.* 1991). Electric arc welders are the largest occupational group with exposure to artificial broad-spectrum UVR. It is estimated that more than 500,000 welders in the United States have been occupationally exposed to broad-spectrum UVR. Occupational exposure to artificial broad-spectrum UVR depends on both the source of exposure and the protective methods used to decrease exposure. Some artificial broad-spectrum UVR sources (such as germicidal lamps in some uses) are self-contained and present no risk to workers. Other occupational uses, such as use of UVR in laboratories, UV photography, and UV lasers, inevitably lead to broad-spectrum UVR exposure, which may include intense short-term exposures (IARC 1992).

Regulations

FDA

Performance standards for sunlamps and other devices that emit ultraviolet radiation have been developed

User instructions and warning labels must accompany sunlamps and other devices that emit ultraviolet radiation

Guidelines

ACGIH

Threshold limit values (TLVs) have been developed for over 60 different wavelengths (ranging from 180 to 400 nm) in the ultraviolet spectrum. In addition to these TLVs, specific protections for the eye to exposures from UV radiation in the 315 to 400 nm spectral range also have been developed[1]

NIOSH

Comprehensive recommendations for standards have been developed that include various exposure limits, labeling and warning sign requirements, and numerous work practice requirements[1]

[1]See *Introduction* for information on where to obtain additional detail on regulations and recommendations.

REFERENCES

Atillasoy, E. S., R. Elenitsas, E. R. Sauter, P. W. Soballe and M. Herlyn. 1997. UVB induction of epithelial tumors in human skin using a RAG-1 mouse xenograft model. J Invest Dermatol 109(6): 704-9.

Autier, P., J. F. Dore, F. Lejeune, K. F. Koelmel, O. Geffeler, P. Hille, *et al.* 1994. Cutaneous malignant melanoma and exposure to sunlamps or sunbeds: an EORTC multicenter case-control study in Belgium, France and Germany. EORTC Melanoma Cooperative Group. Int J Cancer 58(6): 809-13.

Brash, D. E., J. A. Rudolph, J. A. Simon, A. Lin, G. J. McKenna, H. P. Baden, A. J. Halperin and J. Ponten. 1991. A role for sunlight in skin cancer: UV-induced *p53* mutations in squamous cell carcinoma. Proc Natl Acad Sci U S A 88(22): 10124-8.

Chen, Y. T., R. Dubrow, T. Zheng, R. L. Barnhill, J. Fine and M. Berwick. 1998. Sunlamp use and the risk of cutaneous malignant melanoma: a population-based case-control study in Connecticut, USA. Int J Epidemiol 27(5): 758-65.

Dyer, J. R. 1965. Introduction. In Applications of Absorption Spectroscopy of Organic Compounds. Englewood Cliffs, NJ: Prentice-Hall, Inc. p. 3-21.

Farmer, K. C. and M. F. Naylor. 1996. Sun exposure, sunscreens, and skin cancer prevention: a year-round concern. Ann Pharmacother 30(6): 662-73.

Griffiths, H. R., P. Mistry, K. E. Herbert and J. Lunec. 1998. Molecular and cellular effects of ultraviolet light-induced genotoxicity. Crit Rev Clin Lab Sci 35(3): 189-237.

IARC. 1992. Solar and Ultraviolet Radiation. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 55. Lyon, France: International Agency for Research on Cancer. 316 pp.

Kim, Y. O., H. J. Chung, S. T. Chung, J. H. Kim, J. H. Park, K. S. Kil and D. H. Cho. 1999. Phototoxicity of melatonin. Arch Pharm Res 22(2): 143-50.

Miller, S. A., S. L. Hamilton, U. G. Wester and W. H. Cyr. 1998. An analysis of UVA emissions from sunlamps and the potential importance for melanoma. Photochem Photobiol 68(1): 63-70.

Morrison, W. L. 1992. Phototherapy and photochemotherapy. Adv Dermatol 7: 255-270.

Phillips, R. 1983. Sources and Applications of Ultraviolet Radiation. London: Academic Press.

Quinn, A. G. 1997. Ultraviolet radiation and skin carcinogenesis. Br J Hosp Med 58(6): 261-4.

Reid, C. D. 1996. Chemical photosensitivity: another reason to be careful in the sun. FDA Consumer Magazine. May 1996. http://www.fda.gov/fdac/features/496_sun.html.

Rosenthal, F. S., S. K. West, B. Munoz, E. A. Emmett, P. T. Strickland and H. R. Taylor. 1991. Ocular and facial skin exposure to ultraviolet radiation in sunlight: a personal exposure model with application to a worker population. Health Phys 61(1): 77-86.

Sikes, R. G. 1998. The history of suntanning: a love/hate affair. J Aesthetic Sci 1(2): 6-7.

Smith, K. C., ed. 1989. The Science of Photobiology. 2nd ed. New York, Plenum. p. 47-53.

Sterenborg, H. J., F. R. de Gruijl, G. Kelfkens and J. C. van der Leun. 1991. Evaluation of skin cancer risk resulting from long term occupational exposure to radiation from ultraviolet lasers in the range from 190 to 400 nm. Photochem Photobiol 54(5): 775-80.

Swerdlow, A. J., J. S. English, R. M. MacKie, C. J. O'Doherty, J. A. Hunter, J. Clark and D. J. Hole. 1988. Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. Bmj 297(6649): 647-50.

Swerdlow, A. J. and M. A. Weinstock. 1998. Do tanning lamps cause melanoma? An epidemiologic assessment. J Am Acad Dermatol 38(1): 89-98.

Walter, S. D., W. D. King and L. D. Marrett. 1999. Association of cutaneous malignant melanoma with intermittent exposure to ultraviolet radiation: results of a case-control study in Ontario, Canada. Int J Epidemiol 28(3): 418-27.

Walter, S. D., L. D. Marrett, L. From, C. Hertzman, H. S. Shannon and P. Roy. 1990. The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. Am J Epidemiol 131(2): 232-43.

Westerdahl, J., C. Ingvar, A. Masback, N. Jonsson and H. Olsson. 2000. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer 82(9): 1593-9.

Westerdahl, J., H. Olsson, A. Masback, C. Ingvar, N. Jonsson, L. Brandt, P. E. Jonsson and T. Moller. 1994. Use of sunbeds or sunlamps and malignant melanoma in southern Sweden. Am J Epidemiol. 140(8): 691-9.

Wikonkal, N. M. and D. E. Brash. 1999. Ultraviolet radiation induced signature mutations in photocarcinogenesis. J Investig Dermatol Symp Proc. 4(1): 6-10.

Yarosh, D. B. and M. L. Kripke. 1996. DNA repair and cytokines in antimutagenesis and anticarcinogenesis. Mutat Res. 350(1): 255-60.

Ziegler, A., D. J. Leffell, S. Kunala, H. W. Sharma, M. Gailani, J. A. Simon, *et al.* 1993. Mutation hotspots due to sunlight in the *p53* gene of nonmelanoma skin cancers. Proc Natl Acad Sci U S A. 90(9): 4216-20.

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The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review

The International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer

Exposure to solar ultraviolet (UV) radiation is a known cause of skin cancer. Sunbed use represents an increasingly frequent source of artificial UV exposure in light-skinned populations. To assess the available evidence of the association between sunbed use and cutaneous malignant melanoma (melanoma) and other skin cancers, a systematic review of the literature till March 2006 on epidemiological and biological studies on sunbed use was performed in Pubmed, ISI Web of Science, Embase, Pascal, Cochrane library, Lilacs and Medcarib. Search for keywords in the title and in the abstract was done systematically and supplemented by manual searches. Only case–control, cohort or cross-sectional studies were selected. Data were abstracted by means of a standardized data-collection protocol. Based on 19 informative studies, ever-use of sunbeds was positively associated with melanoma (summary relative risk, 1.15; 95% CI, 1.00–1.31), although there was no consistent evidence of a dose–response relationship. First exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on 7 informative studies (summary relative risk, 1.75; 95% CI, 1.35–2.26). The summary relative risk of 3 studies of squamous cell carcinoma showed an increased risk. For basal cell carcinoma, the studies did not support an association. The evidence does not support a protective effect of the use of sunbeds against damage to the skin from subsequent sun exposure. Young adults should be discouraged from using indoor tanning equipment and restricted access to sunbeds by minors should be strongly considered.
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Key words: artificial UV; sunbeds; melanoma; skin cancer; meta-analysis

Sun exposure is the main environmental cause of skin cancer, and ultraviolet (UV) radiation is the solar wavelength involved in skin cancer, including the malignant cutaneous melanoma.[1] People may also be exposed to UV radiation through many artificial sources at home and in the workplace, with some individuals receiving high doses. Sources of artificial UV radiation include various lamps used in medicine, industry, business and research, as well as for domestic and cosmetic purposes. Sunbeds and sunlamps used for tanning purposes are the main source of deliberate exposure to artificial UV radiation.[†] Although the contexts of sun exposure and indoor tanning differ, both deliver UV radiation, and their health effects would therefore be expected to be similar.

UV radiation wavelengths range between 100 and 400 nm and are broadly categorized into UVA (>315–400 nm), UVB (>280–315 nm) and UVC (100–280 nm). Modern indoor tanning equipment mainly emits in the UVA range, but a fraction (*i.e.*, <5%) of this spectrum is in the UVB range.

Before 1990, UVB was usually considered the only carcinogenic part of the solar spectrum, but since then UVA as well has been suspected of having carcinogenic potential. In 1992, the International Agency for Research on Cancer (IARC) classified UVB and UVA radiation, as well as "use of sunlamps and sunbeds," as "probably carcinogenic to humans" (Group 2A of the IARC classification of carcinogenic agents).[1] More recently, the 10th Report on Carcinogens published by the National Toxicology Program in the USA classified UVA radiation as a "known to be a human carcinogen."[2] Biological mechanisms by which chronic sun exposure causes squamous cell cancer (SCC) of the skin have become better known and chronic exposure to high UVB doses is now considered as the main environmental cause of that skin cancer.[3] Biological mechanisms implicated in basal cell carcinoma (BCC) start to be better known. In contrast, we still have poor knowledge of the UV wavelength and the dose delivery pattern at skin level implicated in the genesis of melanoma and of BCC.[4]

Indoor tanning is widely practiced in most developed countries, particularly in Northern Europe and the USA, and is gaining popularity even in sunny countries such as Australia.[5,6] The likely impact of this fashion on skin cancer incidence is of substantial concern, mainly for cutaneous malignant melanoma (hereafter melanoma), a cancer of poor prognosis when diagnosed at an advanced stage.

This paper summarizes a systematic review of epidemiological and experimental studies on use of indoor tanning equipment and skin cancer developed by a Working Group convened by IARC.

UV spectra from sunlight and indoor UV tanning appliances

During a sunny day on the Mediterranean coast, the solar UV spectrum at noon contains 4–5% UVB and 95–96% UVA. When UV output of a typical indoor tanning appliance is calculated in terms of biological activity, as estimated by the erythema-effective irradiance, the emission of many tanning appliances is equivalent to or exceeds the emission of the midday sun in southern Europe.[7,8] The UV intensity of powerful tanning appliances may be 10–15 times higher than that of the midday sun,[8] leading to UVA doses per unit of time received by the skin during a typical tanning session that are well above those experienced during ordinary daily activities or even during sunbathing. As a result, the annual UVA doses received by frequent indoor tanners may be 1.2–4.7 times those received from the sun, in addition to those received from the sun.[9] This widespread repeated exposure to high doses of UVA constitutes a new phenomenon for human beings.

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[†]The device used for tanning may be referred to as sunbed, sunlamp, artificial UV, artificial light or tanning bed, among other terms. Also, a number of terms are used to define a place where indoor tanning may occur: solarium, tanning salon, tanning parlor, tanning booth, indoor tanning salon, indoor tanning facility. In addition, indoor tanning may also occur in non-commercial premises. For the purpose of this report, the term *indoor tanning equipment* has been used throughout.

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In the 1990s, regulations in some countries (*e.g.*, France, Sweden) limited to 1.5% the maximum percentage of UVB in the UV output of tanning appliances. However, in practice, the UV output and spectral characteristics (*i.e.*, amounts of UVA, UVB, visible light and infrared radiation) of tanning appliances vary considerably. The proportion of UVB in UV energy output could vary from 0.5 to 4%,[10,11] and may attain an emission spectrum similar to the sun spectrum in the UVB range.[8] These differences are due to sunbed design (*e.g.*, the numbers and type of fluorescent tubes, the presence of high pressure UV lamps, the materials composing filters, the distance from canopy to the skin), sunbed power and tube ageing.

Biological effects of exposure to artificial UV radiation relevant to carcinogenesis

A large body of experimental and epidemiological data strongly indicates that the spectrum of UV radiation reaching the Earth's surface causes skin cancer.[1,12,13] UVB is a complete carcinogen that is absorbed by DNA and can damage DNA directly.[13]

Evidence of the mutagenic properties of UVA in humans has been found in several studies.[12–14] UVA radiation does cause UVB-like cyclobutane pyrimidine dimers and 6-4 photoproducts, albeit with a much lower efficacy than does UVB radiation. Most of the DNA damage induced by UVA is indirect, through the absorption of UVA photons by other cellular structures (chromophores), with formation of reactive oxygen species that can transfer UVA energy to DNA *via* mutagenic oxidative intermediates.[15]

Skin of human volunteers exposed to UVA lamps used in tanning appliances show DNA damage, *p53* mutations induced by oxidative damage and alterations of the p53 protein similar to those observed after sun exposure or after exposure of experimental animals.[16–18]

UVA penetrates deeper into human skin than does UVB. Because UVA represents the largest proportion of the UV spectrum of tanning appliances and of solar radiation reaching the Earth's surface, far more UVA than UVB reaches the basal layers of the epidermis where melanocytes and early keratinocytic cells are located.

Both UVA and UVB radiation can affect the immune response that may be involved in the promotion of melanoma,[15,19,20] but the 2 types of radiation seem to act differently.[21,22] UVB induces immunosuppression at both the local and systemic levels, while UVA does not induce systemic immune suppression.[23]

To date, evidence obtained from experimental studies on the involvement of high UVB doses in the causation of SCC is consistent with observations in humans. In contrast, experimental studies give conflicting results regarding the roles of UVB and UVA in the induction of melanoma in humans. The same uncertainties hold true for BCC, a type of tumor that shares some epidemiological characteristics of melanoma.

Experiments carried out in animals cannot reproduce the complex interplay in individuals between highly variable natural susceptibilities to UV radiation, sun exposure behaviors and exposure to various sources of UV radiation. During indoor tanning, such interrelationships may be critical, as users are more inclined than the average population to engage in outdoor tanning activities,[24] and indoor tanning sessions often precede or follow active sun exposure or outdoor tanning.

Effects of artificial UV on human skin

Skin redness or burning are reported by 18–55% of users of indoor tanning equipment in Europe and North America.[25] Although UVB is far more potent than UVA in causing sunburn, high fluxes of UVA are capable of inducing skin redness in individuals sensitive to sunlight or with only moderate tanning ability.

In individuals who tan easily, exposure to tanning appliances will lead first to the oxidation of melanin already present in superficial keratinocytic layers of the skin, known as immediate pigment darkening.[26] A more permanent tan is acquired with accumulation of exposure, depending on tanning ability and on the amount of UVB present in the UV spectrum of the lamps.

Immediate pigment darkening has no photoprotective effect against UV-induced skin redness or sunburn.[27] Moreover a UVA-induced permanent tan provides little photoprotection[28,29] and the skin thickening caused by UVA affords only very little photoprotection.[30] Studies in humans show that a prevacation tan induced artificially offers virtually no protection against sun-induced DNA damage.[31–33]

Exposure to artificial UV for tanning purposes

Few people had used indoor tanning equipment before 1980 but by the end of the 1990s more than 60% of women and 50% of men aged 18–50 years in Northern Europe reported having ever used indoor tanning equipment.[34] Indeed, prevalence of indoor tanning is increasing so rapidly in many countries that current estimates may be outdated rapidly. The most frequent motivations for indoor tanning are the acquisition of a so-called safe tan and preparation of the skin before sun exposure.[25]

Use of indoor tanning equipment is more prevalent among women and among both men and women younger than 35 years. Earliest studies in Sweden and in the USA tended to find indoor tanning to be more prevalent among adolescents with fair skin types who are more prone to sunburn.[35–37] More recent studies in the USA found either the opposite[38–40] or no association.[41]

Few studies have assessed the compliance of indoor tanning facility operators or consumers with recommendations and regulations. Overall, information provided by tanning salon operators on health risks and on duration and frequency of exposure is often incomplete, and there is a lack of identification of highly sun-sensitive subjects or of subjects taking photosensitizing medications.[6,42–44]

About 17–35% sunbed users reported that they did not wear eye protection.[10,41,43] In some surveys, 16% of sunbed users may have had more than 100 sessions per year,[10] and most users tend to exceed the recommended exposure times.[41,44,45]

Since 1989, a total of 16 studies (18 reports) have examined prevalence of indoor tanning among children and adolescents aged 8–19 years in Australia, Europe and the USA.[46,47] All studies showed a frequent use by adolescents and children, sometimes at a very young age. According to the most recent studies, 30% of adolescents in Sweden and 24% of adolescents in the USA aged 13–19 years reported ever-use of indoor tanning equipment and 8 and 12% respectively were frequent users (10 times per year or more). In a recent survey in the United Kingdom, while 7% of children aged 8–11 years reported exposure to a sunbed in the past 6 months, as many as 48% expressed a desire to use a sunbed.[48]

Epidemiological studies on indoor tanning and skin cancer

As existing animal models of human melanoma are inconsistent, evidence of an association between indoor tanning and skin cancer must be sought predominantly from epidemiological studies. Few studies have addressed this topic specifically, but some studies included 1 or more secondary questions about indoor tanning. We systematically analyzed the results from the relevant studies and compiled them in a metaanalysis.

Methods

The methodology used for the literature search is summarized in Table I. The minimal common information about exposure to indoor tanning appliances for all studies was "ever exposed." For those studies wherein "ever exposed to indoor tanning appliances *versus* never" was not strictly assessed[49,50] we used the information closest to this category.

Most estimates included all subjects and combined sexes in the analysis. Some studies presented results separately for women and men, with no combined data, in which case both estimates were

included. Since the studies used different age categories for classifying age at first exposure, we considered as "young exposure" those exposures that started before 35 years of age.

Every measure of association adjusted for the maximum number of confounding variables, and corresponding confidence interval (CI), was transformed into logarithms of relative risk (log RR) and the corresponding variance was calculated.[51] Where no estimates were reported, the crude estimates were calculated from tabular data, using asymptotic Mantel-Haenszel methods to evaluate the 95% CI of the log odds ratio.

The homogeneity of the effects across studies was assessed using the large sample test based on the χ^2-test. The summary relative risk was estimated using random effects models even when heterogeneity was found to be not statistically significant, in order to be conservative. Publication bias was investigated by funnel plot regression.[52]

TABLE I – METHOD USED FOR THE LITERATURE SEARCH

The literature to March 2006 was searched using the following databases: Pubmed, ISI Web of Science (Science Citation Index Expanded), Embase, Pascal, Cochrane library, Lilacs and Medcarib. The following keywords and their corresponding French translation were used for search in the PASCAL database: skin cancer, squamous cell carcinoma, SCC, basal cell carcinoma, BCC and melanoma for diseases. To define exposure, the following keywords were used: sunbed, sunlamp, artificial UV, artificial light, solaria, solarium, indoor tanning, tanning bed, tanning parlour, tanning salon and tanning booth.

Search for keywords in the title and in the abstract was done systematically. Manual search was done of references cited in the selected articles, and in selected reviews or books on melanoma and skin cancer. All participants of the working group were asked to report any additional published or submitted study. No language restriction was applied.

Primary inclusion criteria were developed for the selection of relevant articles, which were case–control, cohort or cross-sectional studies published as an original article. Ecological studies, case reports, reviews and editorials were not considered eligible.

The selected articles were reviewed, and data were abstracted by means of a standardized data-collection protocol. When another article on the same study was published simultaneously, additional relevant or missing information was retrieved from the companion paper.

Studies on melanoma

We identified 23 studies on use of indoor tanning equipment and melanoma (Table II).[34,49,50,53–73] All studies used the case–control design, except for 1 cohort study.[50] A case–control study was considered population-based when cases were derived from a population-based cancer registry and controls were selected from the general population. Of these 23 studies, 4 studies were excluded from the metaanalysis because they did not include estimates of the relative risk for cutaneous melanoma associated with exposure to tanning appliances.[53,55,57,62]

Studies used for the metaanalysis included a total of 7,355 cases. The first study was published in 1981 and the last in 2005. Fifteen studies were carried out in European countries, 4 of which in Scandinavian countries, and 2 were in the United States, 1 in Canada and 1 in Australia.

Studies on basal cell and squamous cell carcinomas

Nine case–control studies have examined the association between indoor tanning and either BCC or SCC of the skin.[74–82] All studies reported a risk estimate except one,[74] which was therefore excluded. A further 3 studies that did not distinguish between

TABLE II – CHARACTERISTICS OF THE STUDIES CONSIDERED FOR THE METAANALYSIS ON MELANOMA

Reference	Country	Number		Relative risk[2]
		Cases	Controls	
Cohort study				
Veierød *et al.* (2003)[50]	Norway, Sweden	187	106,379[1]	1.55 (1.04–2.32)
Population-based case–control studies				
Adam *et al.* (1981)[54]	UK	169	207	2.93 (1.16–7.40)
Gallagher *et al.* (1986)[55]	Canada	595	595	[3]
Holman *et al.* (1986)[56]	Australia	511	511	1.1 (0.6–1.8)
Osterlind *et al.* (1988)[59]	Denmark	474	926	0.73 (0.53–1.01)
Zanetti *et al.* (1988)[60]	Italy	208	416	0.9 (0.4–2.0)
Beitner *et al.* (1990)[62]	Sweden	523	505	[3]
Walter *et al.* (1990)[63]	Canada	583	608	[4]
Westerdahl *et al.* (1994)[70]	Sweden	400	640	1.3 (0.9–1.8)
Holly *et al.* (1995)[68]	USA	452	930	0.94 (0.74–1.2)
Chen *et al.* (1998)[69]	USA	624	512	1.13 (0.82–1.54)
Walter *et al.* (1999)[64]	Canada	583	608	1.54 (1.16–2.05)
Westerdahl *et al.* (2000)[73]	Sweden	571	913	1.2 (0.9–1.6)
Other case-control studies				
Klepp and Magnus (1979)[53]	Norway	78	131	[3]
Holly *et al.* (1987)[57]	USA	121	139	[3]
Swerdlow *et al.* (1988)[58]	UK	180	120	2.94 (1.41–6.17)
MacKie *et al.* (1989)[61]	UK	280	180	1.3 (0.2–7.9) for men; 1.2 (0.5–3.0) for women
Dunn-Lane *et al.* (1993)[65]	UK	100	100	1.16 (0.54–2.47)
Garbe *et al.* (1993)[66]	Germany	280	280	1.5 (0.9–2.4)
Autier *et al.* (1994)[67]	Belgium, France, and Germany	420	447	0.97 (0.71–1.32)
Naldi *et al.* (2000)[71]	Italy	542	538	0.78 (0.45–1.37)
Kaskel *et al.* (2001)[49]	Germany	271	271	1.00 (0.6–1.8)
Bataille *et al.* (2004)[72]	UK	413	416	1.19 (0.84–1.68)
Bataille *et al.* (2005)[34]	Belgium, France, the Netherlands, Sweden, UK	597	622	0.90 (0.71–1.14)

ALM, acral lentiginous melanoma; HC, histologically confirmed; LMM, lentigo maligna melanoma; M, melanoma; MM, malignant melanoma; NM, nodular melanoma; SSM, superficial spreading melanoma.

[1]Cohort size.–[2]Values in parentheses are 95% CI .–[3]Because no estimate of risk was reported in these studies, we did not include them in the metaanalysis.–[4]The study by Walter *et al.* (1990)[63] was reanalyzed in the 1999 publication. We used the relative risk adjusted for potential confounders presented in the 1999 publication.

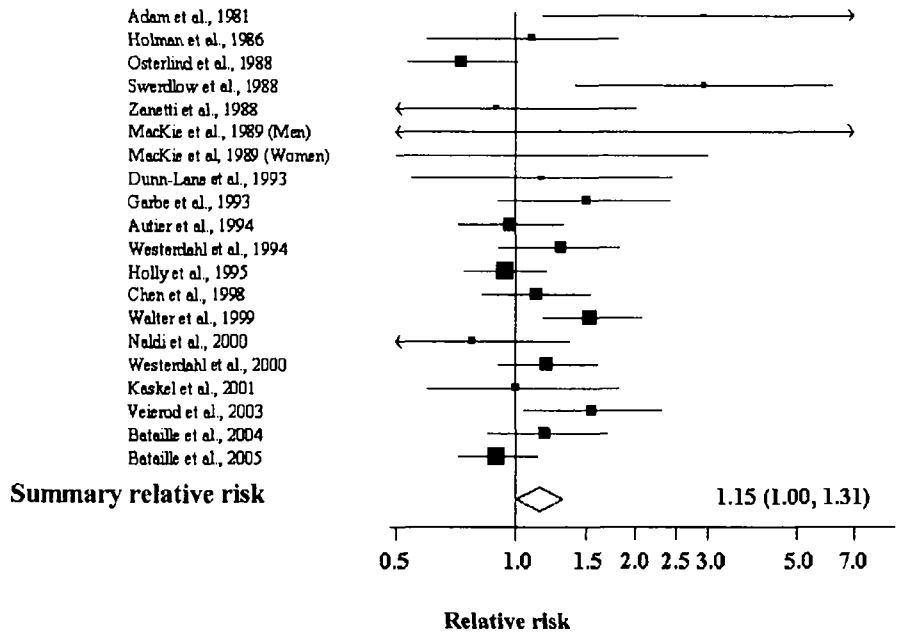

FIGURE 1 – Relative risk for cutaneous melanoma associated with ever use of indoor tanning equipment: estimates of 19 studies and summary estimate (relative risks were presented separately for men and women in the study by MacKie *et al.*[61]).

TABLE III – METAANALYSIS OF EPIDEMIOLOGICAL STUDIES ON INDOOR TANNING AND RISK FOR MELANOMA, SQUAMOUS CELL CARCINOMA AND BASAL CELL CARCINOMA

Exposure	Number of studies	Summary relative risk[1]	Heterogeneity[2] (p value)
Melanoma			
Ever use of indoor tanning equipment	19	1.15 (1.00–1.31)	0.013
First exposure in youth	7	1.75 (1.35–2.26)	0.55
Exposure distant in time	5	1.49 (0.93–2.38)	0.018
Exposure recent in time	5	1.10 (0.76–1.60)	0.81
Squamous cell carcinoma			
Ever use of indoor tanning equipment	3	2.25 (1.08–4.70)	0.10
Basal cell carcinoma			
Ever use of indoor tanning equipment	4	1.03 (0.56–1.90)	0.06

[1]Values in parentheses are 95% CI.–[2]χ^2-test: the degrees of freedom are given by the number of risk estimates included minus 1.

these 2 major types of skin cancer[75–77] were also excluded from review, leaving 5 studies for consideration.

Relative risk for melanoma

Thirteen of 19 studies presented positive estimates for "ever" *versus* "never" exposed to indoor tanning equipment, but only 4 were statistically significant[50,54,58,64] (Fig. 1). Seven of these studies reported only crude relative risks, and 1 adjusted for age and sex only. Results of the metaanalysis are shown in Table III. The summary estimate indicated a significant positive association between "ever" *versus* "never" indoor tanning and melanoma (RR, 1.15; CI, 1.00–1.31) and the χ^2-test for heterogeneity was statistically significant.

To decrease the influence of possible biases, estimates were calculated including only the cohort and the 9 population-based case–control studies. The summary relative risk was very similar apart from having wider CIs (RR, 1.17; CI, 0.96–1.42). In an analysis restricted to the 8 studies that adjusted for confounders related to sun exposure and sun sensitivity,[50,60,61,64,69–71,73] the summary relative risk remained similar to that obtained from all 19 studies, but the CI widened (RR, 1.19; CI, 0.33–4.30).

Seven studies presented estimates relevant for the evaluation of "first exposure in youth" *versus* "never" (Fig. 2). All relative risks were adjusted for confounders related to sun exposure or sun sensitivity, except in the study by Walter *et al.*[64] A significant 75% increase in risk was detected (Table III) and the χ^2-test for heterogeneity was nonsignificant.

Five studies investigated time since exposure and reported estimates that allowed comparisons between recent and more distant exposure.[34,58,63,67,69] Metaanalytic estimates were greater for exposures more distant in time when compared to those for more recent exposures (Table III).

There was some indication for a dose-effect relationship in 2 studies,[67,70] but not in the other two.[69,73] But metrics used for assessing duration were all different and therefore did not permit metaanalytic synthesis. Only 4 studies explored the role of natural sensitivity to sunlight on risk associated with indoor tanning, and overall, they found no consistent result.[34,64,72,73]

Type of indoor tanning equipment

No epidemiological study has been able to explore in a rigorous way amounts of UVA and UVB received by indoor tanning users. The study by Chen *et al.*[69] obtained information concerning the type of sunbed or sunlamp used (*e.g.*, desktop models, floor models, beds or walk-in booths). This information was obtained by showing to subjects pictures of various types of sunlamps and sun-

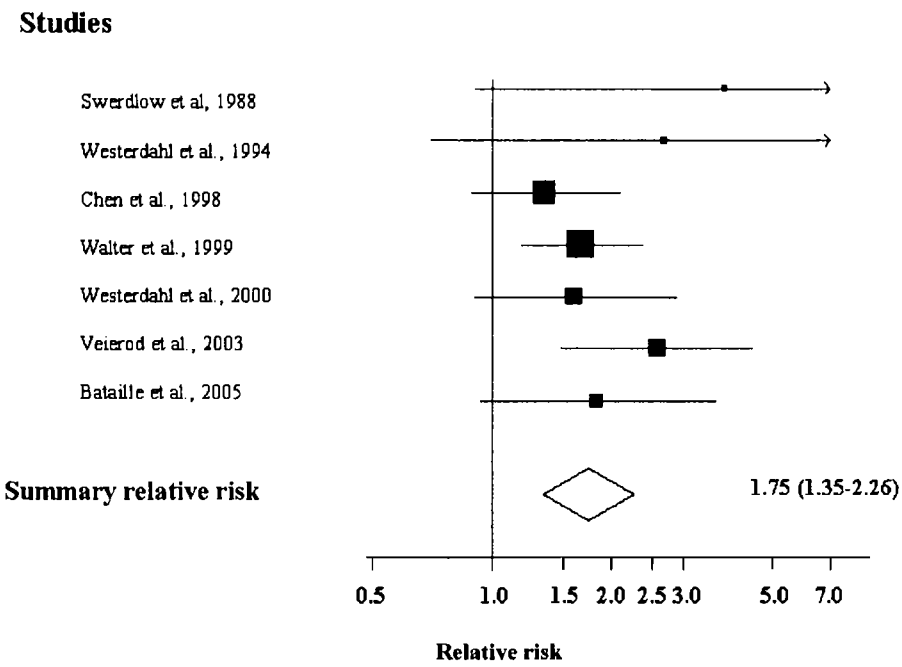

FIGURE 2 – Relative risk for cutaneous melanoma associated with first use of indoor tanning equipment at age <35 years: estimates of 7 studies and summary estimate.

beds. The study found a nonsignificant elevated risk of malignant melanoma associated with the use of desktop sunlamps and heavyweight floor-model sunbeds and a statistically significant tripled risk associated with use of more than 2 types of sunlamps, compared with no use of sunbeds. The study by Bataille *et al.*[34] reported no impact of the type of device used on melanoma risk.

The relative risks of melanoma associated with ever-use of sunbed/sunlamp reported in the studies did not vary with year of publication or first year of study period, and funnel plot regression gave no indication of publication bias (ever-use of sunbed/sunlamps, $p = 0.80$; first exposure in youth, $p = 0.10$). This observation suggests that the apparent increased risk for ever use and for age at first use were unlikely to be explained by the earlier types of indoor tanning appliance used.

Before 1980, exposure to artificial UV radiation was more likely to take place at home with devices that emitted greater amounts of UVB radiation, whereas exposure in the 1980s increasingly occurred in commercial salons using equipment that emitted mainly UVA. The Norway–Swedish prospective study provided evidence that the increased melanoma risk associated with exposure to tanning appliances was not due to the type of UV lamps used before 1983.[83]

Relative risk for squamous cell carcinoma and basal cell carcinoma

The metaanalysis was based on the 5 studies[78–82] reporting type-specific risk estimates (Table III). Metaanalytic estimates suggested a significant effect of exposure to indoor tanning appliances for SCC, but not for BCC. Funnel plot regression gave no indication of publication bias ($p = 0.26$ and 0.77 for SCC and BCC, respectively).

The study by Karagas *et al.*[81] gave the most detailed results, and the trends were consistent with the results reported for melanoma. Results were adjusted for sun sensitivity but not for sun exposure, since adjustment for sun exposure did not change the risk estimates. Depending on age at first use, the risks for BCC and SCC were found to increase by 10% (OR, 1.1; CI, 0.9–1.5) and 20% (OR, 1.2; CI, 0.9–1.6) respectively for each decade younger the person was at first use of indoor tanning equipment.

Discussion

Investigation of the association between indoor tanning and skin cancers poses challenging problems, as indoor tanning has been in widespread use only recently. Based on our knowledge about the relationship between sun exposure and risk for melanoma, it could be stated that associations after long latency periods, such as would be expected for melanoma and BCC, may not be detectable yet. Also, since the fashion of indoor tanning has been increasing steadily, the failure to distinguish between distant and recent exposures in most epidemiological studies may mask an actual increase in risk with exposure early in life.

Our systematic review of published studies mainly from Europe and North America of the association of use of indoor tanning equipment with skin cancers revealed an association of age at first use of less than 35 years with melanoma risk. These studies consistently indicated a moderate strength of association, with a summary relative risk of 1.75 (1.35–2.26). This result suggests a greater vulnerability of younger people to the carcinogenic impact of indoor tanning. Also, it is in agreement with the knowledge that age at exposure may influence the relative risk for skin cancer associated with UV exposure, and that exposure to sunlight in childhood is an important contributing factor for melanoma risk in adults.[84,85]

The association with ever-use of such equipment, or use more than 15–20 years prior to diagnosis of melanoma, was weak, and evidence regarding a dose–response relationship was scant. The evidence is limited by concerns over characterization of exposure and recall of exposure by individuals, potential confounding by sun exposure or other variables and the low power to detect associations that become evident only following a prolonged lag period after exposure. Our results are similar to a previous metaanalysis,[86] but our systematic review is more exhaustive and included more studies.

In Scandinavian countries use of indoor tanning equipment has been popular since the late 1970s and the prevalence of use in those countries is the highest in the world. In the Norwegian–Swedish prospective study the highest risk for melanoma was found in women who used indoor tanning equipment at least once per month when they were 20–29 years old. These results support the hypothesis that a certain lag period is needed before the impact

of exposure to tanning appliances on melanoma incidence becomes apparent. It also underlines the greater vulnerability of younger subjects to harmful effects of indoor tanning.

The positive association between use of indoor tanning equipment and melanoma risk reported here is consistent with the knowledge that melanoma is caused primarily by exposure to solar radiation. The limited evidence for a positive association between indoor tanning and SCC is consistent with its known dependence on dose of UV radiation to the skin. Thus the biological plausibility of a causal association between indoor tanning and risk for melanoma and SCC is strong.

On balance, the evidence pertaining to the strength, consistency, dose–response and temporal sequence of the association of the use of indoor tanning equipment with melanoma risk, and of the coherence and biologic plausibility of the association, leads us to conclude that there is convincing evidence to support a causal relationship, particularly with exposure before the age of 35 years. This evidence is strongly suggestive and further studies could clarify our understanding of this association and allow more definitive conclusions.

We are cognizant of the importance of this issue for the health of light-skinned populations. The strength of the existing evidence suggests that policy makers should strongly consider enacting measures such as restricting minors and discouraging young adults from using indoor tanning equipment, in order to protect the general population from additional risk for melanoma and squamous cell skin cancer.

References

1. IARC. Solar and ultraviolet radiation. Lyon: International Agency for Research on Cancer, 1992. IARC monographs on the evaluation of carcinogenic risks to humans, vol. 55.
2. National Toxicology Program. 10th Report on Carcinogens: substances profiles. Research Triangle Park, US Department of Health and Human Services, Public Health Service, 2002.
3. de Gruijl FR, van Kranen HJ, Mullenders LH. UV-induced DNA damage, repair, mutations and oncogenic pathways in skin cancer. J Photochem Photobiol B 2001;63:19–27.
4. de Gruijl FR. Photocarcinogenesis: UVA vs. UVB radiation. Skin Pharmacol Appl Skin Physiol 2002;15:316–20.
5. Paul CL, Girgis A, Tzelepis F, Walsh RA. Solaria use by minors in Australia: is there a cause for concern? Aust N Z J Public Health 2004; 28:90.
6. Paul CL, Stacy F, Girgis A, Brozek I, Baird H, Hughes J. Solaria compliance in an unregulated environment: the Australian experience. Eur J Cancer 2005;41:1178–84.
7. Wester U, Boldemann C, Jansson B, Ullén H. Population UV-dose and skin area—do sunbeds rival the sun? Health Phys 1999;77:436–40.
8. Gerber B, Mathys P, Moser M, Bressoud D, Braun-Fahrlander C. Ultraviolet emission spectra of sunbeds. Photochem Photobiol 2002; 76:664–8.
9. Miller SA, Hamilton SL, Wester UG, Cyr WH. An analysis of UVA emissions from sunlamps and the potential importance for melanoma. Photochem Photobiol 1998;68:63–70.
10. MacGintley J, Martin CJ, MacKie RM. Sunbeds in current use in Scotland: a survey of their output and patterns of use. Br J Dermatol 1998;139:428–38.
11. Wright AL, Hart GC, Kernohan E, Twentyman G. Survey of the variation in ultraviolet outputs from ultraviolet A sunbeds in Bradford. Photodermatol Photoimmunol Photomed 1996;12:12–16.
12. Pfeifer GP, You YH, Besaratinia A. Mutations induced by ultraviolet light. Mutat Res 2005;571:19–31.
13. Griffiths HR, Mistry P, Herbert KE, Lunec J. Molecular and cellular effects of ultraviolet light-induced genotoxicity. Crit Rev Clin Lab Sci 1998;35:189–237.
14. Robert C, Muel B, Benoit A, Dubertret L, Sarasin A, Stary A. Cell survival and shuttle vector mutagenesis induced by UVA and UVB radiation in a human cell line. J Invest Dermatol 1996;106:721–8.
15. Halliday G. Inflammation, gene mutation and photoimmunosuppression in response to UVR-induced oxidative damage contributes to photocarcinogenesis. Mut Res 2005;571:107–20.
16. Woollons A, Clingen PH, Price ML, Arlett CF, Green MH. Induction of mutagenic DNA damage in human fibroblasts after exposure to artificial tanning lamps. Br J Dermatol 1997;137:687–92.
17. Whitmore SE, Morison WL, Potten CS, Chadwick C. Tanning salon exposure and molecular alterations. J Am Acad Dermatol 2001;44: 775–80.
18. Persson AE, Edstrom DW, Backvall H, Lundeberg J, Ponten F, Ros AM, Williams C. The mutagenic effect of ultraviolet-A1 on human skin demonstrated by sequencing the p53 gene in single keratinocytes. Photodermatol Photoimmunol Photomed 2002;18:287–93.
19. Kripke ML. Antigenicity of murine skin tumors induced by UV light. J Natl Cancer Inst 1974;53:1333–6.
20. Singh RK, Gutman M, Reich R, Bar-Eli M. Ultraviolet B irradiation promotes tumorigenic and metastatic properties in primary cutaneous melanoma via induction of interleukin-8. Cancer Res 1995;55:3669–74.
21. Phan TA, Halliday GM, Barnetson RS, Damian DL. Spectral and dose dependence of ultraviolet radiation-induced immunosuppression. Front Biosci 2006;11:394–411.
22. Aboutalebi S, Strickland FM. Immune protection, natural products, and skin cancer: is there anything new under the sun? J Drugs Dermatol 2006;5:512–7.
23. Ullrich SE. Mechanisms underlying UV-induced immune suppression. Mutat Res 2005;571:185–205.
24. Autier P, Joarlette M, Lejeune F, Lienard D, Andre J, Achten G. Cutaneous malignant melanoma and exposure to sunlamps and sunbeds: a descriptive study in Belgium. Melanoma Res 1991;1:69–74.
25. Autier P. Perspectives in melanoma prevention: the case of sunbeds. Eur J Cancer 2004;40:2367–76.
26. Pedeux R, Al-Irani N, Marteau C, Pellicier F, Branche R, Ozturk M, Franchi J, Dore JF. Thymidine dinucleotides induce S phase cell cycle arrest in addition to increased melanogenesis in human melanocytes. J Invest Dermatol 1998;111:472–7.
27. Black G, Matzinger E, Gange RW. Lack of photoprotection against UVB-induced erythema by immediate pigmentation induced by 382 nm radiation. J Invest Dermatol 1985;85:448–9.
28. Gange RW, Blackett AD, Matzinger EA, Sutherland BM, Kochevar IE. Comparative protection efficiency of UVA- and UVB-induced tans against erythema and formation of endonuclease-sensitive sites in DNA by UVB in human skin. J Invest Dermatol 1985;85: 362–4.
29. Rivers JK, Norris PG, Murphy GM, Chu AC, Midgley G, Morris J, Morris RW, Young AR, Hawk JL. UVA sunbeds: tanning, photoprotection, acute adverse effects and immunological changes. Br J Dermatol 1989;120:767–77.
30. Sheehan JM, Potten CS, Young AR. Tanning in human skin types II and III offers modest photoprotection against erythema. Photochem Photobiol 1998;68:588–92.
31. Hemminki K, Bykov VJ, Marcusson JA. Re: Sunscreen use and duration of sun exposure: a double-blind, randomised trial. J Natl Cancer Inst 1999;91:2046–7.
32. Bykov VJ, Marcusson JA, Hemminki K. Protective effects of tanning on cutaneous DNA damage in situ melanoma. Dermatology 2001; 202:22–6.
33. Ruegemer J, Schuetz B, Hermann K, Hein R, Ring J, Abeck D. UV-induced skin changes due to regular use of commercial sunbeds. Photodermatol Photoimmunol Photomed 2002;18:223–7.
34. Bataille V, Boniol M, De Vries E, Severi G, Brandberg Y, Sasieni P, Cuzick J, Eggermont A, Ringborg U, Grivegnee AR, Coebergh JW, Chignol MC, et al. A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. Eur J Cancer 2005;41:2141–9.
35. Mermelstein RJ, Riesenberg LA. Changing knowledge and attitudes about skin cancer risk factors in adolescents. Health Psychol 1992; 11:371–6.
36. Boldeman C, Beitner H, Jansson B, Nilsson B, Ullen H. Sunbed use in relation to phenotype, erythema, sunscreen use and skin diseases. A questionnaire survey among Swedish adolescents. Br J Dermatol 1996;135:712–6.
37. Robinson JK, Rademaker AW, Sylvester JA, Cook B. Summer sun exposure: knowledge, attitudes and behaviors of Midwest adolescents. Prev Med 1997;26:364–72.
38. Cokkinides VE, Weinstock M, O'Connell MC, Thun MJ. Use of indoor tanning sunlamps by US youth, ages 11–18 years, and by their parent or guardian caregivers: prevalence and correlates. Pediatrics 2002;109:1124–30.
39. Demko CA, Borawski EA, Debanne SM, Cooper KD, Stange KC. Use of indoor tanning facilities by white adolescents in the United States. Arch Pediatr Adolesc Med 2003;157:854–60.
40. Geller AC, Colditz GA, Oliveria S, Emmons K, Jorgensen C, Aweh GN, Frazier AL. Use of sunscreen, sunburning rates, and tanning bed use among more than 10,000 US children and adolescents. Pediatrics 2002;109: 1009–14.

41. Oliphant JA, Forster JL, McBride CM. The use of commercial tanning facilities by suburban Minnesota adolescents. Am J Public Health 1994;84:476–8.
42. Culley CA, Mayer JA, Eckhardt L, Busic AJ, Eichenfield LF, Sallis JF, Quintana PJ, Woodruff SI. Compliance with federal and state legislation by indoor tanning facilities in San Diego. J Am Acad Dermatol 2001;44:53–60.
43. Rhainds M, De Guire L, Claveau J. A population-based survey on the use of artificial tanning devices in the province of Quebec, Canada. J Am Acad Dermatol 1999;40:572–6.
44. Kwon HT, Mayer JA, Walker KK, Yu H, Lewis EC, Belch GE. Promotion of frequent tanning sessions by indoor tanning facilities: two studies. J Am Acad Dermatol 2002;46:700–5.
45. Hornung RL, Magee KH, Lee WJ, Hansen LA, Hsieh YC. Tanning facility use: are we exceeding Food and Drug Administration limits? J Am Acad Dermatol 2003;49:655–61.
46. Lazovich D, Forster JL, Sorensen G, Emmons K, Stryker JE, Demierre MF, Hickle A, Remba N. Characteristics associated with use or intention to use indoor tanning among adolescents. Arch Pediatr Adolesc Med 2004;158:918–24.
47. Lazovich D, Forster J. Indoor tanning by adolescents: prevalence, practices and policies. Eur J Cancer 2005;41:20–7.
48. Hamlet N, Kennedy K. Reconnaissance study of sunbed use by primary school children in Lanarkshire. J Public Health 2004;26:31–3.
49. Kaskel P, Sander S, Kron M, Kind P, Peter RU, Krahn G. Outdoor activities in childhood: a protective factor for cutaneous melanoma? Results of a case-control study in 271 matched pairs. Br J Dermatol 2001;145:602–9.
50. Veierød MB, Weiderpass E, Thorn M, Hansson J, Lund E, Armstrong B, Adami HO. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003;95:1530–8.
51. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987;9:1–30.
52. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. Stat Med 2001;20:641–54.
53. Klepp O, Magnus K. Some environmental and bodily characteristics of melanoma patients. A case-control study. Int J Cancer 1979;23: 482–6.
54. Adam SA, Sheaves JK, Wright NH, Mosser G, Harris RW, Vessey MP. A case-control study of the possible association between oral contraceptives and malignant melanoma. Br J Cancer 1981;44:45–50.
55. Gallagher RP, Elwood JM, Hill GB. Risk factors for cutaneous malignant melanoma: the Western Canada Melanoma Study. Recent Results Cancer Res 1986;102:38–55.
56. Holman CD, Armstrong BK, Heenan PJ, Blackwell JB, Cumming FJ, English DR, Holland S, Kelsall GR, Matz LR, Rouse IL, Singh A, Ten Seldam REJ et al. The causes of malignant melanoma: results from the West Australian Lions Melanoma Research Project. Recent Results Cancer Res 1986;102:18–37.
57. Holly EA, Kelly JW, Shpall SN, Chiu SH. Number of melanocytic nevi as a major risk factor for malignant melanoma. J Am Acad Dermatol 1987;17:459–68.
58. Swerdlow AJ, English JS, MacKie RM, O'Doherty CJ, Hunter JA, Clark J, Hole DJ. Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. Br Med J 1988;297:647–50.
59. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. Int J Cancer 1988;42:319–24.
60. Zanetti R, Rosso S, Faggiano F, Roffino R, Colonna S, Martina G. A case-control study on cutaneous malignant melanoma in the province of Torino, Italy. Rev Epidemiol Santé Publique 1988;36:309–17 [in French].
61. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. Lancet 1989;2:487–90.
62. Beitner H, Norell SE, Ringborg U, Wennersten G, Mattson B. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. Br J Dermatol 1990;122:43–51.
63. Walter SD, Marrett LD, From L, Hertzman C, Shannon HS, Roy P. The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. Am J Epidemiol 1990;131:232–43.
64. Walter SD, King WD, Marrett LD. Association of cutaneous malignant melanoma with intermittent exposure to ultraviolet radiation: results of a case-control study in Ontario, Canada. Int J Epidemiol 1999; 28:418–27.
65. Dunn-Lane J, Herity B, Moriarty MJ, Conroy R. A case control study of malignant melanoma. Ir Med J 1993;86:57–59. Erratum in: Ir Med J 1993;86:135.
66. Garbe C, Weiss J, Kruger S, Garbe E, Buttner P, Bertz J, Hoffmeister H, Guggenmoos-Holzmann I, Jung EG, Orfanos CE. The German melanoma registry and environmental risk factors implied. Recent Results Cancer Res 1993;128:69–89.
67. Autier P, Dore JF, Lejeune F, Koelmel KF, Geffeler O, Hille P, Cesarini JP, Lienard D, Liabeuf A, Joarlette M, Chemaly P, Hakim K, et al., for the EORTC Melanoma Cooperative Group. Cutaneous malignant melanoma and exposure to sunlamps or sunbeds: for the EORTC multicenter case-control study in Belgium, France and Germany. Int J Cancer 1994;58:809–13.
68. Holly EA, Aston DA, Cress RD, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. Am J Epidemiol 1995;141: 923–33.
69. Chen YT, Dubrow R, Zheng T, Barnhill RL, Fine J, Berwick M. Sunlamp use and the risk of cutaneous malignant melanoma: a population-based case-control study in Connecticut, USA. Int J Epidemiol 1998;27:758–65.
70. Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N, Brandt L, Jonsson PE, Moller T. Use of sunbeds or sunlamps and malignant melanoma in southern Sweden. Am J Epidemiol 1994;140:691–9.
71. Naldi L, Gallus S, Imberti GL, Cainelli T, Negri E, La Vecchia C, on behalf of the Italian Group for Epidemiological Research in Dermatology. Sunlamps and sunbeds and the risk of cutaneous melanoma. Eur J Cancer Prev 2000;9:133–4.
72. Bataille V, Winnett A, Sasieni P, Newton-Bishop JA, Cuzick J. Exposure to the sun and sunbeds and the risk of cutaneous melanoma in the UK: a case-control study. Eur J Cancer 2004;40:429–35.
73. Westerdahl J, Ingvar C, Masback A, Jonsson N, Olsson H. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer 2000;82:1593–9.
74. Boyd AS, Shyr Y, King LE Jr. Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. J Am Acad Dermatol 2002;46:706–9.
75. O'Loughlin G, Moriarty MJ, Herity B, Daly L. A re-appraisal of risk factors for skin carcinoma in Ireland. A case-control study. Ir J Med Sci 1985;154:61–5.
76. Herity B, O'Loughlin G, Moriarty MJ, Conroy R. Risk factors for non-melanoma skin cancer. J Ir Med 1989;82:151–2.
77. Hogan DJ, To T, Wilson ER, Miller AB, Robson D, Holfeld K, Lane P. A study of acne treatments as risk factors for skin cancer of the head and neck. Br J Dermatol 1991;125:343–8.
78. Aubry F, MacGibbon B. Risk factors of squamous cell carcinoma of the skin. A case-control study in the Montreal region. Cancer 1985; 55:907–11.
79. Bajdik CD, Gallagher RP, Astrakianakis G, Hill GB, Fincham S, McLean DI. Non-solar ultraviolet radiation and the risk of basal and squamous cell skin cancer. Br J Cancer 1996;73:1612–4.
80. Corona R, Dogliotti E, D'Errico M, Sera F, Iavarone I, Baliva G, Chinni LM, Gobello T, Mazzanti C, Puddu P, Pasquini P. Risk factors for basal cell carcinoma in a Mediterranean population: role of recreational sun exposure early in life. Arch Dermatol 2001;137:1162–8.
81. Karagas MR, Stannard VA, Mott LA, Slattery MJ, Spencer SK, Weinstock MA. Use of tanning devices and risk of basal cell and squamous cell skin cancers. J Natl Cancer Inst 2002;94:224–6.
82. Walther U, Kron M, Sander S, Sebastian G, Sander R, Peter RU, Meurer M, Krahn G, Kaskel P. Risk and protective factors for sporadic basal cell carcinoma: results of a two-centre case-control study in southern Germany. Clinical actinic elastosis may be a protective factor. Br J Dermatol 2004;151:170–8.
83. Veierød MB, Weiderpasss E, Lund E, Armstrong BK, Adami HO. Re: A retrospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2004;96:337–8.
84. Autier P, Doré JF, for EPIMEL and EORTC Melanoma Cooperative Group. Influence of sun exposures during childhood and during adulthood on melanoma risk. Int J Cancer 1998;77:533–7.
85. Whiteman DC, Whiteman CA, Green A. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12:69–82.
86. Gallagher RP, Spinelli JJ, Lee TK. Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. Cancer Epidemiol Biomarkers Prev 2005;14:562–6.

Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity.

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In a population-based, matched, case-control study from southern Sweden of 571 patients with a first diagnosis of cutaneous malignant melanoma and 913 healthy controls aged 16-80 years, the association between sunbed use and malignant melanoma was evaluated. A total of 250 (44%) cases and 372 (41%) controls reported ever having used sunbeds. A significantly elevated odds ratio for developing malignant melanoma after regular exposure to sunbeds was found, adjusted for hair colour, raised naevi, skin type and number of sunburns (odds ratio (OR) 1.8, 95% confidence interval (CI) 1.2-2.7). A dose-response relationship between total number of sunbed uses and melanoma risk was only found up to the level of 250 times. The OR was higher in individuals younger than age 36 years (adjusted OR 8.1, 95% CI 1.3-49.5 for regular vs. never use). The association seemed to be true only for subjects with black/dark brown or light brown hair and among females. Lesions of the extremities showed the strongest association of increased risk with sunbed use. An increased risk was related to commercial exposure and to exposure during the winter. The results substantiate the hypothesis that exposure to sunbeds might increase the risk of developing malignant melanoma.

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The health effects of using solaria and potential cost-effectiveness of enforcing solaria regulations in Australia

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CONTENTS

Acronyms

AIHW	Australian Institute of Health and Welfare
ARPANSA	Australian Radiation Protection and Nuclear Safety Agency
BCC	Basal cell carcinoma
CFR	Case-fatality rate
CI	Confidence interval
CIE	Commission Internationale de l'Éclairage
GP	General practitioner
IARC	International Agency for Research on Cancer
ICNIRP	International Commission on Non-Ionising Radiation Protection
MED	Minimum erythemal dose
NMSC	Non-melanocytic skin cancer
PBS	Pharmaceutical Benefits Scheme
QIMR	Queensland Institute of Medical Research
RR	Relative risk
SCC	Squamous cell carcinoma
SED	Standard erythemal dose
SPF	Sun protection factor
UK	United Kingdom
US	United States
USFDA	United States Food and Drug Administration
USFTC	Unites States Federal Trade Commission
UVA	Ultraviolet radiation in the A wavelength band (315-400 nm)
UVB	Ultraviolet radiation in the B wavelength band (280-315 nm)
UVC	Ultraviolet radiation in the C wavelength band (100-280 nm)
UVR	Ultraviolet radiation
WHO	World Health Organisation

Executive Summary

In line with several leading international organisations, there is growing concern about the Australian solarium industry among the state Cancer Councils and other health agencies, due to increased patronage of solaria and the associated risk of skin cancer. Following a recent intense period of media attention on this issue in Australia, this report has been generated to investigate the health effects of solaria use and to estimate the costs and benefits to the Commonwealth Government should they decide to fortify existing regulatory controls of the industry.

The actual size of the solaria industry is unknown and difficult to quantify though recent audits have shown that solarium businesses have at least quadrupled since 1992 and that Victoria has seen the largest growth. Compared to the situation outside Australia, the prevalence and frequency of the general population's usage of solaria is fairly low (approximately 0.6-3.0%). However, the prevalence of use among adolescents and females is higher with one study showing 12% of NSW school children had used solaria. At this time, we know little about the change of solarium usage over time, or of consumer patterns and predictors of use. However, the increased supply of these services is partly reflected in their increased demand. Studies indicate that the level of compliance with the Australian/New Zealand Standard on Solaria for Cosmetic Purposes (AS/NZS 2635:2002) within the market is poor to many behavioural elements of the Standard, including prohibiting individuals with skin type I, obtaining parental consent for youths under 18 years and obtaining consent from every consumer prior in regard to use. Compliance with the technical elements of the Standard is unknown (i.e., sunlamp emission intensity, replacement of ageing lamps, operator training levels). Based on overseas trends, the level of ultraviolet (UV) emissions in the UVB waveband from sunbeds is likely to be in the range of 4-6% of the total UV emissions from the sunbed, or similar to that of solar UVB.

Ultraviolet radiation (UVR) is the principal causative factor of malignant melanoma and keratinocytic skin cancers. Both UVB and UVA wavelengths are classified as carcinogenic to humans by world health authorities. Australia has among the highest ambient UVR levels in the world with most States having more intense UVR in winter than in a European summer. Australia also has the highest rates of skin cancer in the world with over 9,500 new cases of melanoma diagnosed in 2003. Melanoma incidence has increased rapidly by approximately 40% from 1993-2003, the highest increase of any cancer in Australia. The change in the incidence of keratinocytic skin cancers since 2002 is unknown, but is also likely to have increased. Skin cancer is the most expensive cancer to treat in Australia and costs are continuing to rise rapidly in real terms. The known treatment costs to the Government are likely to be a fraction of all costs for the treatment of sun-damaged skin through Medicare Australia.

It is of particular concern that the additive effect of Australians using artificial UVR against already intense levels of solar UVR (i.e., 'photoaddition') will mean that the existing high burden of skin cancer will increase. There is compelling evidence that individuals who use artificial indoor tanning devices will increase their risk of skin cancer. Results from a meta-analysis of 21 studies investigating the association between solarium use and risk of skin cancer show an increased

risk for developing melanoma (by 22%) and squamous cell carcinoma (by 78%), an increased risk of melanoma for first users under 35 years (by 98%) and for women (by 71%). The risk also appears to be increased for basal cell carcinomas (18%), although these latter findings were inconclusive.

Using a crude mathematical model combining data parameters for solar and artificial UVR doses, population prevalence of indoor and outdoor tanning, and melanoma mortality and incidence figures, we estimated that currently the number of new cases of melanoma attributable to indoor tanning devices is in the range of 12-62 per year. In terms of mortality, less than 1% of all UVR-caused melanoma deaths would be attributable to solarium use (or approximately 1-7 melanoma deaths) each year.

A decision-analytic model was created to project the future cost and health effects comparing current solaria practice with enforcing solarium regulations, based on the current Standard, thereby effectively restricting youths under 15 years and prohibiting persons with skin type I. The health effects were measured in terms of new cases of melanomas and squamous cell carcinomas (SCCs), life years gained and life years lost due to premature melanoma mortality. The costs were limited to those incurred by Medicare Australia for the diagnosis, treatment and care of individuals with skin cancers.

If the Government were to regulate the industry, we estimate that around 20-35 melanomas and 240-320 SCCs would be avoided and 35 life years gained per 100,000 persons. The corresponding cost-savings generated from avoided health care costs are expected to be approximately $300,000 per 100,000 persons. For all young Australians, we could expect that over their lifetime, over 1,000 melanomas and 12,000 SCCs would be avoided and at least $12.2 million would be saved. These estimations are sensitive to the relative risk estimates for skin cancers and solarium use and discount rates.

In summary, there are strong arguments for government intervention in the solarium market to ensure that health risks are minimised and solaria practices are monitored. There is clear evidence that solarium users are increasing their risk of skin cancer. Reports indicate that there is market failure in this industry as operators are unaware of and/or failing to comply with the voluntary code of practice which aims to minimize these increased health risks. Given the huge burden imposed by skin cancer in Australia now, growth in the solaria industry will inflate this human and economic burden in years to come. Results from a cost-effectiveness analysis suggest that by enforcing solaria regulations the government can expect favourable cost and health benefits.

A Prospective Study of Pigmentation, Sun Exposure, and Risk of Cutaneous Malignant Melanoma in Women

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Background: Although sun exposure is an established cause of cutaneous malignant melanoma, possible interactions with host factors remain incompletely understood. Here we report the first results from a large prospective cohort study of pigmentation factors and sun exposure in relation to melanoma risk. *Methods:* The Women's Lifestyle and Health Cohort Study included 106 379 women from Norway and Sweden who were aged 30–50 years in 1991 or 1992 when they completed an extensive questionnaire on personal characteristics and exposures. Linkages to national registries ensured complete follow-up through December 31, 1999. Poisson regression models were used to estimate relative risks (RRs). All statistical tests were two-sided. *Results:* During an average follow-up of 8.1 years, 187 cases of melanoma were diagnosed. Risk of melanoma was statistically significantly associated with increasing body surface area (RR for $\geq$1.79 m^2 versus $\leq$1.61 m^2 = 1.60, 95% confidence interval [CI] = 1.03 to 2.48; P_{trend} = .02), number of large asymmetric nevi on the legs (RR for $\geq$7 nevi versus 0 nevi = 5.29, 95% CI = 2.33 to 12.01; P_{trend}<.001), hair color (RR for red versus dark brown or black = 4.05, 95% CI = 2.11 to 7.76; P_{trend}<.001), sunburns per year at ages 10–19, 20–29, and 30–39 years (P_{trend}<.001, P_{trend} = .03, and P_{trend} = .05, respectively), and use of a device that emits artificial light (solarium) one or more times per month (P = .04). *Conclusions:* Our results confirm previous findings that hair color, number of nevi on the legs, and history of sunburns are risk factors for melanoma and suggest that use of a solarium is also associated with melanoma risk. Adolescence and early adulthood appear to be among the most sensitive age periods for the effects of sunburn and solarium use on melanoma risk. However, it may be too early to see the full effect of adult exposures in this cohort. [J Natl Cancer Inst 2003;95:1530–8]

Cutaneous malignant melanoma (hereafter called melanoma) imposes a considerable public health burden. The incidence of melanoma varies more than 150-fold around the world, with the highest rates occurring among white or predominantly white populations in Australia, New Zealand, North America, and northern Europe *(1)*. Rates of melanoma in Norway and Sweden have more than tripled since 1958–1962, the first years that

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reliable information was available from cancer registries; rates are now higher there than they are elsewhere in Europe *(2)* and are predicted to increase *(3)*.

Although sun exposure is the major established risk factor for melanoma *(4,5)*, geographic differences in melanoma incidence cannot be attributed solely to differences in the intensity of solar exposure. Within Europe, for example, the incidence of melanoma is higher at northern latitudes, which generally have lower solar intensities, than at southern latitudes, which generally have higher solar intensities *(2)*, although in both Norway and Sweden, an inverse relationship between melanoma incidence and latitude has been noted *(6,7)*. Hence, the effect of UV light on melanoma risk may be strongly modified by other factors, such as differences in sun sensitivity and the nature of the exposure to the sun *(8)*.

A number of studies have examined factors that influence the association between sun exposure and the risk of melanoma. An intermittent pattern of sun exposure, which is typically assessed by measures of sun-intensive activities, such as outdoor recreation or vacations, is associated with increased risk of melanoma *(9)*. In addition, many studies *(4,5,9,10)* have reported that sunburn, which is an indicator of an intermittent pattern of sun exposure, is positively associated with the risk of melanoma. Results of many studies have suggested that childhood is a critical period for sun exposure *(9)*, and ecologic studies have shown more consistent associations than case–control studies between childhood sun exposure and melanoma risk *(11)*. Host factors such as eye color, hair color, skin color, the number of nevi, and skin reaction to chronic and acute sun exposure have also been associated with the risk of melanoma *(4,12)*.

Most of what is known about the association between sun exposure and melanoma risk comes from results of case–control studies. The Nurses' Health Study is, as far as we know, the only cohort study to examine the association between sun exposure and malignant melanoma; however, a case–control design within the cohort was used in these analyses *(13,14)*. Case–control studies are limited by the potential for differential bias in recall of sun exposure between case patients and control subjects *(15,16)*. Prospective cohort studies can overcome such limitations because the exposure information is collected prior to disease occurrence. Here we report the first results from the Norwegian–Swedish Women's Lifestyle and Health Cohort Study, which was initiated in 1991. This study is the first prospective cohort study, to our knowledge, to examine the associations between pigmentation factors and sun exposure and the risk of malignant melanoma.

Subjects and Methods

Study Population

For practical reasons, women were enrolled in the Norwegian–Swedish Women's Lifestyle and Health Cohort Study in both 1991 and 1992. In Norway, a nationwide random sample of 100 000 women who were born between 1943 and 1957 (i.e., aged 34–49 years at inclusion) was drawn from the National Population Register at Statistics Norway (Oslo, Norway). In Sweden, a random sample of 96 000 women who were born between 1943 and 1962 (i.e., aged 30–50 years at inclusion) and were residing in the Uppsala Health Care Region (which comprises about one-sixth of the Swedish population) was drawn from the National Population Register at Statistics Sweden (Stockholm, Sweden).

All women received a letter inviting them to participate in the study. The letter also requested that they provide written informed consent and contained a comprehensive questionnaire that was to be completed and returned in a prepaid envelope. Identical questions relevant to the analysis presented here were included in the questionnaires sent to women in the two countries. The study was approved by the Data Inspection Boards in both countries and by the regional Ethical Committees, and all women gave written informed consent to participate.

Host Factors and Exposure Information

In the questionnaires, study participants were asked to categorize their natural hair color (dark brown/black, brown, blond, or red) and their eye color (brown, gray/green, or blue) and to categorize the number of asymmetric nevi larger than 5 mm on their legs from toes to groin (0, 1, 2–3, 4–6, 7–12, 13–24, or ≥25 nevi). A brochure that was included with the questionnaire provided color pictures with three examples of asymmetric nevi.

Participants recorded their sun sensitivity according to their reactions to both acute and chronic exposure to the sun. Regarding acute sun exposure, the questionnaire asked the women to choose from among four categories to describe how their skin reacts to heavy sun exposure at the beginning of the summer: the skin turns brown without first becoming red, the skin turns red, the skin turns red with pain, or the skin turns red with pain and blisters. The women were asked to describe how their skin reacts to long-lasting or chronic sun exposure according to four categories: the skin turns deep brown, brown, or light brown, or the skin never turns brown.

Participants were asked to report their histories of sunburn and sunbathing vacations and on the frequency of their use of a solarium (i.e., a sun bed or a sunlamp that emits artificial UV light) when they were aged 10–19, 20–29, 30–39, or 40–49 years. For each age period, the participant was asked to report the number of times per year she had been burned by the sun so severely that it resulted in pain or blisters that subsequently peeled by choosing from among five categories: never, one time per year at most, two or three times per year, four or five times per year, or six or more times per year. Participants reported the average number of weeks per year spent on sunbathing vacations in southern latitudes (typically southern Europe, e.g., Spain or Greece) or within Norway or Sweden for each age period by choosing from among five categories: never, 1 week per year, 2–3 weeks per year, 4–6 weeks per year, or ≥7 weeks per year. Participants reported their average use of a solarium during each age period by choosing from among six categories: never, rarely, one time per month, two times per month, three or four times per month, or more than one time per week. The questionnaires also contained questions about the participant's current height and weight, current and past contraceptive use, reproductive history, prevalent diseases, and lifestyle.

Follow-up and Endpoints

Start of follow-up was defined as the date of receipt of the returned questionnaire. Person-years were calculated from the start of follow-up to the date of diagnosis of primary melanoma, to the date of emigration or death, or to the end of follow-up (December 31, 1999), whichever occurred first. Each resident of Norway and Sweden is assigned a unique national registration number that includes the person's date of birth; those registration numbers are entered into the nationwide databases that were

used in this study. By linkage of cohort data to the national cancer registries in Norway and Sweden, this national registration number allowed us to identify cancer cases. Information on death and emigration was gathered by linkage to Statistics Norway and Statistics Sweden.

A total of 57584 (57.6%) of the Norwegian women and 49259 (51.3%) of the Swedish women returned completed questionnaires; the overall response rate was 54.5%. We excluded four women because of the lack of vital status information in the available register files, 18 women who had emigrated or died before the start of follow-up, 198 women who did not adequately answer the questions regarding sun exposure or personal characteristics (i.e., sun sensitivity of skin, hair color, eye color, and number of asymmetric nevi), and 244 women who were diagnosed with melanoma prior to the start of follow-up.

Statistical Analysis

Participants' geographic regions of residence were defined according to four categories: the southern region of Norway, the middle region of Norway, the northern region of Norway, and the Uppsala Health Care Region in Sweden. The latitudes of the population center of mass within each Norwegian county, which were provided by the Norwegian Mapping Authority, together with the observed number of melanoma cases in those counties, formed the basis for our definitions of the three Norwegian regions. The southern region of Norway includes Vest-Agder, Aust-Agder, Rogaland, Vestfold, Østfold, and Telemark counties, with population centers of mass located at 58°24′–59°31′ N; the middle region of Norway includes Oslo, Akershus, Buskerud, Hordaland, Oppland, Hedmark, and Sogn og Fjordane counties, with population centers of mass located at 59°58′–61°30′ N; the northern region of Norway includes Møre og Romsdal, Sør-Trøndelag, Nord-Trøndelag, Nordland, Troms, and Finnmark counties, with population centers of mass located at 62°44′–70°22′ N. The Uppsala Health Care Region in Sweden has the population center of mass located at 59°86′ N. Body surface area was calculated according to the formula *(17)* $\text{weight}^{0.425} \times \text{height}^{0.725} \times 71.84$ and categorized by quartiles. We combined the upper two categories of the variables concerning acute and chronic exposures to sun because of the small numbers in each category and analyzed nevus counts in three categories: 0, 1, 2–6, and ≥7 (only two categories, 0 and ≥1, were used when testing interaction effects). In the age period–specific analyses of sunburns, sunbathing vacations, and solarium use, we combined the upper categories of these variables because of small numbers. For each of the variables (sunburns, sunbathing vacations, and solarium use), new variables were constructed to combine the exposure during the three age periods that were recorded for all women (i.e., 10–19, 20–29, 30–39 years).

We used Poisson regression analysis to estimate the association between sun exposure or personal characteristics and the risk of melanoma. The statistical significance of independent variables and interaction effects was tested by using the likelihood ratio test. We tested for trends across categories of variables by assigning equally spaced values (e.g., 1, 2, 3, or 4) to the categories and treating the variables as continuous variables in the Poisson regression analysis. All analyses were adjusted for attained age (i.e., age at study entry plus the duration of follow-up), which was categorized by 5-year intervals (for analyses of women aged 40 years or older, we used only two age categories, <50 years and 50–60 years), and all multivariable models also included geographic region of residence. The analyses of personal characteristics included mutual adjustments for statistically significant variables. The multivariable models used in the analyses of sunburn, sunbathing vacations, and use of a solarium included hair color. In addition, each age-specific model for use of a solarium included the corresponding numbers of age-specific sunburns and sunbathing vacations. Results are presented as relative risks (RRs) with 95% confidence intervals (CIs). All P values are two-sided, and a 5% level of statistical significance was used.

Results

The final study sample consisted of 106379 Norwegian and Swedish women. During an average 8.1 years of follow-up (median = 8.3 years, range = 0.01–8.6 years) corresponding to 866668 person-years of observation, 187 incident cases of melanoma were reported to the Cancer Registries in Norway and Sweden. These incident cases occurred among 183 women for whom melanoma was their first cancer diagnosis and four women for whom melanoma was their second cancer diagnosis. All incident cancer cases were histopathologically confirmed as invasive melanoma. Characteristics of the study cohort and of the incident cases of malignant melanoma and their frequencies are summarized in Table 1. Melanomas on the lower limbs were observed most frequently, followed by melanomas on the trunk. Classification of subtypes was less frequently performed in Sweden than in Norway. Seventy-one percent of the Norwegian cases were classified as superficial spreading melanoma (Table 1).

Table 2 summarizes the associations between personal characteristics and the risk of melanoma. Calculated body surface area was positively associated with the risk of melanoma (P_{trend} = .02), as was hair color (P_{trend}<.001). Compared with women who had dark brown or black hair, women with blond hair had an approximately twofold higher risk of melanoma, whereas women with red hair had an approximately fourfold higher risk. Eye color was not associated with melanoma risk. We also found no statistically significant association between tanning of the skin after heavy or repeated sun exposure and the risk of melanoma, although an indication of a trend was seen for skin color after repeated sun exposure. The number of large asymmetric nevi on the legs was a strong predictor of melanoma risk: women with seven or more nevi had an approximately fivefold higher risk of melanoma than women with no nevi (P_{trend}<.001). Mutual adjustment for all statistically significant variables listed in Table 2 did not appreciably change any of the multivariable relative risks presented in the table (data not shown).

Risks of melanoma increased with increasing numbers of sunburns women reported having during the second, third, and fourth decade of life (Table 3). The estimated risk of melanoma was highest for women who reported having sunburns during adolescence (i.e., the 10–19-year age period), whereas no association between risk and sunburns during the fifth decade of life (i.e., the 40–49-year age period) was observed. Next, we combined the information about the number of sunburns at ages 10–19, 20–29, and 30–39 years into one new variable. Women who had one or no sunburns per year during these three periods were used as the reference category. The other categories were sunburns two or more times per year during the adult years (i.e., 20–29 years and/or 30–39 years), sunburns two or more times

Table 1. Characteristics of participants in the Norwegian–Swedish Women's Lifestyle and Health Cohort Study and of the incident cases of cutaneous malignant melanoma during follow-up from 1991–1992 through 1999

Characteristics	Norway (n = 57 311)*	Sweden (n = 49 068)*	Total (N = 106 379)*
Mean age at study entry, y (range)	41.1 (34–49)	39.6 (30–50)	40.4 (30–50)
Person-years of follow-up	468 982	397 686	866 668
Number of incident cases of melanoma	121	66	187
Mean age at diagnosis of melanoma, y (range)	45.7 (35.4–54.0)	45.3 (31.9–57.5)	45.6 (31.9–57.5)
Site of melanoma, No. (%)			
Trunk	32 (26)	19 (29)	51 (27)
Upper limb	12 (10)	10 (15)	22 (12)
Lower limb	60 (50)	29 (44)	89 (48)
Other†	17 (14)	8 (12)	25 (13)
Histologic type of melanoma, No. (%)			
Superficial spreading melanoma	86 (71)	5 (8)	91 (49)
Nodular melanoma	16 (13)	2 (3)	18 (10)
Lentigo malignant melanoma	2 (2)	0 (0)	2 (1)
Malignant melanoma, not otherwise specified	17 (14)	59 (89)	76 (41)
Body surface area in m^2‡, No. (%) (n = 103 333)			
≤1.61	13 985 (25)	11 696 (25)	25 681 (25)
1.62–1.69	13 929 (25)	11 680 (25)	25 609 (25)
1.70–1.78	14 361 (26)	11 802 (25)	26 163 (25)
≥1.79	13 896 (25)	11 984 (25)	25 880 (25)
Skin color after heavy sun exposure in the beginning of the summer, No. (%) (n = 105 595)			
Brown	14 856 (26)	11 532 (24)	26 388 (25)
Red	27 584 (49)	23 243 (48)	50 827 (48)
Red with pain	11 342 (20)	11 421 (23)	22 763 (22)
Red with pain and blisters	2999 (5)	2618 (5)	5617 (5)
Skin color after repeated sun exposure, No. (%) (n = 103 312)			
Deep brown	8797 (16)	7979 (16)	16 776 (16)
Brown	31 394 (58)	30 029 (62)	61 423 (59)
Light brown	13 453 (25)	10 129 (21)	23 582 (23)
Never brown	900 (2)	631 (1)	1531 (1)
Hair color, No. (%) (n = 103 027)			
Dark brown, black	9348 (17)	13 813 (29)	23 161 (23)
Brown	21 500 (39)	20 939 (43)	42 439 (41)
Blond	22 241 (41)	12 185 (25)	34 426 (33)
Red	1495 (3)	1506 (3)	3001 (3)
Eye color, No. (%) (n = 102 710)			
Brown	6345 (12)	6738 (14)	13 083 (13)
Gray, green, or mix	21 062 (39)	17 130 (36)	38 192 (37)
Blue	27 170 (50)	24 265 (50)	51 435 (50)
Total No. of asymmetric nevi >5 mm on legs, No. (%) (n = 100 980)			
0	47 704 (89)	38 997 (82)	86 701 (86)
1	3438 (6)	4842 (10)	8280 (8)
2–3	1595 (3)	2424 (5)	4019 (4)
4–6	416 (1)	713 (2)	1129 (1)
≥7	324 (1)	527 (1)	851 (1)

*Because of missing values, the number of women will differ in the presentation of personal characteristics below. The total number of women (n) is presented for each personal characteristic.

†Head/neck and skin unspecified.

‡Calculated according to the following formula *(17)*; $\text{weight}^{0.425} \times \text{height}^{0.725} \times 71.84$.

per year during adolescence (i.e., 10–19 years), and sunburns two or more times per year during all three age decades (i.e., 10–19, 20–29, and 30–39 years). We observed increased risk of melanoma for the upper two categories of this new variable and a statistically significant positive trend (Table 3). Collapsing the upper three categories into one gave a multivariable relative risk of 1.70 (95% CI = 1.23 to 2.34; $P = .002$) for sunburns two or more times per year for at least one of the three age decades as compared with a maximum of one sunburn per year in all three decades. No statistically significant interaction was found between this dichotomous sunburn variable and the number of nevi on the legs ($P = .84$).

We found suggestive evidence for an association between increasing risk of melanoma and increasing number of weeks women spent on sunbathing vacations at ages 30–39 years (Table 4). Although most of the point estimates and all of the trends pertaining to this association were not statistically significant, we consistently observed a risk increase of approximately 60%–70% for the highest compared with the lowest exposure category for women who took sunbathing vacations between the ages of 10 and 39 years. Increased risk, albeit not statistically significant and with no appreciable trend, was also observed when information on sunbathing vacations from these three decades of life was combined into a new variable in a way analo-

Table 2. Relative risks (RRs) and 95% confidence intervals (CIs) of cutaneous malignant melanoma according to personal characteristics*

Characteristic	No. of cases	Age-adjusted RR (95% CI)	Multivariable RR† (95% CI)
Body surface area, m^2‡ (n = 103 333)			
≤1.61	32	1.00 (referent)	1.00 (referent)
1.62–1.69	44	1.38 (0.87 to 2.17)	1.37 (0.87 to 2.17)
1.70–1.78	57	1.74 (1.13 to 2.68)	1.73 (1.12 to 2.66)
≥1.79	52	1.60 (1.03 to 2.49)	1.60 (1.03 to 2.48)
		P_{trend} = .02	P_{trend} = .02
Skin color after heavy sun exposure at the beginning of summer (n = 105 595)			
Brown	36	1.00 (referent)	1.00 (referent)
Red	100	1.45 (0.99 to 2.12)	1.45 (0.99 to 2.13)
Red with pain/red with pain and blisters	51	1.34 (0.88 to 2.06)	1.36 (0.89 to 2.08)
		P_{trend} = .21	P_{trend} = .19
Skin color after repeated sun exposure (n = 103 312)			
Deep brown	21	1.00 (referent)	1.00 (referent)
Brown	107	1.39 (0.87 to 2.22)	1.40 (0.87 to 2.23)
Light brown/never brown	51	1.62 (0.97 to 2.69)	1.60 (0.96 to 2.67)
		P_{trend} = .07	P_{trend} = .07
Hair color (n = 103 027)			
Dark brown, black	26	1.00 (referent)	1.00 (referent)
Brown	57	1.18 (0.74 to 1.88)	1.16 (0.73 to 1.84)
Blond	82	2.10 (1.35 to 3.26)	1.96 (1.25 to 3.07)
Red	14	4.13 (2.16 to 7.91)	4.05 (2.11 to 7.76)
		P_{trend}<.001	P_{trend}<.001
Eye color (n = 102 710)			
Brown	18	1.00 (referent)	1.00 (referent)
Gray, green, or mix	63	1.18 (0.70 to 1.99)	1.15 (0.68 to 1.94)
Blue	97	1.36 (0.82 to 2.25)	1.33 (0.80 to 2.20)
		P_{trend} = .17	P_{trend} = .19
Total No. of asymmetric nevi >5 mm on legs (n = 100 980)			
0	128	1.00 (referent)	1.00 (referent)
1	26	2.15 (1.41 to 3.28)	2.29 (1.50 to 3.49)
2–6	16	2.14 (1.27 to 3.60)	2.30 (1.36 to 3.87)
≥7	6	4.92 (2.17 to 11.15)	5.29 (2.33 to 12.01)
		P_{trend}<.001	P_{trend}<.001

*Poisson regression analysis. All statistical tests were two-sided.

†Multivariable models included attained age and region of residence.

‡Calculated according to the following formula *(17)*: $weight^{0.425} \times height^{0.725} \times 71.84$.

gous to that described above for sunburns (Table 4). Collapsing the upper three categories of this new variable gave a multivariable relative risk of 1.51 (95% CI = 0.95 to 2.40; P = .07) for sunbathing vacations one or more weeks per year in at least one of the three age decades as compared with never going on sunbathing vacations in any of the three decades. No statistically significant interaction was found between this dichotomous variable for sunbathing vacations and the number of nevi on the legs (P = .58).

We had limited power to examine the association between the use of a solarium during adolescence and melanoma risk because only 2% of the women in the study reported having such exposure. However, we found that compared with women who never used a solarium at ages 20–29 years, women who reported using a solarium once or more per month during that age period had a relative risk of melanoma of 2.58 (95% CI = 1.48 to 4.50; P_{trend} = .006) (Table 5). Use of a solarium at ages 30–39 years and 40–49 years also appeared to be associated with a risk, although not a statistically significantly increased risk, of melanoma (Table 5). In a multivariable analysis of the combined variable for solarium use during the 10–39-year age period, women who used a solarium one or more times per month in at least one of the three decades between ages 10 and 39 had a statistically significantly higher risk of melanoma than women who had never or rarely used a solarium during those three decades (RR = 1.55, 95% CI = 1.04 to 2.32; P = .04) (Table 5).

The multivariable models in Tables 3–5 include hair color as a measure of sun sensitivity. Additional adjustment for skin color after repeated sun exposure gave similar results and did not affect the conclusions (data not shown).

Discussion

Results of our prospective analysis suggest that hair color, the number of large asymmetric nevi on the legs, and body surface area are important personal characteristics that contribute to the risk of melanoma. The number of sunburns was also an important predictor of melanoma risk, and the strongest effects were associated with the number of sunburns women experienced during adolescence; there was similar, albeit weaker, evidence for an association between the number of sunbathing vacations taken in Norway, Sweden, or more southern latitudes and melanoma risk. Using a solarium one or more times per month, particularly during the 20–29-year age period, adjusted for numbers of sunburns and sunbathing vacations, was statistically significantly associated with melanoma risk.

The incidence of melanoma observed in our study was higher among the Norwegian women than among the Swedish women. The crude incidence rates of melanoma, which we calculated from the data presented in Table 1, were 25.8 cases per 100 000 person-years of follow-up for the Norwegian women and 16.6 cases per 100 000 person-years of follow-up for the Swedish

Table 3. Relative risks (RRs) and 95% confidence intervals (CIs) of cutaneous malignant melanoma according to annual number of sunburns during different age periods*

Age period and number of sunburns	Frequencies, No. (%)	No. of cases	Age-adjusted RR (95% CI)	Multivariable RR† (95% CI)
10–19 years (n = 95 472)				
0	21 747 (23)	22	1.00 (referent)	1.00 (referent)
≤1/year	52 452 (55)	94	1.80 (1.13 to 2.86)	1.64 (1.03 to 2.62)
≥2/year	21 273 (22)	55	2.70 (1.65 to 4.44)	2.42 (1.46 to 4.02)
			P_{trend}<.001	P_{trend}<.001
20–29 years (n = 97 442)				
0	20 346 (21)	28	1.00 (referent)	1.00 (referent)
≤1/year	58 458 (60)	102	1.29 (0.85 to 1.96)	1.24 (0.81 to 1.88)
≥2/year	18 638 (19)	43	1.76 (1.09 to 2.84)	1.69 (1.04 to 2.76)
			P_{trend} = .02	P_{trend} = .03
30–39 years (n = 94 850)				
0	30 588 (32)	48	1.00 (referent)	1.00 (referent)
≤1/year	54 199 (57)	99	1.15 (0.82 to 1.63)	1.15 (0.81 to 1.62)
≥2/year	10 063 (11)	27	1.71 (1.07 to 2.74)	1.71 (1.06 to 2.76)
			P_{trend} = .04	P_{trend} = .05
40–49 years‡ (n = 45 269)				
0	20 031 (44)	43	1.00 (referent)	1.00 (referent)
≤1/year	22 260 (49)	44	0.92 (0.61 to 1.41)	0.92 (0.61 to 1.41)
≥2/year	2978 (7)	6	0.94 (0.40 to 2.21)	0.96 (0.41 to 2.27)
			P_{trend} = .74	P_{trend} = .77
Combined, 10–39 years (n = 90 633)				
≤1/year, 10–39 years	64 807 (72)	99	1.00 (referent)	1.00 (referent)
≥2/year, 20–29 years and/or 30–39 years	5873 (6)	13	1.47 (0.82 to 2.62)	1.54 (0.86 to 2.75)
≥2/year, 10–19 years	7357 (8)	20	1.82 (1.13 to 2.95)	1.66 (1.02 to 2.70)
≥2/year, 10–39 years	12 595 (14)	34	1.83 (1.24 to 2.70)	1.79 (1.20 to 2.68)
			P_{trend}<.001	P_{trend} = .002

*Poisson regression analysis. All statistical tests were two-sided.

†Multivariable models included attained age, region of residence, and hair color.

‡Included only women who were aged 40 years or older when answering the questionnaire.

women. These incidence rates are in accordance with crude incidence rates reported for Norwegian and Swedish women for 1993 through 1997 (23.3 cases per 100 000 person-years for Norwegian women and 17.3 cases per 100 000 person-years for Swedish women) *(3)*. Age-adjusted incidence rates of melanoma have been consistently higher among Norwegian than among Swedish women since the 1960s.

We observed a strong association between hair color and melanoma risk but not between eye color and melanoma risk. These results are consistent with results of a pooled analysis of data derived from published case–control studies, in which the reported relative risks were 2.38 (95% CI = 1.90 to 2.97) for individuals who have red hair compared with those who have black or dark brown hair and 1.55 (95% CI = 1.35 to 1.78) for individuals who have blue eyes compared with those who have brown eyes *(12)*. However, the association we observed between cutaneous sensitivity to the sun (i.e., burning or tanning) and melanoma risk was much weaker than that reported in a retrospective Australian study *(18)*. Our findings, that hair color but not eye color was statistically significantly associated with melanoma risk, agree with those of two Danish case–control studies *(19,20)*; in addition, the association between melanoma risk and cutaneous sun sensitivity reported in those two studies was also much weaker than that for hair color. A Swedish case–control study *(21)* also found that hair and eye color and skin type were statistically significantly associated with melanoma risk, although the associations were considerably weaker for eye color and skin type than for hair color, whereas an early Norwegian case–control study *(22)* that used hospital-based control subjects found that tolerance to sun exposure, but not hair or eye color, was associated with melanoma risk. We speculate that hair color may be the best measure (combining accuracy of measurement and predictive capacity) of sun sensitivity in homogeneous fair-skinned populations, such as those of Scandinavia. By contrast, reported sun sensitivity may be a less reliable measure of sun sensitivity in these populations because it depends on an individual's experience with repeated and quite heavy sun exposure, which many Scandinavian subjects may not have.

In agreement with the results of several case–control studies *(23–25)*, the results of our cohort study show that the number of asymmetric nevi larger than 5 mm on the legs was the strongest host risk factor for melanoma. The participants self-reported such nevi on their legs, guided by color pictures of dysplastic nevi in a brochure that was enclosed with the questionnaire. The method we used for this self-reporting has been shown to have limited accuracy for the diagnosis of one or more dysplastic nevi, with an estimated sensitivity of 29% and a specificity of 85% *(26)*. Hence, the relative risk of 5.3 for melanoma in the presence of seven or more large nevi on the legs that we observed in our study may underestimate the excess risk. Increased surveillance and more frequent excision of suspected lesions might, on the other hand, spuriously inflate the risk of melanoma among subjects with asymmetric nevi. However, such an effect seems unlikely because all incident cases were histopathologically confirmed invasive malignant melanomas.

Our results confirm the positive association between past history of sunburn and melanoma reported previously by the majority of case–control studies *(9,10)*. Our effect estimates were higher for sunburns that occurred during adolescence than for those that occurred later in life; however, it may be too early to

Table 4. Relative risks (RRs) and 95% confidence intervals (CIs) of cutaneous malignant melanoma according to the average number of weeks per year spent on sunbathing vacations to southern latitudes or within Norway or Sweden during different age periods*

Age period and annual weeks on sunbathing vacation	Frequencies, No. (%)	No. of cases	Age-adjusted RR (95% CI)	Multivariable RR† (95% CI)
10–19 years (n = 93 418)				
0	45 298 (48)	77	1.00 (referent)	1.00 (referent)
1 week/year	19 921 (21)	35	1.10 (0.74 to 1.65)	1.21 (0.80 to 1.83)
2–3 weeks/year	20 086 (22)	32	1.02 (0.67 to 1.54)	1.09 (0.71 to 1.65)
≥4 weeks/year	8113 (9)	20	1.56 (0.95 to 2.55)	1.67 (1.01 to 2.74)
			P_{trend} = .22	P_{trend} = .12
20–29 years (n = 96 029)				
0	26 460 (28)	41	1.00 (referent)	1.00 (referent)
1 week/year	28 723 (30)	55	1.28 (0.85 to 1.92)	1.36 (0.90 to 2.05)
2–3 weeks/year	32 997 (34)	53	1.08 (0.71 to 1.62)	1.13 (0.74 to 1.70)
≥4 weeks/year	7849 (8)	19	1.67 (0.96 to 2.88)	1.79 (1.03 to 3.11)
			P_{trend} = .26	P_{trend} = .18
30–39 years (n = 93 845)				
0	24 293 (26)	33	1.00 (referent)	1.00 (referent)
1 week/year	28 858 (31)	56	1.42 (0.93 to 2.19)	1.49 (0.97 to 2.30)
2–3 weeks/year	33 144 (35)	65	1.43 (0.94 to 2.18)	1.45 (0.95 to 2.21)
≥4 weeks/year	7550 (8)	16	1.56 (0.86 to 2.84)	1.63 (0.89 to 2.97)
			P_{trend} = .10	P_{trend} = .08
40–49 years‡ (n = 45 211)				
0	13 806 (31)	23	1.00 (referent)	1.00 (referent)
1 week/year	12 801 (28)	36	1.70 (1.01 to 2.87)	1.87 (1.11 to 3.18)
≥2–3 weeks/year	18 604 (41)	31	1.01 (0.59 to 1.73)	1.06 (0.61 to 1.81)
			P_{trend} = .87	P_{trend} = .98
Combined, 10–39 years (n = 88 450)				
0, 10–39 years	15 799 (18)	21	1.00 (referent)	1.00 (referent)
≥1 week/year, 20–29 and/or 30–39 years	27 851 (31)	53	1.42 (0.86 to 2.36)	1.45 (0.87 to 2.40)
≥1 week/year, 10–19 years	1751 (2)	3	1.37 (0.41 to 4.59)	1.46 (0.43 to 4.92)
≥1 week/year, 10–39 years	43 049 (49)	79	1.44 (0.89 to 2.34)	1.56 (0.95 to 2.56)
			P_{trend} = .27	P_{trend} = .13

*Poisson regression analysis. All statistical tests were two-sided.

†Multivariable models included attained age, region of residence, and hair color.

‡Included only women who were aged 40 years or older when answering the questionnaire.

Table 5. Relative risks (RRs) and 95% confidence intervals (CIs) of cutaneous malignant melanoma according to solarium use during different age periods*

Age period and solarium use	Frequencies, No. (%)	No. of cases	Age-adjusted RR (95% CI)	Multivariable RR† (95% CI)
10–19 years (n = 85 847)				
Never	84 182 (98)	152	1.00 (referent)	1.00 (referent)
Rarely or ≥1 time/month	1665 (2)	4	1.65 (0.61 to 4.47)	1.52 (0.56 to 4.12)
			P = .36	P = .44
20–29 years (n = 89 142)				
Never	71 133 (80)	123	1.00 (referent)	1.00 (referent)
Rarely	11 618 (13)	19	1.16 (0.70 to 1.92)	1.11 (0.67 to 1.85)
≥1 time/month	6391 (7)	18	2.32 (1.35 to 3.99)	2.58 (1.48 to 4.50)
			P_{trend} = .009	P_{trend} = .006
30–39 years (n = 87 890)				
Never	44 338 (50)	78	1.00 (referent)	1.00 (referent)
Rarely	28 383 (32)	51	1.03 (0.72 to 1.48)	0.93 (0.64 to 1.34)
≥1 time/month	15 169 (17)	36	1.40 (0.93 to 2.10)	1.42 (0.93 to 2.16)
			P_{trend} = .15	P_{trend} = .19
40–49 years‡ (n = 41 409)				
Never	17 345 (42)	27	1.00 (referent)	1.00 (referent)
Rarely	14 514 (35)	33	1.46 (0.88 to 2.43)	1.39 (0.82 to 2.33)
≥1 time/month	9550 (23)	22	1.48 (0.84 to 2.60)	1.67 (0.93 to 2.99)
			P_{trend} = .14	P_{trend} = .08
Combined, 10–39 years (n = 79 616)				
Never/rarely, 10–39 years	65 239 (82)	111	1.00 (referent)	1.00 (referent)
≥1 time/month 10–19, 20–29, or 30–39 years	14 377 (18)	34	1.45 (0.98 to 2.14)	1.55 (1.04 to 2.32)
			P = .07	P = .04

*Poisson regression analysis. All statistical tests were two-sided.

†Multivariable models included attained age, region of residence, hair color, and the corresponding number of age-specific sunburns and weeks on annual summer vacations.

‡Included only women who were aged 40 years or older when answering the questionnaire.

see the full effect of sunburns later in life in our cohort of women. Systematic reviews of case–control studies *(10,11)* have not found evidence of an overall stronger effect of sunburns in early life than in later life. Furthermore, the reported dose–response gradients of melanoma risk with frequency of sunburn were comparable during childhood and adulthood in a recent large multicenter case–control study from Europe *(27)*. However, it is possible that the case–control studies have underestimated the effects of sunburn during childhood and adolescence because of high recall error from the very long recall period for most subjects. All of our study subjects were younger than 50 years when they answered the questionnaire, giving a shorter recall period than in many case–control studies *(9)* that include subjects up to 70 years old or older.

Sun exposure during sunbathing vacations is usually intense and intermittent, and results of previous case–control studies *(10)* suggest that there is a positive association between the incidence of melanoma and high levels of intermittent sun exposure. We recorded the number of sunbathing vacations in Norway and Sweden (at latitudes higher than 58° N, where UV levels are low, even in summer) and those in southern latitudes in the same variable, which may explain the lack of a strong association between sunbathing vacations and melanoma in our study. Previous Scandinavian studies show inconsistencies in their results on sunbathing and melanoma risk. One Swedish study *(21)* and a Danish study *(28)* found associations between vacations spent in sunny places and melanoma risk, whereas another Swedish study *(29)* did not.

Our results provide stronger evidence than those of other studies that solarium use is associated with an increased risk of melanoma; we found that overall, regular (i.e., one or more times per month) solarium use at any age was associated with a statistically significant 55% increase in risk of melanoma after adjustment for sun sensitivity and measures of sun exposure. Although other studies *(30–34)* have reported positive associations between melanoma risk and exposure to artificial UV light, these associations often apply to specific subgroups of the study population (e.g. the youngest subjects with melanoma), or they have not been adjusted for possible confounding with sun exposure. A recent review *(35)* concluded that there was insufficient evidence to determine whether or not tanning lamps cause melanoma. The more consistent and overall statistically significant association between melanoma risk and solarium use observed in our study, which may be due to the relative youth of our cohort, adds substantially to the existing evidence that artificial UV light for recreational tanning increases risk of melanoma.

Our study has several important strengths. First, because all physicians, hospital departments, and histopathologic laboratories in Norway and Sweden are obliged to report malignant diseases to the cancer registries, and the cancer registries match regularly against the death registers at Statistics Norway and Statistics Sweden, respectively, we had a complete follow-up and histopathologic confirmation of all incident cases of melanoma. Second, our study had a prospective design, such that detailed information on host factors and sun exposure was collected prior to melanoma diagnosis. Error in measurement of these factors is inevitable in epidemiologic studies of skin cancer *(26,36,37)* but can be assumed to be non-differential in the present study. By contrast, measurement error in case–control studies may be influenced by a diagnosis of skin cancer and therefore may differ in degree between cases and controls *(15,16)*.

Among the limitations of our study were the comparatively small number of cases, the limited detail about the exposure measurements, and the relatively short follow-up period for solar and artificial UV light exposure during midlife. In addition, we did not adjust for the multiple comparisons made in this study. Instead, we chose to evaluate the individual associations on their own merits and with respect to results from prior studies. Finally, because our cohort included only women, our results may not be generalizable to both sexes. In Norway and Sweden, incidence rates of melanoma tend to be slightly higher among women than among men *(3)*. However, previous case–control studies *(9)* have not focused on whether there are sex differences in the associations between pigmentation characteristics or sun exposure and the risk of melanoma.

The results of our cohort study suggest that public health recommendations for melanoma prevention should include a combination of information on inherent predisposition and the effects of exposure to UV radiation. Hair color and large asymmetric nevi on the legs were the most important host factors associated with risk, and our results for sunburn, sunbathing vacations, and use of a solarium support current recommendations for the avoidance of UV exposure, especially intermittent exposure, either from natural or from artificial sources. Although our study cohort is still too young to fully assess whether UV exposure during adolescence is more critical than UV exposure during adulthood for melanoma risk, there is great potential to explore this question and the important issue of interactions between risk factors in future follow-up studies of these Norwegian and Swedish women.

REFERENCES

(1) Parkin MD, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827–41.

(2) Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2000: cancer incidence, mortality and prevalence worldwide. Version 1.0. IARC CancerBase No. 5. Lyon (France): IARC Press; 2001.

(3) Møller B, Fekjaer H, Hakulinen, T, Tryggvadóttir L, Storm HH, Talbäck M, et al. Prediction of cancer incidence in the Nordic countries up to the year 2020. Eur J Cancer Prev 2002;11 Suppl 1:S1–96.

(4) Armstrong BK, English DR. Cutaneous malignant melanoma. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 2nd ed. New York (NY): Oxford University Press; 1996. p. 1282–312.

(5) Green A, Trichopoulos D. Skin cancer. In: Adami HO, Hunter D, Trichopoulos D. Textbook of cancer epidemiology. New York (NY): Oxford University Press; 2002. p. 281–300.

(6) Eklund G, Malec E. Sunlight and incidence of cutaneous malignant melanoma. Effect of latitude and domicile in Sweden. Scand J Plast Reconstr Surg 1978;12:231–41.

(7) Magnus K. Incidence of malignant melanoma of the skin in Norway, 1955–1970. Variations in time and space and solar radiation. Cancer 1973; 32:1275–86.

(8) Armstrong BK. Melanoma of the skin. Br Med Bull 1984;40:346–50.

(9) International Agency for Research on Cancer (IARC). IARC monographs on the evaluation of carcinogenic risks in humans. Vol. 55. Solar and ultraviolet radiation. Lyon (France): IARC; 1992.

(10) Elwood JM, Jopson J. Melanoma and sun exposure: an overview of published studies. Int J Cancer 1997;73:198–203.

(11) Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 2001;12:69–82.

(12) Bliss JM, Ford D, Swerdlow AJ, Armstrong BK, Cristofolini M, Elwood JM, et al. Risk of cutaneous melanoma associated with pigmentation characteristics and freckling: systematic overview of 10 case-control studies. Int J Cancer 1995;62:367–76.

(13) Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MC, et al. Moles and site-specific risk of nonfamilial cutaneous malignant melanoma in women. J Natl Cancer Inst 1989;81:948–52.
(14) Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Bronstein BR, Mihm MC, et al. Nonfamilial cutaneous melanoma incidence in women associated with sun exposure before 20 years of age. Pediatrics 1989;84: 199–204.
(15) Weinstock MA, Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE. Recall (report) bias and reliability in the retrospective assessment of melanoma risk. Am J Epidemiol 1991;133:240–5.
(16) Cockburn M, Hamilton A, Mack T. Recall bias in self-reported melanoma risk factors. Am J Epidemiol 2001;153:1021–6.
(17) Geigy scientific tables. Vol. 1. Units of measurement, body fluids, composition of the body, nutrition. 8th ed. Basel (Switzerland): Ciba-Geigy; 1981. p. 227.
(18) Holman CD, Armstrong BK. Pigmentary traits, ethnic origin, benign nevi, and family history as risk factors for cutaneous malignant melanoma. J Natl Cancer Inst 1984;72:257–66.
(19) Østerlind A, Tucker MA, Hou-Jensen K, Stone BJ, Engholm G, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. I. Importance of host factors. Int J Cancer 1988;42:200–6.
(20) Lock-Andersen J, Drzewiecki KT, Wulf HC. Eye and hair colour, skin type and constitutive skin pigmentation as risk factors for basal cell carcinoma and cutaneous malignant melanoma. A Danish case-control study. Acta Derm Venereol 1999;79:74–80.
(21) Beitner H, Norell SE, Ringborg U, Wennersten G, Mattson B. Malignant melanoma: aetiological importance of individual pigmentation and sun exposure. Br J Dermatol 1990;122:43–51.
(22) Klepp O, Magnus K. Some environmental and bodily characteristics of melanoma patients. A case-control study. Int J Cancer 1979;23:482–6.
(23) Augustsson A, Stierner U, Rosdahl I, Suurkula M. Common and dysplastic naevi as risk factors for cutaneous malignant melanoma in a Swedish population. Acta Derm Venereol 1991;71:518–24.
(24) Tucker MA, Halpern A, Holly EA, Hartge P, Elder DE, Sagebiel RW, et al. Clinically recognized dysplastic nevi. A central risk factor for cutaneous melanoma. JAMA 1997;277:1439–44.
(25) Bataille V, Grulich A, Sasieni P, Swerdlow A, Newton Bishop J, McCarthy W, et al. The association between naevi and melanoma in populations with different levels of sun exposure: a joint case-control study of melanoma in the UK and Australia. Br J Cancer 1998;77:505–10.
(26) Titus-Ernstoff L, Thorn M, Tosteson TD, Brahme EM, Yuen J, Baron JA, et al. The accuracy of skin self-examination for atypical nevi. Epidemiology 1996;7:619–23.
(27) Pfahlberg A, Kölmel KF, Gefeller O; FEBIM Study Group. Timing of excessive ultraviolet radiation and melanoma: epidemiology does not support the existence of a critical period of high susceptibility to solar ultraviolet radiation-induced melanoma. Br J Dermatol 2001;144:471–5.
(28) Østerlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. Int J Cancer 1988;42:319–24.
(29) Westerdahl J, Olsson H, Ingvar C. At what age do sunburn episodes play a crucial role for the development of malignant melanoma. Eur J Cancer 1994;30A:1647–54.
(30) Swerdlow AJ, English JS, MacKie RM, O'Doherty CJ, Hunter JA, Clark J, et al. Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. BMJ 1988;297:647–50.
(31) Walter SD, Marrett LD, From L, Hertzman C, Shannon HS, Roy P. The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. Am J Epidemiol 1990;131:232–43.
(32) Autier P, Dore JF, Lejeune F, Koelmel KF, Geffeler O, Hille P, et al. Cutaneous malignant melanoma and exposure to sunlamps or sunbeds: an EORTC multicenter case-control study in Belgium, France and Germany. Int J Cancer 1994;58:809–13.
(33) Westerdahl J, Olsson H, Masback A, Ingvar C, Jonsson N, Brandt L, et al. Use of sunbeds and sunlamps and malignant melanoma in southern Sweden. Am J Epidemiol 1994;140:691–9.
(34) Westerdahl J, Ingvar C, Måsbäck A, Jonsson N, Olsson H. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer 2000;82:1593–9.
(35) Swerdlow AJ, Weinstock MA. Do tanning lamps cause melanoma? An epidemiologic assessment. J Am Acad Dermatol 1998;38:89–98.
(36) Westerdahl J, Anderson H, Olsson H, Ingvar C. Reproducibility of a self-administered questionnaire for assessment of melanoma risk. Int J Epidemiol 1996;25:245–51.
(37) English DR, Armstrong BK, Kricker A. Reproducibility of reported measurements of sun exposure in a case-control study. Cancer Epidemiol Biomarkers Prev 1998;7:857–63.

NOTES

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Current Perspective

Perspectives in melanoma prevention: the case of sunbeds

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Abstract

The incidence of cutaneous malignant melanoma (melanoma) and of basal cell carcinoma is still increasing in most fair-skinned populations. The fashion of intermittent exposure to solar ultraviolet (UV) radiations is considered the main cause of this increase. In 20 years time, tan acquisition through exposure to artificial sources of UV radiations has become frequent among fair-skinned adolescents and young adults. Modern sunbeds are powerful sources of UV radiations that do not exist in the nature, and repeated exposures to high doses of UVA constitute a new phenomenon in humans. A large prospective cohort study on 106,379 Norwegian and Swedish women conducted between 1991 and 1999 has provided evidence for a significant, moderate increase in melanoma risk among regular sunbed users. Failure of past case-control studies to document with consistency the sunbed-melanoma association was probably due to a too short latency period between sunbed use and melanoma diagnosis, and to too few subjects with high total durations of sunbed use. Regulations of sunbed installation, operation and use should become standardised across the 25 European Union countries. Enforcement of regulations in tanning parlours remains inadequate. In contrast, the existence of regulations is presented by many tanning salon operators as a guarantee that sunbed use is safe. We stress the need for the control of information disseminated by the "tanning industry" on suppositions that sunbed use is safer than sun exposure, and on the hypothetical health benefits of tanning. New fluorescent UV lamps are proposed that have a spectrum similar to the midday sun. Given the known association between intermittent sun exposure and melanoma, public-health authorities should reconsider the soundness of the commercialisation of these lamps.
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Keywords: Melanoma; Skin cancer; Ultraviolet radiation; Epidemiology; Prevention

1. Introduction

The incidence of cutaneous malignant melanoma (melanoma) has steeply increased in the past 50 years in most fair-skinned populations. For instance, from 1970 until 1997, a 2.5-fold increase in melanoma incidence was observed in Finland, and a 3.6-fold increase in White Americans [1,2]. From 1979 until 1998, a 2.4-fold increase was observed in Scotland [3], and from 1980 and 2000, a 2.8-fold increase was estimated for France [4]. Risk factors for the basal cell carcinoma (BCC) are similar to risk factors for melanoma [5]. The incidence of BCC is also increasing sharply in most fair-skinned communities, mainly in females [6].

The fashion of intermittent sun exposure that took place after 1950 is considered as the main cause of the increases in melanoma and in BCC. The depletion in ozone observed in the stratospheric layers of the atmosphere is not likely to contribute to the raising incidence of these skin cancers. The ultraviolet (UV) radiation is deemed to represent the part of the solar spectrum involved in the genesis of melanoma [7]. In spite of increasing knowledge on the association between sun exposure and the considerable rise in skin cancer incidence, exposure to artificial sources of UV radiation has become popular in all fair-skinned populations around the world. These artificial sources of UV radiation have various

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denominations, e.g., tanning machines, UVA-tanning devices, indoor tanning, sunbeds, and solarium. The sunbed fashion could contribute to the increase in skin cancer occurrence, in particular, of melanoma [8].

In this paper, we delineate the public-health issues involved in sunbed use in 2004, and we stress the need to promote actions going beyond the regulations of sunbed use, especially actions aiming at controlling the information disseminated by the "tanning industry" on supposed safety and hypothetical health benefits of sunbed use.

2. Sunbed use is an intentional sun exposure behaviour

The melanoma epidemic affects mainly skin areas usually covered by clothes, like the trunk, shoulders and limbs, while lower increases in melanoma incidence are observed on the more chronically sun exposed body sites, like the head and neck [3,9]. Likewise, the increase in BCC incidence is mainly observed on body sites that are not chronically exposed to sunlight [6]. This epidemiological feature points to the role attributed to the intermittent sun exposure in the genesis of most melanoma and BCCs. The most intense form of intermittent sun exposure is the intentional sun exposure (ISE) that is essentially motivated by the acquisition of a tan or by the possibility to go uncovered in the sun [10]. During ISE, significant portions of the trunk and of the limbs are generally uncovered. Sunbathing and sunbed use are the most typical ISE behaviours, and people attracted to sunbathing activities are also more attracted to indoor tanning [11].

In Europe, the sunbed fashion follows a strong South-to-North gradient. The sunbed fashion started in the 1980s in the Nordic countries and extended in more Southern countries in the 1990s. Surveys in Europe and North America indicate that between 15% and 35% of women, and between 5% and 10% of men 15–30 years old have used sunbeds [12–14]. In Sweden, after 1995, 70% of females and 50% of males 18–50 years old reported sunbed use [15,16]. In the late 1990s, the indoor tanning fashion rapidly extended to Mediterranean areas like the north of Italy [17,18]. In the State of Victoria, Australia – a sunny area with high records of skin cancers – 9% of subjects 14–29 years old reported sunbed use in the past years [19]. A substantial proportion of sunbeds are used in private facilities. In Germany or Nordic countries, home-made solaria are not uncommon.

3. The role of UVA and UVB in melanoma occurrence is still unknown

At present, there are no scientific data indicating that intentional exposure to UV radiations emitted by sunbeds is less harmful than intentional exposure to sunlight.

The UV radiation reaching the earth's surface comprises UVB (280–319 nm) and UVA (320–400 nm) radiations. During a sunny day on the Mediterranean coast, the solar UV spectrum at noon contains approximately 5% of UVB and approximately 95% of UVA. UVB is far more efficient than UVA at inducing the synthesis of melanin, and producing a deep, persistent tan. UVB is also 1000 times more potent than UVA at inducing skin erythema (painless skin reddening) or sunburn (painful skin reddening, sometimes with blisters).

Until end of the 1980s, UVB was considered as the carcinogenic part of the solar spectrum, and a shift in usage occurred towards low pressure fluorescent tubes emitting essentially in the UVA range, yielding the so-called "UVA-tanning".

At the end of the 1980s, UVA was also suspected of having carcinogenic potential. In 1992, the International Agency for Research of Cancer classified UVB and UVA radiations, as well as sunbeds, as "agents that are probably carcinogenic to humans" (group 2A of the IARC classification of carcinogenic agents) [7].

Biological mechanisms by which chronic sun exposure causes squamous cell cancer (SCC) of the skin are better known (e.g., the UVB-induced mutations found in the *p53* gene). In contrast, we still have a poor knowledge of the biological mechanisms by which solar radiations are involved in the genesis of melanoma and BCC in humans.

3.1. Long-term health effects of high UVA doses are unknown

In large powerful tanning units, the UVA irradiation intensity may be 10–15 times higher than that of the midday sun [20]. When UV output is calculated in terms of biological activity, as estimated by the erythema-effective irradiance, the emission of many sunbeds is equivalent or surpasses the emission of the midday sun on the Mediterranean Sea [20,21]. Such powerful sources of UVA radiations do not exist in nature, and repeated exposures to high doses of UVA constitute a new phenomenon in humans. If the role of UVA in melanoma occurrence is uncertain, the UVA doses per unit of time received by the skin during a typical sunbed session are far higher than what is experienced during daily life or during sunbathing. We have little idea of the likely long-term medical consequences of such exposure. Worries are further reinforced by knowledge that UVA penetrates deeper than UVB into the skin. A recent study discovered DNA lesions typical of UVA action in the basal epithelial layer of the human skin, the skin region where most melanocytes are situated [22].

3.2. The questionable concept of "UVA-tanning"

The term "UVA-tanning" is misleading, as the output of a sunbed equipped with low pressure fluorescent lamps always contains some UVB, which is critical for the induction of a deep, persistent tan. In addition, most of the DNA damage observed in the skin of sunbed users is due to the fraction of UVB emitted by the fluorescent lamps [23].

In the 1990s, regulations in some countries (e.g., Sweden, France) limited the maximum proportion of UVB in the total UV energy output of sunbeds to 1.5%. However, in the real world, the UV output and spectral characteristics of sunbeds vary considerably. The proportion of UVB in UV energy output could vary from 0.5% to 4% [24,25], and may attain an emission spectrum similar to the sun spectrum in the UVB range [20]. These differences are due to sunbed design (e.g., the numbers and type of fluorescent tubes, the presence of high-pressure UV lamps, the materials of the filters, the distance from the canopy to the skin), to sunbed power, and to tube aging.

3.3. Sunbed-induced sunburns

Sunburn experience during childhood or during adulthood is a risk factor for melanoma, and the risk increases with increasing numbers of sunburns [26]. Skin erythema or burns are reported by 18–55% of sunbed users [12,13,16,27]. Although UVB is more potent than UVA for triggering sunburn, high fluxes of UVA are capable of inducing skin erythemal reactions after 10–20 min in a subject who is naturally susceptible to sunburns and having moderate tanning ability (i.e., Fitzpatrick skin phototype 2). The same subject engaging in unprotected sunbathing in the midday sun would incur an erythemal reaction after 20 min.

The high frequency of sunburn experience by sunbed users shows that sunbed use is very close in nature to sunbathing, and there is no reason to believe that sunburns experienced during sunbed sessions would convey less melanoma risk than sunburns experienced during sun exposure.

4. Epidemiological data on sunbed use and melanoma

As there is no valid animal model for human melanoma, and because we are still ignorant about the effects of UV radiation(s) and melanoma occurrence, the study of any eventual link between sunbed use and melanoma left to epidemiological investigations.

Seven epidemiological case-control studies specifically addressed the possible association between increasing amounts of sunbed use and melanoma [12,15,28–32]. Two reviews concerning six studies [33,34] concluded that some data raised the possibility of a moderate positive association between sunbed use and melanoma. However, overall, the results lacked consistency and no conclusive evidence could be drawn from these six studies on the influence of sunbed use on melanoma occurrence. A seventh case-control study conducted in the UK explored sunbed use before 1989 [32]. It showed no dose-response relationship between amounts of sunbed use and melanoma.

In 2003, MB Veierød and co-workers published the results of a prospective cohort study of 106,379 women in Norway and Sweden who were followed for an average of 8.1 years from 1991 until 1999 [26]. During the follow-up, 187 cases of melanoma were diagnosed. After adjustment for intermittent sun exposure and host characteristics, the study found a 55% increase in melanoma risk (95% Confidence Interval: 4–132%) among the 18% of women aged 10–39 years old who reported having used sunbed at least once a month when they were 10–19, 20–29 or 30–39 years old. An increase in melanoma risk was observed for all age groups, from 20 to 49 years old. Twelve sunbed sessions per year correspond to the 12-session tanning programme proposed by many commercial tanning facilities. Hence, the results of the Norwegian–Swedish study were consistent with the existence of a moderate association between regular sunbed use at least once a month and melanoma occurrence.

5. What are the differences between the Norway–Sweden and case-control studies?

5.1. Methodological limitations of case-control studies

In the seven case-control studies, exposure to sunbeds was assessed retrospectively, and compared between patients with melanoma (i.e., the cases) to subjects without melanoma (i.e., the controls). These case-control studies could suffer from three limitations:

1. Case-control studies are not optimal designs for demonstrating an increase in Relative Risk when additive risks are small, i.e., an estimated Relative Risk of between 1.00 and 1.99.
2. The answers of melanoma patients on their past sunbed use could be biased because, at the moment of the interview, they knew they had a melanoma (interview bias).
3. The selection of controls may have included subjects more inclined to have had more sunbed use than average (selection bias).

The Norwegian–Swedish study was a longitudinal cohort design. Sunbed use was assessed retrospectively, but before any diagnosis of melanoma. So, the

Norwegian–Swedish study was less prone to interview and selection biases at the inception of the cohort. In addition, prospective cohort studies on large numbers of subjects are more powerful designs than case-control studies, and are thus more appropriate to reveal the existence of moderately elevated risks.

5.2. Changing emission spectrum, latency period and accumulated UV doses

Apart from methodological issues, the negative results of the case-control studies could be due to the following factors:

1. The UV lamps changed over time. Up to the mid-1980s, arc mercury lamps having an emission spectrum rich in UVB (and even UVC) radiations were commonly used as a substitute to the absence of sunshine, e.g., for the synthesis of vitamin D in children. Hence, eventual carcinogenic effects could be attributable to exposure of children to these arc mercury UV lamps, and not to modern tanning devices.
2. The latency period between exposure to artificial UV sources and melanoma occurrence is probably several decades [11]. Five of the seven case-control studies examined sunbed use before 1990, and were conducted in countries where the indoor tanning fashion was still in its early phase. The latency period may be the main reason why case-control studies yielded inconsistent results, since sunbed use was not frequent before 1985.
3. Only a few subjects included in the case-control studies had more than 20 h of cumulative sunbed exposure.

How the Norway–Sweden study addressed these factors?

1. In 1983, commercialisation of arc mercury lamps was banned in Norway and Sweden. A further analysis of the Norway–Sweden study showed that the increased melanoma risk associated with sunbed use was not due to the use of UV lamps before 1983 [35].
2. Women who participated in the Norway–Sweden study were 30 years old or more at cohort inception. The highest melanoma risk was found in women who used sunbeds at least once per month when they were 20–29 years old [increase of 158% (95% CI: 48–350%)]. Lower melanoma risks were found for sunbed use at least once a month during the third or fourth decade of life. This result supports the hypothesis that there is a latency period. In the Nordic countries, the sunbed fashion is popular since the late 1970s, and rates of sunbed use in those countries are the highest in the world. Furthermore, women are approximately two times more inclined than men to utilise sunbeds. Hence, it is probable that the risk of melanoma associated with sunbed use started to become apparent in the Norway–Sweden study in women.
3. The Norway–Sweden study showed that before 1992 18% of the study women used sunbeds at least once a month over 10 years, what is equivalent to at least 40 h of cumulative sunbed use, if one assumes a duration of 20 min for a typical sunbed session.

In conclusion, the results of the Norway–Sweden study are consistent with the existence of a 55% (95% CI: 4–132%) increase in melanoma risk associated with 40 h or more of sunbed use. Further follow-up of the cohort will inform us about the trends in melanoma risk according to amounts of sunbed exposure.

5.3. Are 40 h of sunbed use equivalent to 40 h of sunbathing?

Over a 10-year period, the duration of sunbathing activities may exceed 400 h in suntan enthusiasts. So, how significant are 40 h of sunbed use, compared with 400 h of sunbathing? In fact, durations of sunbed use and of sunbathing are not readily comparable because:

- We do not know if sun exposure or sunbed use would influence melanoma occurrence by acting through the same biological mechanisms.
- If the UVA dose is the key element, then 20 min of sunbed exposure represents a UVA dose equivalent to 2–3 h of sun exposure in the summer midday sun, but the dose rate of UVA received per unit of time by skin cells is 5–10 times higher than that in the sun.
- The erythemal effectiveness of sunbed use is approximately two times that of the midday sun. If sunburns are key indicators of biological events implicated in the genesis of melanoma, then 20 min spent under a sunbed could have the biological significance of 40 min of sunbathing in the summer midday sun.
- Sunscreens are often used during sunbathing, with the net result for suntan worshippers that sunburn occurrence is delayed, and time spent in the sun is longer [36].
- Sunbathing may take place when the sun is less bright, for instance at the end of the afternoon.

So, with our current state of knowledge about the relationship between UV radiations and melanoma, one should be cautious when comparing durations of sunbathing with durations of sunbed use.

6. Skin cancers other than melanoma

Two case-control studies examined past exposure to sunbeds in patients with non-melanoma skin cancer.

One found no association [37]. Another found positive associations between sunbed use and SCC and BCC [38]. In the latter study, the estimated Relative Risk associated with sunbed use was 2.5 (95% CI: 1.7–3.8) for SCC and 1.5 (95% CI: 1.1–2.1) for BCC. These findings are in line with data on non-melanoma skin cancers in patients affected by severe psoriasis and treated with PUVA therapy (a combination of UVA irradiation and oral psoralen).

7. Regulations of commercialisation, installation, operation and use of artificial tanning devices

Since 1990, many countries have issued specific rules for sunbed installation, operation and utilisation. There is a wide variation in the content of these rules. In the European Union, there is no standardisation of regulations on sunbed commercialisation and use. In some countries (e.g., in the UK, Canada and the Netherlands), recommendations are formulated by, or in association with the sunbed industry, or organisations of professional sunbed operators. In the US, the Food and Drug Administration provides standards only for the manufacturing of tanning devices, and regulations for operation and utilisation vary considerably across the States.

An important achievement of regulations is the requirement for better information for consumers, as well as the wearing of protective eyewear to protect the eyes. Table 1 presents a list of criteria that should prevent individuals to use sunbeds. In some countries (e.g., in France), training of commercial tanning facilities is mandatory, and tanning machine operators are instructed to refuse access to the sunbed to the consumer meeting at least one criteria listed in Table 1. The need to have trained operators has prevented the multiplication of automated tanning parlours, working without the surveillance of an operator.

However, regulations and recommendations to consumers are not a panacea because:

1. Their enforcement remains a challenge.
2. They do not apply to the private use of sunbeds.
3. They do not reflect the numerous uncertainties we have on the association between UV exposure and skin cancers, or other UV-induced lesions like the premature skin aging and eye lesions.
4. Their potential impact on hazards associated with sunbed use is probably marginal because after all, they do not prevent individuals from receiving high doses of UV radiation.
5. Indoor tanning operators take advantage of the existence of regulations for asserting that sunbed use is secure.

8. The tanning industry and the concept of "safe tan acquisition"

8.1. The tanning industry

The "tanning industry" can be understood as all commercial activities developed around the behaviours of intentional sun exposure, for tan acquisition or for other reasons like the search of well-being. Products promoted and sold by the tanning industry comprise sunscreens, a variety of oral preparations deemed to increase the resistance to UV aggressions or to facilitate tan acquisition, swim suits permeable to UV radiations, and the use of non-solar sources of UV presented as safe

Table 1
Criteria that should prevent sunbed use*

1. To be less than 18 years of age.
2. To be pregnant.
3. To suffer from a febrile episode.
4. To suffer from significant eye vision impairment.
5. To have red hair.
6. To have melano-compromised skin, i.e., when the skin always sunburns with no ability to tan or has a high susceptibility to sunburn with a poor ability to develop a tan.
7. To have a family history of eye or cutaneous melanoma.
8. To have large numbers of naevus (mole), in the order of more than 30 moles $\geqslant$ 2 mm on the whole body, or one or more naevi larger than 5 mm.
9. To have a tendency to have freckling developing on the face when going in the sun.
10. To have a history of frequent sunburn during childhood or during adulthood.
11. To have pre-malignant (e.g., solar keratosis) or a history of malignant skin lesions.
12. To have a sun damaged skin (wrinkles on the face, or irregular pigmented skin areas on the face and arms).
13. To wear cosmetics. Cosmetics may enhance sensitivity to UV exposure.
14. To be taking medications. Medications may increase sensitivity to UV, and may sometimes lead to severe health complications (e.g., extensive skin burns). Individuals should seek advice from their physician to determine if the medication will make them UV-sensitive.

* After World Health Organisation (WHO) 2003 (60) and International Commission on Non-Ionizing Radiation Protection (ICNIRP) 2003 (8).

alternatives to sunlight. The tanning industry has elaborated a large part of its marketing strategies around the concept of "safe tan acquisition", that is the acquisition of a tan without incurring (or with incurring less) detrimental effects of UV exposure, mainly sunburns, skin cancers, and skin aging.

8.2. The dubious concept of "regulated" or "controlled" tan acquisition

For promoting the idea of the possibility of "safe (or safer) tan acquisition", the sunbed industry has invented the concept of "regulated" or "controlled tanning", as opposed to beach tanning that would be "unregulated" or "uncontrolled" [39,40]. "Controlled" tan acquisition would be safer than sunbathing because of the constancy of several UV-exposure criteria, like, for instance, a constant UV intensity in wavelength and in time. In hot countries, like Italy and Australia, the "controlled tan acquisition" concept is used for convincing consumers that sunbed use represents a good substitute to beach sunbathing.

But the perilous assertion that "controlled" tan acquisition would be less aggressive than 'uncontrolled' tan acquisition is not supported by laboratory experiments, it contradicts recent findings in basic science, and denies epidemiological and behavioural data:

1. Subjects attracted by indoor tanning are also attracted by sunbathing [11]. Hence, for most sunbed users, amounts of indoor UV add to amounts of outdoor UV, with possible interactive processes that could further increase the melanoma risk. In addition, the weak photoprotection against sunburns afforded by a sunbed-induced tan may encourage longer stays in the sun [41].
2. Surveys continually show the ignorance of tanning parlours operators and the lack of enforcement of basic utilisation rules [42–45].
3. DNA damage that is detectable after sunbed exposure is comparable to DNA damage induced by exposure to natural sunlight [46].
4. Tan induction is rather an indicator of skin aggression with DNA damage than a marker of skin photoprotection [47,48].
5. The recurring induction of melanin synthesis could be involved in skin carcinogenesis [49,50].
6. Sunbed use causes sunburns in 18–55% of users, and these acute skin reactions are associated with melanoma and BCC occurrence.
7. The UVB fraction present in the sunbed emission spectrum may still have detrimental effects on the skin.
8. We have no knowledge about the long-term effects of repeated exposures to high UVA doses mixed with some UVB.

8.3. The questionable photoprotection properties of "pre-vacation tan"

The tanning industry and many sun-enthusiasts allege that a "pre-vacation tan" acquired through sunbed use would confer protection against sunburns and other deleterious effects of the sun. But photoprotection against sunburns and DNA photodamage afforded by the facultative pigmentation induced by tanning under the sun is very low, just equivalent to a sun protection factor (SPF) 3 sunscreen [51]. The tan induced by UVA-tanning provides practically no photoprotection [52]. The moderate skin thickening induced by sunbed use would afford even less photoprotection than tanning [53]. Increasing numbers of laboratory data show that a pre-vacation tan offers only little protection against sun-induced DNA damage [41,54,55].

9. New threats on the horizon

9.1. The UV-lamps rich in UVB radiation

Recently, new fluorescent lamps that have an emission spectrum resembling the emission spectrum of the midday sun have been introduced into the market. Exposure to these lamps enables a faster acquisition of a deep tan. Exposure to UVB-rich lamps is similar to intentional sun exposure in the midday sun, and is thus likely to convey the same risk of skin cancer. Given the known association between intermittent sun exposure and melanoma, public-health authorities should reconsider the soundness of the commercialisation of these lamps.

9.2. Age of sunbed users

Age of sunbed users is a new concern: in Sweden, sunbed use is popular among adolescents 14–17 years old [56]. A large survey in 2004 in the schools of Lanarkshire (UK) showed that 7% of children 8–11 years old had used a sunbed [57]. This phenomenon is also observed in Australia [58]. Most countries do not have regulation on a minimal age for indoor tanning [59]. Childhood and adolescence are periods of greater biological vulnerability to UV radiations, and thus prohibition of the use of tanning devices before 18 years old seems wise [8,60].

9.3. The hypothetical health benefits of UV radiations

The subtlest position for the defence of indoor tanning is the recognition of good and bad effects of indoor tanning, but that finally, good effects would outweigh bad effects. The good health effects attributed by the tan-

ning industry to UV radiation are numerous, from the healing of seasonal depression to the prevention of breast, colon and prostate cancers. Advocacy texts issued by the tanning industry seems to come to the conclusion that everything being considered, finally, "controlled skin damage" is somehow good for health [61].

The generation of vitamin D is the main known benefit of UV radiation. Vitamin D synthesis is activated by UVB radiation, not by UVA radiation. In fair-skinned European subjects, if dietary intakes of vitamin D are inadequate, brief periods of exposure to summer sunlight in everyday life on hands and face is all that is needed to initiate vitamin D synthesis. Longer exposures provide no additional benefit in this respect.

UV radiations are used for treating various skin conditions such as psoriasis and dermatitis. Psoriasis patients treated over long periods of time with a combination of UVA and oral psoralen have an increased incidence in non-melanoma skin cancers [52,63], and a significant increase in melanoma incidence was found in one cohort of PUVA-treated psoriasis patients [64,65].

The role that UV radiation would have in the prevention of cancerous diseases is largely based on ecological data and on speculations on as yet unproven biological mechanisms. At present, there is no sound scientific data showing a protective effect of intentional exposure to UV radiation on any cancer in humans.

In North European countries, and in Canada, advertisements recommend sunbed use from November to March to combat the "winter depression" or "seasonal depression", attributed to the absence of days with bright sunshine and to long periods of obscurity. However, light therapy using white fluorescent lights is as effective for the treatment of seasonal depression [66]. Thus there is no reason to promote exposure to potentially harmful UV radiation to treat that condition.

10. How credible is the precautionary principle?

The precautionary principle is frequently evoked in the shaping of health or of environmental policies. In brief, that principle consists of regulating the general public use or the diffusion in the environment of a substance or of a device whose safety remains open to question. In Europe, the precautionary principle is frequently put forward to oppose the development of innovations, even though there is no evidence for a detrimental impact on health or on the environment.

In spite of the scientifically established association between the intermittent exposure to solar UV radiation and melanoma, and of the evidence that melanoma incidence is doubling every 10 or 20 years in many fair-skinned populations, the indoor tanning fashion has undergone a considerable growth in the past 20 years. Hence, although there was far more scientific evidence for possible harmful health effects due to sunbed use than for many other products, the precautionary principle has never been applied for protecting consumers against the many health uncertainties regarding the safety of artificial UV sources, and against the many unverified beliefs utilised for the marketing of the sunbed fashion.

11. The need to control information disseminated by the tanning industry

For most people, information and advertisements disseminated by the tanning industry are the main source of information regarding tan acquisition and sun protection. Behavioural studies in Europe [17,67,68] show that people know about skin cancer and the damaging affect of sunbathing, and about possible dangers associated with sunbed use, but that knowledge does not alter their tanning behaviours in general. In Europe and the USA, recommendations on sunbed

Table 2
Steps to be taken in the regulation of sunbed use and of information given to the general public*

1. Devise regulations for the installation, operation and utilisation, independently of those set by the tanning industry.
2. To prohibit sunbed use before 18 years old.
3. Rendering the use of protective eyewear (goggles) mandatory during sunbed sessions.
4. Use of and speculations on concepts such as "safe", or "controlled", or "regulated" tan acquisition" should not be authorised.
5. Reference to hypothetical health benefits of outdoor or indoor ultraviolet (UV) exposures must be prohibited. The mention of preventive effects on cancers and other major health conditions should not be authorised.
6. The existence of legal regulations on indoor tanning should not be used for advertising purposes, or for issuing claims on the safety of indoor tanning.
7. Requirement to inform consumers visiting tanning parlours on the dangers associated with sunbed use and sun exposure, including, among other things:
   (a) Increased risk of skin cancer, especially melanoma and basal cell carcinoma (BCC).
   (b) Risk of sunburns and skin erythema.
   (c) Risk of premature wrinkles.
   (d) Risk of unpleasant and disgraceful pigmented skin lesions.

* The list should be included in information packages accompanying tanning devices that are acquired for private use.

use and regulations restricting indoor tanning do not make sunbed users more cautious, especially adolescents and young adults [67–71].

The most relevant strategy for curbing sunbed use is to obtain a change in attitudes toward sunbathing and having a tan. In that respect, the principal public health target should be to draw up regulations, independently of those set by the tanning industry, and the control of information and advertisements (Table 2). The tanning industry should no longer have the possibility to have recourse to claims on health benefits of outdoor or indoor tanning in order to convince consumers to use sunbeds.

Indeed, this strategy would concern other segments of the tanning industry, such as sunscreen companies that base their marketing strategy on the possibility of acquiring a healthy and safe tan, thanks to the use of their product.

12. Conclusions

The Norway–Sweden study [26] has provided epidemiological evidence that regular sunbed use is associated with a moderate increase in the risk of melanoma. Large numbers of people use sunbeds on a regular basis, and sunbed use often starts during adolescence. So, in 2004, UV doses accumulated by many people though sunbed use may be far higher than observed in the Norway–Sweden study.

Public-health efforts should continue to disseminate information on the dangers of UV radiations, and to discourage sunbed use.

Regulation of sunbed installation, operation and use is desirable, but enforcement of rules is by far the most difficult challenge. In addition, regulations should become harmonised in the European Union.

Advertisements and information disseminated by the tanning industry to the general public should be controlled. The sunbed manufacturers and operators should no longer be able to claim health benefits of any sort attributable to sunbed use, and to other forms of intentional sun exposure.

Close monitoring of sunbed use and of its immediate consequences (e.g., skin erythema and sunburns) is now well established in Sweden. There are signs of decreasing trends in sunbed use among adolescents and young adults in Sweden [68]. Is the sunbed fashion be levelling off in Sweden? Similar surveys should be conducted in other countries to monitor global exposure to privately owned or commercially operated tanning devises. Boldeman et al. [68] have proposed an international harmonisation of survey tools for the monitoring of sunbed use and sunburn experience. Such an instrument is highly desirable for comparing sunbed use habits and consequences across countries and to follow the impact of policies intended to discourage sunbed use or to combat the "safe tan" concept. The survey tool could also include the monitoring of sun exposure and sun protection habits.

References

1. Parkin DM, Muir C, Whelan SL, Gao YT, Ferlay J, Powell J. *Cancer Incidence in Five Continents*, vol. VI. Lyon, IARC Scientific Publications 120, IARC, 1992.
2. Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J. *Cancer Incidence in Five Continents*, vol. VII. Lyon, IARC Scientific Publication 143, IARC, 1997.
3. MacKie RM, Bray CA, Hole DJ, *et al.* Incidence of and survival from malignant melanoma in Scotland: an epidemiological study. *Lancet* 2002, **360**, 587–591.
4. Remontet L, Estève J, Bouvier AM, *et al.* Cancer incidence and mortality in France over the period 1978–2000. *Rev Epidemiol Santé Publique* 2003, **51**, 3–30.
5. Kricker A, Armstrong BK, English DR, Heenen PJ. Does intermittent sun exposure cause basal cell carcinoma. *Int J Cancer* 1995, **60**, 489–494.
6. de Vries E, Louwman M, Bastiaens M, de Gruijl F, Coebergh JW. Rapid and continuous increases in incidence rates of basal cell carcinoma in the Southeast Netherlands since 1973. *J Invest Dermatol* 2004 (in press).
7. International Agency for Research on Cancer Expert Group. *Solar and Ultraviolet Radiation. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol. **55**. Lyon, 1992.
8. The International Commission on Non-Ionizing Radiation Protection (ICNIRP). Health issues of ultraviolet tanning appliances used for cosmetic purposes. *Health Phys* 2003, **84**, 119–127.
9. de Vries E, Bray FI, Coebergh JWW, Parkin DM. Changing epidemiology of cutaneous malignant melanoma in Europe 1953–1997: rising trends in incidence and mortality but recent stabilization in Western Europe and decreases in Scandinavia. *Int J Cancer* 2003, **107**, 119–126.
10. International Agency for Research on Cancer Expert Group (2001). *Sunscreens. IARC Handbooks of Cancer Prevention*, vol. **5**. Lyon, 2001.
11. Autier P, Joarlette M, Lejeune F, Lienard D, Andre J, Achten G. Cutaneous malignant melanoma and exposure to sunlamps and sunbeds: a descriptive study in Belgium. *Melanoma Res* 1991, **1**, 69–74.
12. Autier P, Doré JF, Lejeune F, *et al.* Cutaneous malignant melanoma and exposure to sunlamps or sunbeds: an EORTC multicenter case-control study in Belgium, France and Germany. *Int J Cancer* 1994, **58**, 809–813.
13. Rhainds M, De Guire L, Claveau J. A population-based survey on the use of artificial tanning devices in the province of Québec, Canada. *J Am Acad Dermatol* 1999, **40**, 572–576.
14. Oliphant JA, Forster JL, McBride CM. The use of commercial tanning facilities by suburban Minnesota adolescents. *Am J Pub Health* 1994, **84**, 476–478.
15. Westerdahl J, Ingvar C, Masback A, Olsson H. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UVA carcinogenicity. *Br J Cancer* 2000, **82**, 1593–1599.
16. Boldeman C, Beitner H, Jansson B, Nilsson B, Ullen H. Sunbed use in relation to phenotype, erythema, sunscreen use and skin diseases. A questionnaire survey among Swedish adolescents. *Br J Dermatol* 1996, **135**, 712–716.
17. Monfrecola G, Fabbrocini G, Posteraro G, Pini D. What do young people think about the dangers of sunbathing, skin cancer

and sunbeds? A questionnaire survey among Italians. *Photodermatol Photoimmunol Photomed* 2000, **16**, 15–18.
18. Naldi L, Gallus S, Imberti GL, Cainelli T, Negri E, La Vecchia C. Sunlamps and sunbeds and the risk of cutaneous melanoma. *Eur J Cancer Prev* 2000, **9**, 133–134.
19. Dobbinson S, Borland R. Reaction to the 1997/98 SunSmart Campaign: results from a representative household survey of Victorians. In: Anti-Cancer Council of Victoria (eds.). *SunSmart Evaluation Studies*. No. 6, Melbourne, 1999.
20. Gerber B, Mathys P, Moser M, Bressoud D, Braun-Fahrlander C. Ultraviolet emission spectra of sunbeds. *Photochem Photobiol* 2002, **76**, 664–668.
21. Wester U, Boldemann C, Jansson B, Ullén H. Population UV-dose and skin area – Do sunbeds rival the sun?. *Health Phys* 1999, **77**, 436–440.
22. Agar NS, Halliday GM, Barnetson RStC, Ananthaswamy HN, Wheeler M, Jones AM. The basal layer in human squamous tumours harbors more UVA than UVB fingerprints mutations: a role for UVA in human skin carcinogenesis. *Proc Natl Acad Sci* 1994, **101**, 4954–4959.
23. Woollons A, Kipp C, Young AR, *et al.* The 0.8% ultraviolet B content of an ultraviolet A sunlamp induces 75% of cyclobutane pyrimidine dimers in human keratinocytes in vitro. *Br J Dermatol* 1999, **140**, 1023–1030.
24. MacGintley J, Martin CJ, MacKie RM. Sunbeds in current use in Scotland: a survey of their output and patterns of use. *Br J Dermatol* 1998, **139**, 428–438.
25. Wright AL, Hart GC, Kernohan E, Twentyman G. Survey of the variation in ultraviolet outputs from ultraviolet A sunbeds in Bradford. *Photodermatol Photoimmunol Photomed* 1996, **12**, 12–16.
26. Veierød MB, Weiderpasss E, Lund E, Thorn M, Hansson J, Armstrong BK, *et al.* A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Inst* 2003, **95**, 1530–1538.
27. Boldeman C, Bränström R, Dal H, Kristjansson S, Rodvall Y, Jansson B, *et al.* Tanning habits and sunburn in a Swedish population age 13–50 years. *Eur J Cancer* 2001, **37**, 2441–2448.
28. Walter SD, Marrett LD, From L, Hertzman C, Shannon HS, Roy P. The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. *Am J Epidemiol* 1990, **131**, 232–243.
29. Swerdlow AJ, English JSC, MacKie RM. Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. *Br Med J* 1988, **297**, 647–650.
30. Chen Y, Dubrow R, Zheng T, Barnhill RL, Fine J, Berwick M. Sunlamp use and the risk of cutaneous malignant melanoma: a population-based case-control study in Connecticut, USA. *Int J Epidemiol* 1998, **27**, 758–765.
31. Westerdahl J, Olsson H, Masbäck A, *et al.* Use of sunbeds or sunlamps and malignant melanoma in southern Sweden. *Am J Epidemiol* 1994, **140**, 691–699.
32. Bataille V, Winnett A, Sasieni P, Newton Bishop JA, Cuzick J. Exposure to the sun and sunbeds and the risk of cutaneous melanoma in the UK: a case-control study. *Eur J Cancer* 2004, **40**, 429–435.
33. Swerdlow AJ, Weinstock MA. Do tanning lamps cause melanoma? An epidemiologic assessment. *J Am Acad Dermatol* 1998, **38**, 89–98.
34. Autier P. Issues about solaria. In Hill D, Elwood M, English D, eds. *Skin Cancer Prevention. Cancer Causes and Control*. Boston, Kluwer Academic Publishers, 2002.
35. Veierød MB, Weiderpasss E, Lund E, Armstrong BK, Adami HO. Re: prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. *J Natl Cancer Int* 2004, **96**, 337–338.
36. Autier P, Doré JF, Négrier S, *et al.* Sunscreen use and duration of sun exposure: a double blind randomized trial. *J Natl Cancer Inst* 1999, **15**, 1304–1309.
37. Bajdik CD, Gallagher RP, Astrakiankis G, Hill GB, Fincham S, McLean DI. Non-solar ultraviolet radiation and the risk of basal and squamous cell skin cancer. *Br J Cancer* 1996, **73**, 1612–1614.
38. Karagas MR, Stannard VA, Mott LA, Slattery MJ, Spencer SK, Weinstok MA. Use of tanning devices and risk of basal cell and squamous cell sin cancers. *J Natl Cancer Inst* 2002, **94**, 224–226.
39. Sayre RM, Dowdy JC. Sunbathing vs. indoor tanning: a realistic perspective. *Photodermatol Photoimmunol Photomed* 2003, **19**, 105–107.
40. de Winter S, Pavel S. Zonnebanken. Onduidelijk effect on huidkankerrisico [Tanning beds: effect on skin cancer risk unclear]. *Ned Tijdschr Geneeskd* 2000, **144**, 467–470 (in Dutch).
41. Hemminki K, Bykov VJ, Marcuson JA. Re: Sunscreen use and duration of sun exposure: a double-blind, randomised trial. *J Nat Cancer Inst* 1999, **91**, 2016–2047.
42. Szepietowski JC, Nowicka D, Soter K, Strzelecka E, Kozera M, Salomon J. Tanning salons in southwest Poland: a survey of safety standards and professional knowledge of the staff. *Photodermatol Photoimmunol Photomed* 2002, **18**, 179–182.
43. Culley CA, Mayer JA, Eckhardt L, *et al.* Compliance with federal and state legislation by indoor tanning facilities in San Diego. *J Am Acad Dermatol* 2001, **44**, 53–60.
44. Moseley H, Davidson M, Ferguson J. A hazard assessment of artificial tanning units. *Photodermatol Photoimmunol Photomed* 1998, **14**, 79–87.
45. Ross RN, Phillips B. Twenty questions for tanning facility operators: a survey of operator knowledge. *Can J Public Health* 1994, **85**, 393–396.
46. Woollons A, Clingen PH, Price ML, Arlett CF, Green MH. Induction of mutagenic damage in human fibroblasts after exposure to artificial tanning lamps. *Br J Dermatol* 1997, **137**, 687–692.
47. Pedeux R, Al-Irani N, Marteau C, Pellicier F, Branche R, Ozturk M, *et al.* Thymidine dinucleotide induce S phase cell cycle arrest in addition to increased melanogenesis in human melanocytes. *J Invest Dermatol* 1998, **111**, 472–477.
48. Eller MS, Maeda T, Magnoni C, Atwal D, Gilchrest BA. Enhancement of DNA repair in human skin cells by thymidine dinucleotides: evidence for a p53-mediated mammalian SOS response. *Proc Natl Acad Sci USA* 1997, **94**, 12627–12632.
49. Kvam E, Tyrell RM. The role of melanin in the induction of oxidative DNA base damage by ultraviolet A irradiation of DNA or melanoma cells. *J Invest Dermatol* 1999, **113**, 209–213.
50. Barker D, Dixon K, Medrano EE, *et al.* Comparison of the responses of human melanocytes with different melanin contents to ultraviolet B irradiation. *Cancer Res* 1995, **55**, 4041–4046.
51. Young AR. Tanning devices – Fast track to skin cancer. *Pigm Cell Res* 2004, **17**, 2–9.
52. Gange RW, Blackett AD, Matzinger EA, Sutherland BM, Kochevar IE. Comparative protection efficiency of UVA- and UVB-induced tans against erythema and formation of endonuclease-sensitive sites in DNA by UVB in human skin. *J Invest Dermatol* 1985, **85**, 362–364.
53. Seehan JM, Potten CS, Young AR. Tanning in human skin types II and III offers modest photoprotection against erythema. *Photochem Photobiol* 1998, **68**, 588–592.
54. Bykov VJ, Marcusson JA, Hemminki K. Protective effects of tanning on cutaneous melanoma. *Dermatology* 2001, **202**, 22–26.
55. Ruegemer J, Schuetz B, Hermann K, Hein R, Ring J, Abeck D. UV-induced skin changes due to regular use of commercial sunbeds. *Photodermatol Photoimmunol Photomed* 2002, **18**, 223–227.
56. Boldeman C, Jansson B, Nilsson B, Ullen H. Sunbed use in Swedish urban adolescents related to behavioral characteristics. *Prev Med* 1997, **26**, 114–119.
57. Hamlet N, Kennedy K. Reconnaissance study of sunbed use by primary school children in Lanarkshire. *J Public Health (Oxf)* 2004, **26**, 31–33.

58. Paul CL, Girgis A, Tzelepis F, Walsh RA. Solaria use by minors in Australia: is there a cause for concern. *Aust N Z J Public Health* 2004, **28**, 90.
59. Dellavalle RP, Parker ER, Cersonsky N, *et al.* Youth access laws: in the dark at the tanning parlor. *Arch Dermatol* 2003, **139**, 443–448.
60. World Health Organization. Artificial tanning sunbeds, risks and guidance. World Health Organization, Geneva, 2003 (Available at url: http://www.who.int).
61. Chouela E. Reply to sunbathing versus indoor tanning: a realistic perspective. *Photochem Photoimmunol Photomed* 2003, **19**, 268.
62. Boffetta P, Gridley G, Lindelöf B. Cancer risk in population-based cohort of patients hospitalised for psoriasis in Sweden. *J Invest Dermatol* 2001, **117**, 1531–1537.
63. Morison WL, Baughman RD, Day RM, *et al.* Consensus workshop on the toxic effects of long-term PUVA therapy. *Arch Dermatol* 1998, **134**, 595–598.
64. Stern RS, Nichols KT, Vakeva LH. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). The PUVA follow-up study. *N Engl J Med* 1997, **336**, 1041–1045.
65. Stern RS. and the PUVA Follow-up Study. The risk of melanoma in association with long-term exposure to PUVA. *J Am Acad Dermatol* 2001, **44**, 755–761.
66. Lam RW, Buchanan A, Mador JA, Corral MR, Remick RA. The effects of ultraviolet-A wavelengths in light therapy for seasonal depression. *J Affect Disorders* 1992, **24**, 237–243.
67. Branstrom R, Brandberg Y, Holm L, Sjoberg L, Ullen H. Beliefs, knowledge and attitudes as predictors of sunbathing habits and use of sun protection among Swedish adolescents. *Eur J Cancer Prev* 2001, **10**, 337–345.
68. Boldeman C, Jansson B, Dal H, Ullen H. Sunbed use among Swedish adolescents in the1990s: a decline with an unchanged relationship to health risk behaviors. *Scand J Public Health* 2003, **31**, 233–237.
69. Knight JM, Kirincich AN, Farmer ER, Hood AF. Awareness of the risk of tanning lamps does not influence behaviour among college students. *Arch Dermatol* 2002, **138**, 1311–1315.
70. Lechner L, De Vries H. Sunbed use at home: risk behaviour and psychosocial determinants. *Eur J Cancer Prev* 2002, **11**, 333–341.
71. Beasley TM, Kittel BS. Factors that influence health risk behaviors among tanning salon patrons. *Eval Health Prof* 1997, **20**, 371–388.

Minireview

Tanning Beds, Sunlamps, and Risk of Cutaneous Malignant Melanoma

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Abstract

Background: **A number of studies have been conducted evaluating the risk of cutaneous malignant melanoma after exposure to sunlamps and/or sunbeds. The proportion of subjects in the individual studies who have reported exposure has, in general, been modest, and the resulting risk estimates for melanoma have been unstable with wide 95% confidence intervals (95% CI). The inconclusive results seen in individual studies have resulted in confusion as to the carcinogenicity of these devices.**

Methods: **We conducted a systematic review and meta-analysis of these studies. A review of the literature from Jan 1, 1984 to April 2004 using MEDLINE identified 12 case-control studies and 1 cohort study which quantitatively evaluated the use of sunlamps and/or sunbeds and subsequent melanoma. After applying exclusion/inclusion criteria, 9 case-control and 1 cohort study provided data for the analysis. Summary odds ratios (OR) and 95% CIs for sunlamp/sunbed use and subsequent melanoma were calculated using a random-effect model.**

Results: **Ten studies provided data for assessment of melanoma risk among subjects who reported "ever" being exposed compared with those "never" exposed. A positive association was found between exposure and risk (summary OR, 1.25; 95% CI, 1.05-1.49). Significant heterogeneity between studies was present. Evaluation of the metrics "first exposure as a young adult" (5 studies) and "longest duration or highest frequency of exposure" (6 studies) also yielded significantly elevated risk estimates (summary OR, 1.69; 95% CI, 1.32-2.18, and 1.61; 95% CI, 1.21-2.12, respectively, with no heterogeneity in either analysis).**

Conclusions: **Results indicate a significantly increased risk of cutaneous melanoma subsequent to sunbed/sunlamp exposure.** (Cancer Epidemiol Biomarkers Prev 2005;14(3): 562–6)

Introduction

There is good experimental and epidemiologic evidence that UV radiation exposure (mainly from sunlight) is causally related to all forms of human skin cancer including cutaneous malignant melanoma (1). Melanoma incidence has most strongly and consistently been associated with reported "intermittent sun exposure" mostly accrued through recreational activities. A quantitative review of studies of sun exposure and melanoma found a positive association between intermittent exposure and risk of cutaneous malignant melanoma in 21 (statistically significant in 16) of 23 studies included in the analysis (2).

Because by its nature, exposure to artificial UV radiation through sunlamp and sunbed use is intermittent in character, there has been consistent concern over the past 15 years that use of such devices for recreational tanning may increase risk of melanoma (3). In addition, data from surveys conducted in Europe (4, 5) and North America (6) indicate that sunbeds are now being used by an increasing proportion of the population, particularly young people.

A series of epidemiologic investigations have attempted to determine the nature of this putative association. However, analysis of sunlamp/sunbed use has been hampered by small numbers of exposed subjects in individual studies. In order to evaluate the strength and consistency of association between use of these devices and melanoma, we have conducted a systematic review and meta-analysis.

Materials and Methods

To identify relevant studies of sunbeds/sunlamps and melanoma, we conducted a MEDLINE database search for the years 1984 to 2004, using the terms "melanoma (etiology, epidemiology) and sunbeds, sunlamps, and solarium" as keywords. We also selected all review articles in English on UV radiation, tanning devices, solaria, and melanoma, and scrutinized these to locate articles with data on sunlamp and sunbed use missed by the MEDLINE search. We did not attempt to locate unpublished data. We chose 1984 as the year of start of our search as that year saw the first publications from large-scale epidemiologic studies of melanoma and UV exposure with good control for phenotype confounders. The search yielded a total of 12 case-control studies reporting risk estimates for melanoma subsequent to sunbed/sunlamp use (7-18). In addition, one cohort study was found which reported on usage among Norwegian and Swedish women (19).

Selection of Studies. All case-control studies of cutaneous malignant melanoma that reported on use of sunlamps, sunbeds, or both were initially considered for the analysis. For inclusion, we required that numbers (or percentages) of exposed cases and controls were presented in the study, and odds ratios (ORs) with 95% confidence intervals (95% CI) were

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available, evaluating at least "ever" versus "never" use of these devices. Because of these requirements, two earlier studies were omitted; one due to missing CIs (7) and the other due to missing data on numbers of exposed cases and controls (8). A study by MacKie et al. (10) was also omitted because it was not possible from the information presented to determine accurately the proportions or numbers of cases and controls exposed. All other studies were included in the analysis.

In order to attempt to make the analysis reflect, as far as possible, recreational rather than medical use of sunlamps/sunbeds, we did not include studies of psoralen and UVA radiation therapy [e.g., that of Stern et al. (20)]. Where studies provided separate estimates of risk for medical and nonmedical use, the estimates for nonmedical use were used. Where separate estimates were not given, the overall ORs and CIs were used. Whenever possible, ORs adjusted for phenotype factors (hair, skin, eye color, phototype, number of nevi, etc.) and sun exposure were used in preference to crude or unadjusted values. The studies of Swerdlow et al. (13) and Osterlind et al. (9) present risk estimates as crude ORs unadjusted for phenotype factors. Swerdlow[5] indicated the "ever versus never exposed" value was adjusted only for age, sex, and region of residence. In the case of the study by Walter et al. (14), risk estimates were calculated as crude and adjusted ORs, and because the two analyses gave "essentially the same effect" (p.236), the authors presented the unadjusted values. Thus, the Walter estimates can be expected to closely approximate adjusted values.

A number of the studies presented data which allowed us to evaluate whether initial exposure to sunbeds/sunlamps occurring earlier in life "as a young adult" conferred a different risk than if exposure began closer to the time of the study. A total of five studies contributed to this analysis and, with the exception of the study of Walter et al. (14), the estimates used were the adjusted values.

Finally, a number of studies attempted to determine whether a dose-response gradient with exposure was seen. We produced summary ORs comparing melanoma risk between subjects with the longest duration or highest frequency of exposure and subjects never exposed. Six studies provided data for this analysis.

Two of the authors (R.P.G. and T.K.L.) examined each of the studies independently to determine which risk estimate was the best indicator of "first exposure as a young adult" and which was the best for "longest duration or highest frequency of use," and after a discussion concerning one study, agreed on the measures considered to be most appropriate.

Summary ORs and 95% CIs were calculated for the three measures of sunlamp/sunbed exposure noted above using the method of DerSimonian and Laird (21). The Q statistic was used as a test for heterogeneity among the original study estimates (22). Published gender-specific ORs (14) or period-specific ORs (15) were treated as separate entries or "studies" in the meta-analysis. Sensitivity analyses were conducted by recalculating summary ORs after eliminating specific studies.

Results

A total of 10 published articles (with 12 ORs) were used in assessing the relationship between ever versus never use of sunlamp/sunbed and melanoma (Table 1). The summary OR showed a modest elevated risk (OR, 1.25; 95% CI, 1.05-1.49). Positive associations were seen in 8 of 10 individual studies, although only 4 risk estimates were statistically significant. One of the studies (9) showed an inverse association. There was significant heterogeneity (Q = 28.9; P = 0.0024) likely due to the studies being conducted over a long period of time with different designs. Also, one study (9) showed results markedly different from the others. Recalculation excluding the Osterlind study substantially reduced but did not eliminate the heterogeneity, and had only a slight effect on the summary OR. Excluding both the Osterlind study and the Swerdlow study (not adjusted for phenotype factors) again had essentially no effect (OR, 1.24; 95% CI, 1.09-1.41). The cohort study of Veierod et al. (19) used "never/rarely" as the index in assessing exposure. We included this measure in the analysis as combining these two groups as the index should give a conservative estimate of risk among users. Excluding the Veierod study made little difference to the summary OR (OR, 1.21; 95% CI, 1.02-1.44).

Five studies contributed data to the analysis of first exposure as a young adult (Table 2) which showed a positive association with subsequent melanoma (OR, 1.69; 95% CI, 1.32-2.18). Confidence intervals for this analysis were wider than those seen for the previous metric because the estimates contributing to the summary ORs were based on relatively small numbers of subjects. All five of the individual studies showed a positive association although only two were statistically significant. This group of estimates showed no evidence of heterogeneity (Q = 3.81; P = 0.58). Recalculation excluding the Swerdlow study (no control for phenotype factors) had only a slight effect on the summary measure (OR, 1.65; 95% CI, 1.28-2.13).

Data from six studies were entered into the analysis of longest duration or highest frequency of use (Table 3). A higher point estimate of risk was seen in this analysis (OR, 1.61; 95% CI, 1.21-2.12) than in the ever versus never analysis, although the CIs for the two estimates overlapped slightly. All six individual study estimates showed a positive association with melanoma. Again, this group of estimates showed no evidence of heterogeneity (Q = 5.90; P = 0.55), and recalculation excluding the Swerdlow study (no control for phenotype factors) had virtually no effect on the summary OR (OR, 1.57; 95% CI, 1.19-2.09).

Discussion

This meta-analysis is subject to a number of limitations. The estimates of risk for melanoma subsequent to using sunlamps/sunbeds are based on published data in a series of 10 articles over a period of 20 years. A pooled analysis of original observations taken in the 10 studies would have provided a more powerful approach to summarizing data on melanoma and sunlamp/sunbed use. However, because the studies had different overall aims, different metrics were used to record duration and/or frequency of sunlamp/sunbed use. With the exception of Westerdahl et al. (17), no study collected all the information (years of use, frequency of exposure per year, and duration of each exposure) needed to conduct a full quantitative assessment of the association. This made pooling of raw data infeasible.

Results of the analysis are, of course, dependent on the choice of measures selected from each study. The overall measure, ever versus never use, is fairly clear-cut, with the caveat that we selected wherever possible the risk estimate and CIs noted "for tanning purposes" rather than total use. Recalculation of summary ORs using values for total sunbed/sunlamp usage rather than use for tanning purposes indicated that our decision did not affect the conclusions reached. The measures used to assess first exposure as a young adult were subject to more judgment. The case-control studies defined a young adult in different ways, with first exposure ages ranging from "less than 25" to "less than 39 years." For the women's prospective cohort study (19), we

[5] Personal communication (April 30, 2004).

Table 1. Exposure to sunlamps and/or sunbeds and cutaneous malignant melanoma: case control and cohort study results

Ever vs. never exposed

Reference	Place and period	Cases	Controls	% Controls exposed	Metric	OR* (95% CI)
Osterlind et al. (9)	East Denmark 1982-1985	474	926	18%	Ever used sunbeds	0.7†,‡ (0.5-1.0)
Swerdlow et al. (13)	UK (Scotland) 1979-1984	180	197	8.3%	Ever used UV lamps or sunbeds	2.9† (1.3-6.4)
Walter et al. (14)	Ontario Canada 1984-1986	583	608	Males 14%	Ever used sunbeds/ sunlamps	Males 1.88† (1.20-2.98)
				Females 21%		Females 1.45† (0.99-2.13) M + F 1.62† (1.21-2.16)
Garbe et al. (11)	Germany 1984-1987	856	705	7%	Use of sunbeds-yes	1.5* (0.9-2.4)
Autier et al. (15)	Germany, Belgium, France 1991-1993	420	447	Males 14%§	Ever exposed to sunlamps for tanning	Sunlamps§ 1.77† (1.00-3.23)
				Females 17%§	Ever exposed to sunbeds for tanning	Sunbeds§ 0.95† (0.64-1.41)
						All§ 1.16† (0.83-1.61)
Westerdahl et al. (16)	South Sweden 1988-1990	400	640	25%	Ever used sunbeds/ sunlamps	1.3* (0.9-1.8)
Holly et al. (12)	San Francisco USA 1981-1986	452	930	38%‖	Ever use of sunlamp	0.94† (0.74-1.2)
Chen et al. (18)	Connecticut USA 1987-1989	624	512	Males 16%	Ever used sunlamp	1.13* (0.82-1.54)
				Females 22%		
Westerdahl et al. (17)	South Sweden 1995-1997	571	913	Males 33%	Ever used sunbeds	1.2 (0.9-1.6)
				Females 57%		
Veierod et al. (19)	Sweden and Norway; female cohort 1991-1999	—	Total cohort, 106,379 women	2%¶ of total female cohort exposed	Exposed ≥1/mo in any month at age 10-39¶	1.55* (1.04-2.32)
Summary OR						
No. studies = 12 (10 investigations, 1 with sex-specific, and 1 with exposure-specific risk estimates)						1.25 (1.05-1.49)

NOTE: Abbreviation: NS, not stated.
*Odds ratio adjusted in the original study for age, sex, host factors, and in some studies, sun exposure.
†Odds ratio unadjusted.
‡Sunbed use only; no OR given for sunlamp use.
§Used for tanning purposes.
‖Study conducted among female subjects only.
¶Comparison group is never/rarely.

defined first exposure as a young adult to be women who used sunbeds for the first time at ages 10 to 19. As this cohort was comprised of women who were recruited in 1991 to 1992 at ages 30 to 50, early exposure would have occurred before 1980.

The longest duration or highest frequency of use analysis combined what we considered to be the best measure of cumulative sunbed/sunlamp exposure available within each study. The intention of this analysis was to compare risk estimates in subjects with maximal cumulative usage to that in

Table 2. Exposure to sunlamps and/or sunbeds and cutaneous malignant melanoma: case control and cohort studies

First exposure as young adult

Reference	Place and period	Cases	Controls	% Controls exposed	Metric	OR* (95% CI)
Swerdlow et al. (13)	UK (Scotland) 1979-1984	180	197	3%	Age at first exposure <30 y	3.8* (0.9-16.5)
Walter et al. (14)	Ontario Canada 1984-1986	583	608	Males 7%	First use <age 30	Males 2.13† (1.13-4.13)
				Females 12%		Females 1.55† (0.94-2.59) M + F 1.75† (1.18-2.59)
Chen et al. (18)	Connecticut USA 1987-1989	624	512	8%	<age 25 at first use of sunlamp	1.35* (0.88-2.08)
Westerdahl et al. (17)	South Sweden 1995-1997	571	913	9%	First exposure at age ≤35	2.3* (1.2-4.2)
Veierod et al. (19)	Sweden and Norway; female cohort 1991-1999	—	Total cohort 106,379 women	2% of total female cohort	Exposed ≥1/mo, age 10-19	1.52* (0.56-4.12)
Summary OR						
No. studies = 6 (5 studies, 1 with sex-separate risk estimates)						1.69 (1.32-2.18)

*Odds ratio adjusted in the original studies for age, sex, host factors, and in some studies, sun exposure.
†Odds ratio unadjusted.

Table 3. Exposure to sunlamps and/or sunbeds and cutaneous malignant melanoma: case control and cohort studies

Longest duration or highest frequency of use

Reference	Place and Period	Cases	Controls	% Controls Exposed	Metric	OR* 95% CI)
Swerdlow et al. (13)	UK (Scotland) 1979-1984	180	197	2%	Duration of use >1 y	3.4* (0.6-20.3)
Walter et al. (14)	Ontario, Canada 1984-1986	583	608	Males 4%	Sunbed/sunlamp use ≥1/mo for ≥12 mo	Males 2.12† (0.90-5.28)
				Females 2%		Females 2.99† (1.08-9.57)
						M + F 2.44† (1.27-4.71)
Autier et al. (15)	Germany, Belgium, France 1991-1993	420	447	Prior to 1980 5%	≥10 h exposure for tanning before 1980	Prior to 1980 2.12* (0.84-5.37)
				1980 or later 2%	≥10 h exposure for tanning 1980 or later	1980 or later 0.99* (0.49-2.00)
Westerdahl et al. (16)	South Sweden 1988-1990	400	640	5%	>10 exposures/y to sunbeds/sunlamps	1.8* (1.0-3.2)
Chen et al. (18)	Connecticut USA 1987-1989	624	512	8%	≥10 uses of sunlamp	1.15* (0.60-2.20)
Westerdahl et al. (17)	South Sweden 1995-1997	571	913	6%	>250 sunbed uses	1.5* (0.7-3.2)
Summary OR						
No. studies = 8 (6 studies, 1 with sex-specific estimates, and one with period-specific estimates)						1.61 (1.21-2.12)

*Odds ratio adjusted in the original studies for age, sex, host factors, and in some studies, sun exposure.
†Odds ratio unadjusted.

subjects "ever exposed" and those "never exposed." This would enable us to determine whether there was a suggestion of a gradient of risk from none to maximal use. Of course those subjects most heavily exposed will also be included in the ever exposed category, so the OR differences seen between the levels of exposure are not independent.

The published articles covered a time period of nearly 20 years. During this time the UV emissions of artificial tanning devices changed in character. Sunlamps used up to the late 1970s were usually used in the home setting (except for medical use) and emitted primarily UVB (sometimes with a small component of UVC). In the early 1980s, two major changes took place. Indoor tanning began to be done largely in commercial salons rather than at home, and salons began to use UVA lamps. Thus, the character of the exposure changed and because of this there is some question whether results from the early studies (9, 13, 14) can be legitimately combined with those of more recent studies. We suggest that combining the results of the studies is appropriate, as there is no convincing human data demonstrating that UVB is more or less strongly related to melanoma than UVA. In fact, there is some evidence that melanocytes exposed *in vivo* to either UVA or to UVB show similar levels of thymine dimer formation (23). In addition, studies have shown that UVA as well as UVB impairs antioxidant function and promotes reactive oxygen species, events known to be involved in cutaneous carcinogenesis (24-27). Finally, the risk estimates from later studies, taken together, do not differ in character from those seen in the earlier investigations.

Finally, although we have used risk estimates adjusted for phenotype factors and, when possible, for sun exposure, it is unlikely that the studies have achieved complete control for these potential confounders. If individuals who use artificial tanning devices are more likely to suntan, as many suspect, then some of the elevated risk seen might be due to recreational sun tanning.

Our results, however, suggest that any exposure to artificial tanning devices modestly, but significantly, increases risk of cutaneous melanoma; however, caution is needed as it is possible that there is unpublished (or unanalyzed) data on sunbed or sunlamp use in existence from previously conducted etiologic studies of melanoma. The subgroup analysis of risk among those exposed "early in adult life" suggests a risk estimate slightly higher than that seen in the ever versus never analysis. We take this to indicate that risk increases with adequate lag time (>10 years) after commencement of exposure. However, as noted above, this lag time is potentially confounded by the change in tanning device emissions from UVB to UVA in the early 1980s. The latter interpretation, however, seems unlikely as risk estimates for exposure during the period when UVA was emitted by sunbeds (17) are similar to those seen during earlier periods.

Summary ORs for those with the longest duration or highest frequency of use suggest a higher risk of melanoma among those most heavily exposed than among those ever exposed. Confidence intervals of the two estimates overlap; however, this does give some indication that a dose-response effect might be found to be present if exposure data were more effectively captured.

If there is a causal relationship between sunlamp/sunbed exposure and melanoma, the public health question is asked: how important is the risk? It is not possible with the data available to answer this question with any certainty. However, a large number of epidemiologic studies have been conducted on the relationship between solar UV exposure and melanoma, and these have been summarized quantitatively by Nelemans et al. (28) and Elwood and Jopson (2). Combining the highest reported levels of "intermittent" exposure produced a summary OR for all studies of 1.71 (95% CI, 1.54-1.90) in the Elwood study, and 1.57 (95% CI, 1.29-1.91) for population-based studies in the Nelemans investigation. These values are similar to that seen for longest duration or highest frequency of use of sunlamps/sunbeds in the present study. Although caution is required due to the possibility of confounding by inadequate control for concurrent sun exposure, the results suggest that artificial UV may be a significant contributor to risk among those with substantial exposure.

In summary, although it is not possible to determine accurately how much sunbed/sunlamp use contributes to individual risk of cutaneous malignant melanoma, it seems clear that any use of these devices elevates risk for cutaneous malignant melanoma. Furthermore, risk further increases with appropriate lag time, and frequency and duration of use seem likely to be positively related to the magnitude of the risk.

References

1. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk to humans. Vol 55. Solar and ultraviolet radiation. Lyon: IARC Press; 1992.
2. Elwood JM, Jopson J. Melanoma and sun exposure; an overview of published studies. Int J Cancer 1997;73:198–203.
3. Young AR. Tanning devices-fast track to skin cancer? Pigment Cell Res 2004;17:2–9.

4. Amir Z, Wright A, Kernohan E, Hart G. Attitudes, beliefs and behavior regarding the use of sunbeds among healthcare workers in Bradford. Eur J Cancer Care 2000;9:76–9.
5. Jerkegren E, Sandreiser L, Brandberg Y, Rosdahl I. Sun-related behavior and melanoma awareness among Swedish university students. Eur J Cancer Prev 1999;8:27–34.
6. Geller AC, Colditz G, Oliveria S, et al. Use of sunscreen, sunburning rates, and tanning bed use among more than 10000 US children and adolescents. Pediatrics 2002;109:1009–14.
7. Gallagher RP, Elwood JM, Hill GB. Risk factors for cutaneous malignant melanoma: the western Canada melanoma study. Recent Results Cancer Res 1986;102:38–55.
8. Holman CDJ, Armstrong BK, Heenan PJ, et al. The causes of malignant melanoma: results from the West Australian Lions melanoma research project. Recent Results Cancer Res 1986;102:18–37.
9. Osterlind A, Tucker MA, Stone BJ, Jensen OM. The Danish case-control study of cutaneous malignant melanoma: II. Importance of UV light exposure. Int J Cancer 1988;42:319–24.
10. MacKie RM, Freudenberger T, Aitchison TC. Personal risk-factor chart for cutaneous melanoma. Lancet 1989;2:487–90.
11. Garbe C, Weiss J, Kruger S, et al. The German Melanoma Registry and environmental risk factors implied. Recent Results Cancer Res 1993;128: 69–89.
12. Holly EA, Aston DA, Cress R, Ahn DK, Kristiansen JJ. Cutaneous melanoma in women I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. Am J Epidemiol 1995;141:923–33.
13. Swerdlow AJ, English JS, MacKie RM, et al. Fluorescent lights, ultraviolet lamps, and risk of cutaneous melanoma. BMJ 1988;297:647–50.
14. Walter SD, Marrett LD, From L, Hertzman C, Shannon HS, Roy P. The association of cutaneous malignant melanoma with use of sunbeds and sunlamps. Am J Epidemiol 1990;131:232–43.
15. Autier P, Dore J-F, Lejeune F, et al. Cutaneous malignant melanoma and exposure to sunlamps and sunbeds: an EORTC multicentre case-control study in Belgium, France and Germany. Int J Cancer 1994;58:809–13.
16. Westerdahl J, Olsson H, Masback A, et al. Use of sunbeds or sunlamps and malignant melanoma in Southern Sweden. Am J Epidemiol 1994;140:691–9.
17. Westerdahl J, Ingvar C, Masback A, Jonsson N, Olsson H. Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer 2000;82:1593–9.
18. Chen Y-T, Dubrow R, Zheng T, Barnhill RL, Fine J, Berwick M. Sunlamp use and risk of cutaneous malignant melanoma: a population-based, case-control study in Connecticut USA. Int J Epidemiol 1998;27:758–65.
19. Veierod MB, Weiderpass E, Thorn M, et al. A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst 2003;95:1530–8.
20. Stern RS, Nichols KT, Vakeva LH; for the PUVA Follow-up Study. Malignant melanoma in patients treated for psoriasis with methoxsalen (psoralen) and ultraviolet A radiation (PUVA). N Engl J Med 1997;336: 1041–5.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
22. Petitti DB. Meta-analysis, decision analysis, and cost effectiveness analysis: methods for quantitative medicine. New York: Oxford University Press; 1994.
23. Young AR, Potten CS, Nikaido O, et al. Human melanocytes and keratinocytes exposed to UVB or UVA *in vivo* show comparable levels of thymine dimers. J Invest Dermatol 1998;111:936–40.
24. Fuchs J, Huflejt, Rothfuss LM, Wilson DS, Carcamo G, Packer L. Acute effects of near ultraviolet and visible light on the cutaneous antioxidant system. Photochem Photobiol 1989;50:739–44.
25. Fuchs J, Huflejt ME, Rothfuss LM, Wilson DS, Carcamo G, Packer L. Impairment of enzymatic and nonenzymatic antioxidants in skin by UVB irradiation. J Invest Dermatol 1989;93:769–73.
26. Sander CS, Hamm F, Elsner P, Thiele JJ. Oxidative stress in malignant melanoma and non-melanoma skin cancer. Br J Dermatol 2003;148: 913–22.
27. Sander CS, Chang H, Hamm F, Elsner P, Thiele JJ. Role of oxidative stress and the antioxidant network in cutaneous carcinogenesis. Int J Dermatol 2004;43:326–35.
28. Nelemans PJ, Rampen FHJ, Ruiter DJ, Verbeek ALM. An addition to the controversy on sunlight exposure and melanoma risk. J Clin Epidemiol 1995;48:1331–42.

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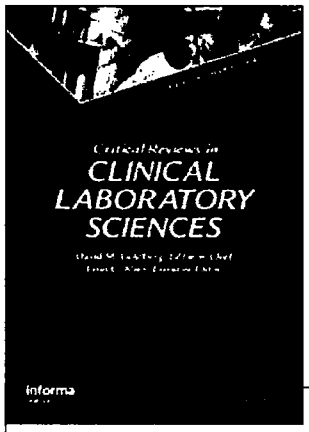

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Molecular and Cellular Effects of Ultraviolet Light-Induced Genotoxicity

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ABSTRACT: Exposure to the solar ultraviolet spectrum that penetrates the Earth's stratosphere (UVA and UVB) causes cellular DNA damage within skin cells. This damage is elicited directly through absorption of energy (UVB), and indirectly through intermediates such as sensitizer radicals and reactive oxygen species (UVA). DNA damage is detected as strand breaks or as base lesions, the most common lesions being 8-hydroxydeoxyguanosine (8OHdG) from UVA exposure and cyclobutane pyrimidine dimers from UVB exposure. The presence of these products in the genome may cause misreading and misreplication. Cells are protected by free radical scavengers that remove potentially mutagenic radical intermediates. In addition, the glutathione-*S*-transferase family can catalyze the removal of epoxides and peroxides. An extensive repair capacity exists for removing (1) strand breaks, (2) small base modifications (8OHdG), and (3) bulky lesions (cyclobutane pyrimidine dimers). UV also stimulates the cell to produce early response genes that activate a cascade of signaling molecules (e.g., protein kinases) and protective enzymes (e.g., haem oxygenase). The cell cycle is restricted via p53-dependent and -independent pathways to facilitate repair processes prior to replication and division. Failure to rescue the cell from replication block will ultimately lead to cell death, and apoptosis may be induced. The implications for UV-induced genotoxicity in disease are considered.

KEY WORDS: DNA damage, UVA, UVB, repair, gene induction, cancer.

I. INTRODUCTION

The organ primarily affected by ultraviolet radiation is the skin. There has been an upsurge of interest in the effects of ultraviolet radiation on skin

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in particular, in recent years, fueled by reports of a reduction in protection of the Earth's surface due to ozone depletion. Epidemiological evidence points strongly toward a link between exposure to sunlight and skin cancers, particularly malignant melanomas, basal cell carcinomas, and squamous cell carcinomas.

The ultraviolet component of sunlight incident on the Earth's surface can be broadly defined as the ultraviolet B (UVB) component, lying between 280 nm and 315 nm, and ultraviolet A (UVA) in the range 315 to 400 nm. UVC (100 to 280 nm) is completely absorbed by the Earth's atmosphere and therefore is unlikely to have a major pathophysiological effect. While all biological macromolecules (DNA, lipid, protein) can absorb UVB energy, this review is restricted to the effects of UV radiation on DNA only. As there is an absolute requirement for the absorption of ultraviolet energy to cause molecular damage, the absorption spectrum of a particular biomolecule governs the nature of the damage induced. DNA absorbs strongly in the UVB region; however, it is only a weak chromophore in the UVA region. Instead, other organic molecules, referred to as photosensitizers, absorb photons of UVA energy and may subsequently transfer this energy via oxygen or via an endogenous radical to other biomolecules.

This section reviews the genotoxicity of ultraviolet light, defining molecular changes induced and methods for their measurement in relation to the functions of DNA in the transfer and expression of genetic information. The effects of UV-DNA damage on repair and protective systems within cells are described, as well as the activity of these systems in disease.

II. MECHANISMS OF UV-INDUCED DAMAGE

The majority of early work investigating the effects of UV has been carried out using isolated DNA. However, these findings are supported by more recent studies in cellular systems such as *E. coli* and fibroblasts. Commonly, DNA-damaging agents induce several genotoxic lesions in DNA and these include strand breaks, either double or single due to deoxyribose degradation or repair, base deletion, or base modification. It is convenient to consider UVB as a direct inducer of DNA damage, whereas UVA exerts its genotoxic effect indirectly, most likely through sensitizer radicals or reactive oxygen species (ROS). These are considered in turn.

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A. Direct Effects — UVB

DNA is the most prominent cellular chromophore for the absorption of UVB.[1] The absorption of energy causes the excitation of a single electron to a higher, less stable, energy level. This reactive intermediate can then degrade or react readily with a variety of biomolecules. While the photochemistry of DNA within cells and organs is more complex, it is well established that three major base modifications are induced directly due to photons from UVB. These are (1) cyclobutane-type pyrimidine dimers, (2) the (6–4) photoproduct, (3) the corresponding Dewar isomer,[2] and (4) thymine glycols. Pyrimidine dimers are the most prevalent (5 to 10 times more frequent than the photoproduct or Dewar isomer). These can exist as either cytosine-cytosine, thymine-thymine, or mixed dimers depending on the wavelength and irradiation conditions.[3] These direct mechanisms of UVB action are well supported by the observation that the absorption spectra for cytosine and thymidine correlate with the action spectrum for dimer formation.[4] However, cytosine in cyclobutane pyrimidine dimers rapidly deaminates to form uracil.[5] There is a degree of sequence specificity in the induction of the (6–4) photoproduct; cytosines 5′ upstream of adjacent pyrimidines are frequent targets for the induction of this lesion. Purine dimers are not reported following UVB irradiation.

UVB can also cause limited numbers of strand breaks, their rate increasing with increasing wavelength, and in addition, single base lesions have also been detected. These are primarily the ring-saturated thymines (5,6-dihydrothymidine) also known as thymine glycols.[6]

There is also evidence for the induction of 8-OHdG following UVB exposure.[7] Primary murine keratinocytes generated a dose-dependent increase in 8-OHdG over the dose range 4 to 750 mJ/cm^2 UVB.

Because DNA is entwined within a core of structural proteins, the histone proteins, it is also common to find DNA-protein crosslinks (DPCs), mostly involving cysteine residues.[8] The frequency of DPCs is an order of magnitude lower for UVB than for an equivalent energy dose of UVA.

B. Indirect Damage

UVA radiation constitutes more than 90% of other radiation reaching the Earth's surface, and historically UVA radiation was considered harmless. However, the genotoxicity of UVA has been firmly established from *in vitro* experiments. Owing to the low absorptivity of DNA between 315

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nm and 400 nm, the damage induced is largely due to the absorption of UVA photons by endogenous non-DNA chromophores. This energy is indirectly transferred to DNA via reactive oxygen intermediates or radicals generated on the absorbing chromophore. Within mammalian cells, these chromophores (photosensitizers) include riboflavin, porphyrins, quinones, and reduced nicotinamide co-factors. Bioactive drugs such as the tetracyclines may also act as photosensitizers.

Initially, following the absorption of UVA photons, an electron is transferred to an orbital of higher energy, either maintaining the same direction of spin to form the unstable singlet species ($t_{1/2}$ psecs-nsecs), or undergoing a spin conversion to the triplet state, ^{3}Sens*, which has a $t_{1/2}$ ~ μs. This longer-lived species has a greater propensity to react with other molecules and can cause direct modification of DNA via a type I reaction.[9]

^{3}Sens* + ^{1}substrate ⇒ ^{1}Sens + ^{3}substrate* ; energy transfer reaction
^{3}Sens* + substrate ⇒ Sens$^{+\cdot}$ + substrate$^{-\cdot}$; one electron transfer
^{3}Sens* + substrate ⇒ adduct ; addition reaction

These reactions contrast with the type II reactions that are oxygen-mediated reactions, see equations below, producing ROS such as singlet oxygen $^1O_2$ or superoxide anion, $O_2^{-\cdot}$.

^{3}Sens + $^3O_2$ ⇒ ^{1}sens + $^1O_2$
^{3}Sens + $^3O_2$ ⇒ sens$^{+\cdot}$ + $O_2^{-\cdot}$.

Because the reactions of UVA-generated ROS with DNA are synonymous with other endogenously generated sources of reactive oxygen species, it is much more difficult to discern the frequency of UVA-induced damage *in vivo*.

An inverse relationship in the pattern of reaction products following UVA damage is seen in DNA when compared with UVB damage. UVA excited photosensitizers promote the formation of three major base lesions, in addition to a much lower level of base loss.[2] These are (1) 8-hydroxydeoxyguanosine (8-OHdG) — singlet oxygen appears to mediate the formation of 8-OHdG from guanosine.[10] 8-OHdG is reported to be induced by UVA at a 10-fold higher rate than strand breaks (SB) in mammalian cells;[11] (2) hydroxyhydroperoxides — using thymine in solution, in the presence of menadione as a photosensitizer, UVA indirectly generates the radical cation of thymine that, in the presence of oxygen, gives rise to isomeric hydroxy-hydroperoxides;[12] (3) Pyrimidine photoproducts; the

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formation of pyrimidine photoproducts has been reported following absorption of UVA photons, but a sixfold greater energy input is required at 365 nm compared with 254 nm to induce the same order of magnitude of lesions.[13] However, the 6–4 photoproducts are not observed,[14,15] possibly because the latter arise exclusively from the singlet state induced by direct energy absorption rather than via a triplet state formed from energy transfer.

Peak *et al.*[16] have demonstrated the induction of DNA SSBs in human cells *in vitro*, throughout the visible region; UVA irradiation in the presence of D_2O enhances SSBs implicating singlet oxygen, because the decay of singlet oxygen is slowed down by an order of magnitude in D_2O compared with H_2O. Furthermore, studies using supercoiled plasmid DNA[17] exposed to singlet oxygen have demonstrated that $^1O_2$ has the capacity to break covalent bonds within DNA. In addition, the generation of the superoxide anion is purported to play an indirect role in the generation of SSBs following dismutation to hydrogen peroxide, H_2O_2, and the site-specific generation of the hydroxyl radical, $^{\cdot}OH$, on the DNA backbone at localized metal ion binding sites.[18] However, the H_2O_2 yield calculated after exposure of epithelial cells in culture to UVA radiation is not sufficient to account for the majority of strand breaks, favoring singlet oxygen as the genotoxic agent.[18a]

The requirement for oxygen in the UVA-mediated induction of DPCs is elegantly demonstrated in studies by Gantt *et al.*,[19] using human cells irradiated at 405 nm in a hypoxic environment that reduces DPC formation. In contrast, incubation in D_2O enhances DPC lesions, by lengthening the half-life of singlet oxygen.

More recently, the formation of glyoxal from DNA treated with reactive oxygen species has been described.[20] The yield of glyoxal is 17-fold greater than 8-OHdG and is likely to arise from deoxyribose degradation during strand breakage. Glyoxal forms adducts at guanine sites, and we predict that such lesions may be found after UVA irradiation.

III. ANALYSIS OF UV-INDUCED DNA MODIFICATION

Despite strong epidemiological evidence, much of the identification of UV as a genotoxic agent relevant to disease has only been possible by the development and refinement of techniques for the accurate identification and determination of lesions. These techniques can be broadly classified as those that measure (1) strand breaks, (2) specific sequences of damage, and (3) specific base lesions.

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A. Strand Break Analysis

DNA remains as a tightly coiled α helical structure in its intact form. However, strand breakage by agents such as UVR reduces the intra- and inter-chain stabilization and is accompanied by a degree of unwinding. This phenomenon is applied in the fluorescence-activated DNA unwinding assay (FADU assay),[21] DNA sedimentation analysis,[22] and also the single cell gel electrophoresis or comet assay.[23] These techniques examine nonextracted DNA, and depend on the binding of a fluorescent dye to DNA for detection; however, the latter is exquisitely more sensitive, requiring 50 comets per analysis. Using the comet assay to study laser-induced UV-B DNA damage, De With *et al.*[24] were able to detect DNA damage in human lymphocytes after a single laser pulse dose of just 12 mJ. In a study of the sensitivity of pigmented cells to UVB-induced strand breakage, using the comet assay, Noz *et al.*[25] showed that common melanocytic nevi have a 30% lower induction of strand breaks compared with foreskin melanocytes. Control experiments with X-ray irradiation indicated that the differences in strand breakage could not be accounted for by intrinsic nuclear characteristics.

However, any study of strand breaks induced by UV is complicated by the difficulty of measuring alkali labile sites, and more critically by excision repair processes,[26] which introduce DNA strand breaks during the removal of bulky base lesions (see Section IV). Furthermore, UV is widely reported to initiate apoptosis (Section V). The comet assay also detects apoptotic cells, where strand breaks are induced by endogenous endonuclease, rather than UV-mediated ROS or deposition of energy.

B. Specific Protein Recognition of Base Damage in DNA

Native DNA is weakly immunogenic, however, after denaturation by UV radiation it can elicit a significantly improved antigenic response. This principle has been exploited in the production of antisera that recognize thymine dimers. Such immunological reagents are powerful tools in the determination of DNA damage induced by UV, which can be used on fixed tissue sections[27] and in whole cell FACS analysis.[28]

Immunological reagents are powerful sequence-specific reagents, as demonstrated by Herbert *et al.*,[29] who described the production of a polyclonal antiserum (that is referred to as 529), the major antigenic epitope of which was identified as a cyclobutane thymidine dimer with an adjacent 3′ or 5′ thymidine. More recently, this antiserum has been used in

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FACS analysis for the determination of DNA damage induced in cultured fibroblasts by UVB (see Figure 1). We have observed a linear increase in 529 binding with increasing UVB dose, where cell viability was only significantly reduced after a dose of 50 mJ/cm^2. By using double staining techniques it is possible to quantify cyclobutane pyrimidine dimer formation induced by UV during different phases of the cell cycle.[30] Using epidermal cells from hairless mice irradiated *in vivo* with UVB, a linear fluorescence/dose relationship was observed.

Mizuno *et al.*[27] describe the production of a monoclonal antibody, TDM–1, which recognizes thymidine dimers and whose reactivity is abrogated following treatment of DNA antigen with photolyase . The antibody was subsequently applied to the measurement of lesions in DNA isolated from irradiated mammalian cells. Hori *et al.*[31] used polyclonal antibodies to study DNA extracted from human skin tumors and controls. These workers observed immunoprecipitates indicative of unrepaired cyclobutane-type pyrimidine dimers in individuals with squamous cell carcinoma and with facial actinic keratosis. An aberration in repair may contribute to misreading and misreplication (Section VI).

More recently, immunocytochemical techniques have been applied in human mononuclear cells, to compare cyclobutane-type pyrimidine dimers, Dewar isomers and 6–4-photoproduct production induced by sunlight compared with UVB alone, generated by a broad spectrum UVB sun lamp.[32] This confirmed that the majority of (6–4) photoproducts are converted to Dewar valence isomers by the UVA component in sunlight, and implies that (6–4) photoproducts are unlikely to contribute directly to sunlight-induced carcinogenesis.

In order to evaluate the frequency of photoproducts formed *in vivo* in UV-irradiated human skin, Chadwick *et al.*[33] used monoclonal antibodies to probe methanol-fixed paraffin sections. The staining of thymine dimers and 6–4 photoproducts in nuclei of epidermal cells showed a minimal change with depth (2.5% loss per cell layer) following 300 nm UVR, confirming the effective penetration and damage induction by UVB in human skin.

The generation of 8-OHdG is widely reported following exposure of DNA to ROS-generating systems.[10,34] However, a recent immunohistochemical investigation into chronic UVB exposure (10 MED 3 times/week for 2 weeks) of the epidermal cells of hairless mice showed a 6-fold increase in nuclear 8-OHdG. This is postulated to arise indirectly from the effects of UVB-inducing lipid peroxidation and inflammation, thereby producing ROS involved in modifying DNA bases.[35]

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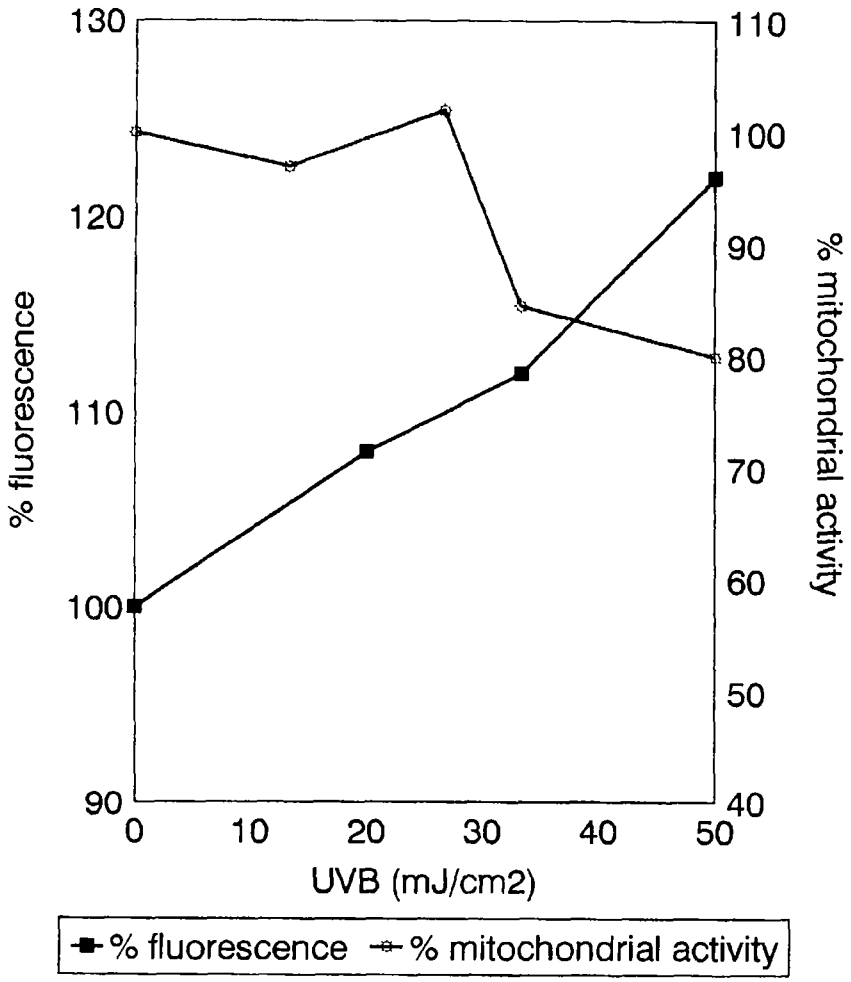

FIGURE 1. RHT cells were exposed to increasing doses of UVB, and after 1 h DNA binding of 529 was determined using a FACscan flow cytometer. In parallel, cell viability was determined using the MTT assay to measure mitochondrial activity. Results are expressed as percent change in fluorescence from control.

In addition to laboratory-generated reagents, there are several DNA binding proteins which recognize UV-induced base lesions that may play a physiological role in marking DNA for repair processes. These proteins can be utilized in assays for UV-DNA damage (Section V.B).

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The recognition of UV-DNA lesions can also be harnessed as a means of detection in the ligation-mediated polymerase chain reaction (LMPCR). This technique can be applied wherever a lesion can be converted into a strand break with a 5′ phosphate group. For example, cyclobutane dimers can be mapped by cutting DNA at the lesion with a dimer-specific endonuclease such as T4 endonuclease V, followed by *E. coli* photolyase to generate ligatable breaks.[36] The alkali sensitivity of (6–4) photoproducts and Dewar isomers can be utilized to generate breaks. Following ligation of an oligonucleotide primer onto the 5′ end of broken DNA, the fragments of a genomic sequence ladder are amplified by PCR.

Tornaletti and Pfeiffer[36] have applied LMPCR to examine the distribution of CPDs and 6–4 photoproducts along the promoter sequences of c-*jun*, proliferating nuclear antigen (PCNA) and c-fos, and described photofootprints at common transcription factor binding sites, including AP-1 and SP-1.

C. Chromatographic Analysis of Photoproducts

Analytical chromatography by HPLC and GC-MS have been used in the identification of UV photoproducts. Franklin *et al.*[37] described the development of an HPLC assay for the separation and quantitation of cyclobutane pyrimidine dimers and (6–4) photoproducts. This has allowed the accurate determination of photoproduct mutagenic potential[38,39] and frequency, where a 10-fold greater yield of cyclobutane pyrimidine dimers is reported relative to (6–4) photoproduct after UVB exposure.[40]

UV-modified bases excised from laser-irradiated DNA in the presence of acetone and acetophenone as photosensitizers have been quantified by HPLC.[41] The level of 8-oxodG was 50% that of pyrimidine dimers using acetone as a sensitizer, whereas after direct excitation of DNA at 254 nm, the yield of 8-oxodG was only 0.8% that of pyrimidine dimers, confirming that 8-oxodG only represents a significant modification following UVA irradiation. The production of 8-oxodG was not increased in D_2O or was it inhibited by SOD and catalase. The authors suggest that direct electron transfer reaction from sensitizer radicals mediated 8-oxodG formation. The formation and detection of oxidized base products after UV irradiation of DNA using GC-MS has been described.[42] Recently, we have described the development of a highly specific and selective assay, using GC-MS for the detection and quantification of cis-syn cyclobeta dithymine (cyclobutane thymine dimers).[43] The absolute determination of lesions will contribute to

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our understanding of the relationship between base lesion and disease development (Section VI).

IV. CELLULAR PROTECTION AGAINST UV-DNA DAMAGE

Maintaining the integrity of DNA is crucial for accurate replication, transcription, and cell survival; therefore, several mechanisms of protection have evolved. In healthy eukaryotic cells, the consequences of UV irradiation on the induction of damage to DNA are minimized by a combination of antioxidant defence systems, detoxification, and repair systems.

A. Antioxidant Defense

The antioxidant repertoire of eukaryotic cells ranges from enzymes that catalyze the removal of specific radical species to low-molecular-weight polypeptides with a non-specific scavenging capacity. Table 1 summarizes the properties and distribution of antioxidants.

The major antioxidant enzymes are present throughout the dermal layers; however, their protective efficacy against UV-induced damage is only poorly understood. Nevertheless, the intranuclear accumulation of these compounds is important for any protective effect to be observed in cellular systems.

An early study on DNA damage examined the effects of addition of exogenous catalase to UVA-irradiated human fibroblasts.[18] These workers demonstrated that alkali-labile sites/single-strand breaks induced by UVA could be virtually eliminated in the presence of catalase, while cytotoxicity was unaffected. This contrasts with the findings of Epe *et al.*,[41] who did not find any protection afforded by catalase or SOD against UVA (333 nm)-induced FPG-protein-sensitive sites in bacteriophage PM2 DNA using acetone as sensitizer (see Section IV). However, these workers did observe protection by azide. This supports the role of a purine radical and points to involvement of different radical intermediates in generating base modifications compared with strand breaks.

The protection afforded by low-molecular-weight scavengers has been investigated. Fischer-Nielsen *et al.*[44] examined the effects of glutathione, ascorbate, and 5-aminosalicylate on 8-oxodG induced by UV (240 to 580 nm) in calf thymus DNA. While all molecules exhibited photoprotective

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TABLE 1
Antioxidant Protection Against DNA Damage Induced by UV Irradiation *In Vitro*

Antioxidant	Activity	UV protection	Ref.
SOD	$O_2^- + O_2^- + 2H^+ \Rightarrow H_2O_2 + O_2$	No protection	41
Catalase	$2H_2O_2 \Rightarrow 2H_2O + O_2$	Protects against UVA strand breaks	18
		No protection	41
Vitamin C	$O_2^- + OH. +$ ascorbate $\Rightarrow$ semi-dehydroascorbate	Protects against UVA-induced 8OHdG	44
		Protects against UVB-induced 8OHdG	7
Vitamin E	Acts as a chain terminator for lipid peroxy radicals	Trolox protects against UVB-induced 8OHdG	7
Carotenoids	Scavenges singlet oxygen	Inhibits epidermal damage	48
GSH	Cofactor for GSH peroxidase and scavenges OH·	Protects against UVA-induced 8OHdG	44
Flavonoids		Quenches 8OHdG induced by UVA	49

activity by reducing levels of 8-OHdG, the presence of exogenous iron promoted 8-OHdG formation. Subsequently, these workers confirmed that preincubation with both ascorbate and 5-aminosalicylate diminished 8-OHdG formation in V79 Chinese hamster ovary cells, confirming that both compounds can act as intranuclear antioxidants.[45]

Despite the strong evidence supporting a direct action for UVB on induction of DNA damage, there are studies that have demonstrated a favorable change in antioxidant defense status following UVB exposure. In a mouse skin model of acute UVB exposure (300 mJ/cm^2), Fuchs *et al.*[46] observed an increase in glutathione reductase and catalase activity, while SOD and GSHPx were unaffected. Furthermore, an inhibitory effect of vitamin C, selenite, and trolox on 8-oxodG formation was observed in mouse keratinocytes preincubated with antioxidants that had been irradiated with 500 mJ/cm^2 UVB.[7]

The carotenoids represent a class of small molecules that have a photoprotective function in the protection of plants from UV damage.

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However, they are becoming of increasing interest in skin protection. The primary species scavenged by β carotene is singlet oxygen, which is believed to be generated close to the surface of the skin, and exogenous carotenes have been shown to inhibit epidermal damage and tumor formation induced by UV in mouse models.[47,48] An investigation into the effects of soybean isoflavone genistein on 8-OHdG induced by UV demonstrated that this flavonoid was a powerful quenching agent. Moreover, it was less effective against Fenton-induced 8-OHdG formation, suggesting a different mechanism for adduct formation by UV light.[49]

However, there remains no consensus as to the efficacy of scavengers to prevent the pathologies described in Section VI.

B. Detoxification

The glutathione-*s*-transferase (GST) multigene family represents a major group of detoxification enzymes found in the endoplasmic reticulum, which are particularly concentrated in the liver. It is likely that the level of expression of particular isoforms is critical in determining the toxicity of cells to any given insult. GST expression is governed by both transcriptional and posttranscriptional control, and many isozymes are induced via the antioxidant-responsive element, the xenobiotic-responsive element or the glucocorticoid enhancer element. ROS, as generated during UVA irradiation, induce GSTs that detoxify toxic carbonyl, epoxide, and peroxide-containing metabolites produced by the effects of ROS.

In humans, there are marked differences in isozyme expression. In addition, 50% of the population carry deletions in GSTM1, while 16% have deletion of GSTT1. These enzymes catalyze the conjugation of glutathione to carcinogenic intermediates, and epidemiological studies have associated the null genotype with an increased risk of cancer. In a recent report, Kerb *et al.* [50] have investigated whether genetic variation at the GST loci GST T1 and GST M1 influences UVB sensitivity in healthy individuals. After controlling for skin type, homozygous carriers of GST T1 deletion presented with the most intensive inflammatory reaction post-UVB irradiation. The lack of GST M1 alleles were also common in the induction of an intense inflammatory response, while a combination of null phenotypes at both loci was associated with the most intense inflammatory reactions. These findings implicate a heritable GST deficiency as a risk for UV sensitivity and potentially for cancer induction. The mechanisms by which GSTs influence tumor number and accrual remain speculative, but are likely to involve repair processes.

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C. DNA Repair of UV-Induced Lesions

The genetic stability of any cell requires not only the regulated mechanism of DNA replication, but also efficient repair mechanisms for both spontaneous and induced DNA lesions. Failure of such mechanisms can lead to various clinical manifestations such as cancer and degenerative disorders.[51] The importance of the repair mechanisms in relation to UV-induced pathogenesis has been well highlighted over the years.[52-55]

Intrinsic and extrinsic agents causing DNA lesions can be removed primarily by three repair mechanisms: direct reversal, base excision, and nucleotide excision. These repair mechanisms are well understood in unicellular organisms, and in recent years much more has become understood in the mammalian system. The parallel nature of these mechanisms between both systems is discussed further.

1. Direct Reversal

Direct reversal of DNA damage involves mechanisms that 'undo' the damage. Examples of such mechanisms include: enzymatic photoreactivation, repair of spore photoproduct, repair of O^6-guanine and O^4-thymine alkylations, and finally the repair of single-strand breaks by direct rejoining. These have been observed in prokaryotic and/or eukaryotic systems and are shown in Table 2.

The mechanism of alkyl transfer is of great importance in humans. To date there are no known diseases associated with O^6-methylguanine DNA methyltransferase (MGMT) dysfunction; however, O^6-guanine and O^4-thymine adducts are mutagenic lesions and are therefore potentially tumorigenic.[67] The human MGMT is a monomeric protein (M_r = 21,700) and has the capacity to transfer larger alkyl groups such as ethyl and butyl on the O^6 position of guanine. In *E. coli* there are two types of MGMT referred to as Ogt and Ada. The former is similar in nature to the human MGMT, while the latter functions not only in the methyl transfer from O^6-methylguanine, but from phosphotriesters as well. Ada also appears to be involved in the positive regulation of 'alkylation-defense' genes.

2. Base Excision Repair

The mechanism of base-excision repair eliminates non-bulky lesions, that is, those that do not distort the actual helical structure of DNA.[68]

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TABLE 2
Examples of DNA Repair by Direct Reversal Observed in Both Eukaryotic and/or Prokaryotic Systems

Direct reversal example	Enzyme	Mechanism of repair	Ref.
Photoreactivation	Cyclobutane-pyrimidine dimer (Pyr<>Pyr) Photolyase: present in many biological systems but lacking in certain placental animals and microorganisms; human homologs identified but lacking photolyase activity	A light-dependent mechanism involving the enzymatic monomerization of *cis-syn* pyrimidine dimers (*tran-syn* cyclobutyl dimers are also monomerized but with less efficiency)	56–60
	6–4 Photoproduct Photolyase: present in *Drosophila*: silkworm, frog, and rattlesnake; human homologs identified but lacking photolyase activity	A light initiated reaction involving the enzymatic monomerization of the pyrimidine dimers as well as the reversal of the substituent migration (i.e., the return of the substituent from C^6 position back to the C^4 position of adjacent dimers	61, 62
	Blue-light photoreceptor: present in plants and many organisms; both human photolyase homologs appear to possess FAD and pterin cofactor and therefore may have functional homology to plant blue-light photoreceptors	Proteins believed to mediate DNA repair and/or blue-light-regulated developmental processes in plants through a photoinduced electron transfer reaction	
Spore photoproduct (SP)	SP lyase, present in *Bacillus subtilis* spores exposed to 254 nm UV	A light-dependent mechanism involving the repair of 5-thyminyl–5,6-dihydrothymine adducts	65
O^6-guanine and O^4-thymine alkylations	O^6-methylguanine DNA methyltransferase (MGMT), a suicide enzyme found in all species	An irreversible mechanism involving the transfer of the methyl group from O^6- and O^4-DNA alkylations to a cysteine residue in the enzyme	66, 67
Direct rejoining of single-strand breaks	DNA ligase	A mechanism involving the enzymatic rejoining of intact and undamaged single-strand breaks	

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Alkylating agents and ionizing radiation are typical examples of insults that can generate such adducts. The excision of these modified/damaged bases involves the action of a specific class of enzyme, the DNA glycosylases. These catalyse the hydrolysis of the *N*-glycosylic bond that links the adduct to the deoxyribose-phosphate backbone. The resulting apurine or apyrimidine (AP) deoxyribose or AP site is processed further by cleavage of the phosphodiester bond immediately 3′ to this site. Only some DNA glycosylases have both hydrolase and β-lyase activity. To date a number of DNA glycosylases have been characterized and reviewed.[69] Some of these DNA glycosylases important in the repair of both direct and indirect UV damage are summarized in Table 3.

AP hydrolases or the 'true' AP endonuclease eliminate AP sites generated by glycosylase or spontaneous base loss and can also trim the 3′ sites of strand breaks generated by ROS or ionizing radiation. In *E. coli* there are two types of these hydrolases: exonuclease III and endonuclease IV. One human AP endonuclease (APE, HAP1, APEX, REF1) has been characterized and appears to have a high degree of sequence homology to exo. III.[85] The enzyme is a 36-kDa monomer and also appears to have the capacity to activate transcription factors Fos and Jun via the cysteine residue on the N-terminus of the enzyme.[86]

Following excision of the adduct, the gap is filled by the action of a DNA polymerase. Studies have yet to confirm whether this involves proliferating cell nuclear antigen (PCNA)-independent Polβ and/or PCNA-dependent Polδ and Polε.[87] Experiments using a purified nuclear extract from bovine testis indicate that perhaps Polβ is better suited to fill short gaps.[88] The poly (ADP-ribose) polymerase also appears to increase in activity during strand breaks and DNA nicks.[89] However, its precise contribution to DNA repair remains unclear.[90] The final stage of base excision repair involves the ligation of a nucleotide to its neighbor and thus sealing the DNA strand.

Recent work with Chinese hamster ovary extracts reveal that mammalian cells may repair AP sites via two distinct pathways. The first pathway is the single nucleotide gap-filling reaction, as described above, while the second pathway appears PCNA dependent and involves the removal of a short oligonucleotide containing the abasic site and approximately seven 3′ flanking nucleotides.[91]

3. Nucleotide Excision Repair

Perhaps the most important mechanism of DNA repair to UVB-induced damage involves the nucleotide excision repair system (Figure 2).[57]

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TABLE 3
Some Human DNA-Glycosylases Important in the Repair of Direct and Indirect UV-Induced Damage

Class of DNA damage	Example	Human glycosylase type	Human protein M_w	AP lyase activity	Other equivalents	Ref.
Oxidized purines	7,8-dihydro-8-oxoguanine (8OHdG)	8OHdG glycosylase (hOGG1)	39 kDa	Yes	*E. coli* FAPy (30.2 kDa)	70–76
					S. cerevisiae OGG1 (43 kDa) [8OHdG opposite C]	
					S. cerevisiae OGG2 (~37 kDa) [8OHdG opposite G]	
					Mus Musculus (mogg1)	
Oxidized pyrimidines	Thymine glycol	Thymine glycol glycosylase (hNTH1)	34.3 kDa	Yes	*E. coli* (endonulease III and VII)	77–80
					S. cerevisiae (NTG1)	
					S. pombe (nth)	
Pyrimidine dimers	Cyclobutane pyrimidine dimer	No known human equivalent	?	Yes	*E. coli* T4 endonuclease V	81, 82
					M. luteus (pdg)	
Uracil DNA	Uracil	Uracil DNA glycosylase (UNG1)	26 kDa	No	*E. coli* (UNG)	83, 84
					S. cerevisiae (UNG1)	

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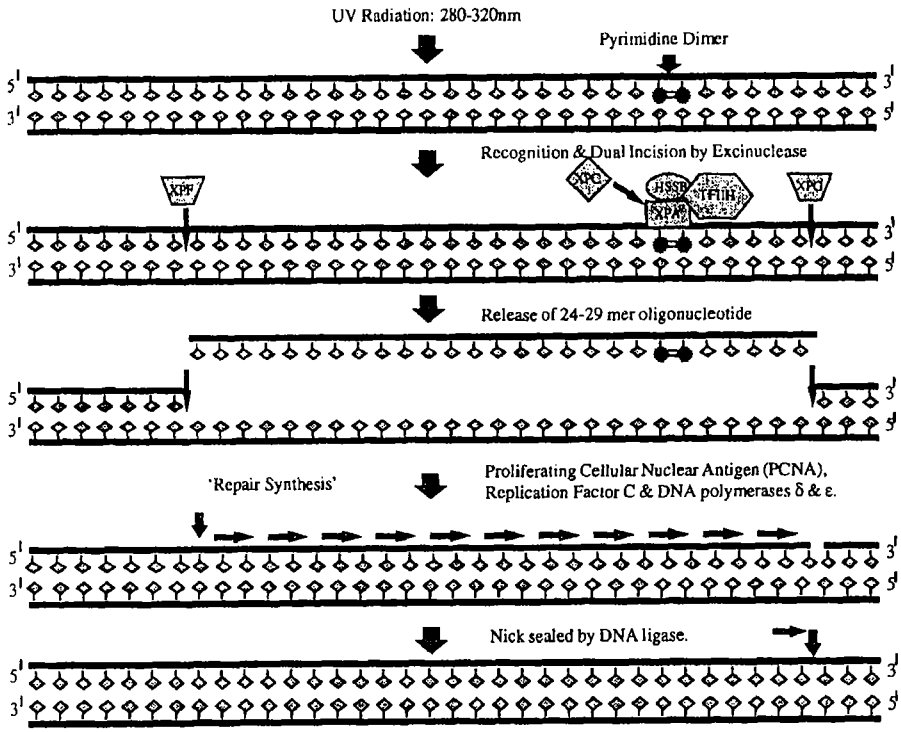

FIGURE 2. The pyrimidine dimer is recognized by the Xeroderma Pigmentosum (XP) complementation group, XPA. This polypeptide binds to the damage and allows entry of the HSSB* complex, which further recruits TFIIH* and XPF-ECC1* complex. The XPB and XPD components of TFIIH possess helicase properties that aid the ATP-dependent unwinding of DNA at the site of damage to allow for dual incision. XPG excises the DNA at the 5th phosphodiester 3′ to the adduct, while XPF excises approximately 20 bases 5′ the damage. The 24–29 oligonucleotide is released, and the resulting gap is filled by the action of proliferating cellular nuclear antigen (PCNA), replication factor C and DNA polymerases δ and ε. This repair synthesis begins at the 5′ end and works long to the 3′ end. The final 3′ nick is sealed by the action of a DNA ligase. (*Components of these excinuclease complexes have been detailed in Table 4.)

This mechanism allows the removal of bulky adducts, such as cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts. It is also important to note that lesions repaired by the direct reversal or base excision route can also be removed by nucleotide excision repair.[92] Recently, Reardon *et al.* (1997) demonstrated the removal of 8OHdG via this pathway.[93]

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This mechanism is principally similar to base excision repair; however, it involves the excision of an oligonucleotide containing the lesion as opposed to a single adduct. The dual incisions, either side of the lesion, are by a multisubunit ATP-dependent nuclease (excinuclease). In *E. coli* three subunits are required to make such incisions, whereas in humans 16 polypeptides are required. In both systems the excinuclease cuts the 5th phosphodiester bond 3′ to the lesion; however, at the 5′ end the position of the cut varies such that the excised oligomer generated is a 12–13mer in *E. coli* and a 24–29mer in humans. Components of the human excinuclease have been detailed in Table 4.[95–100]

Once the oligomer containing the lesion dissociates from DNA, repair synthesis resumes. This involves the action of PCNA, replication factor C

TABLE 4
16 Polypeptides Associated with the Human Exinuclease Involved in Nucleotide Excision Repair

Polypeptide	Protein (M_r)	Excinuclease component	Proposed activity in repair
1	XPA (p31)	XPA	Recognizes and binds to damage; allows entry of HSSB
2	p70	HSSB (RPA)	XPA-HSSB complex recruits TFIIH and XPF-ECC1 complex
3	p34		
4	p11		
5	XPB/ ERCC3 (p89)		XPB and XPD of TFIIH have helicase properties and thus aid the ATP-dependent unwinding of DNA at the damage site, allowing assess for dual incision; TFIIH plays a role in transcription-coupled repair
6	XPD/ ERCC2 (p80)		
7	Yeast TFB1 (p62)		
8	Yeast SSL1 (p44)	TFIIH	
9	Cdk7 (p41)		
10	CyclinH (p38)		
11	p34		
12	XPC (p125)	XPC	Helps stablize the precision complex
13	HHRA-D23B (p58)		
14	XPF/ERCC4 (p112)	XPF	5′-incision (endonuclease activity: hydrolase)
15	ERCC1 (p33)		
16	XPG/ ERCC5 (p160)	XPG	3′-incision (endonuclease activity: lyase)

Note: XP refers to the complementation groups of the human disease Xeroderma Pigmentosum and ERCC indicate the rodent excision repair cross complementing genes.

Adapted from Sancar.[94]

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(RPC), and DNA polymerases, namely, Polδ and Polε. After the excision gap is filled the sequence is sealed into place by the action of one of four DNA ligases.[101]

The rate of repair is influenced by many factors, one being the 'physical' nature of the adduct.[102] Using immunodetection, Young *et al.* followed the time course of repair and showed that both 6–4 photoproducts and CPDs are rapidly removed *in vivo* (within 2 h), the rate of removal being greater for the photoproducts.[103] Elegant studies by Henriksen *et al.* demonstrated the half-life of repair for UVA (365 nm)-induced lesions in lymphocytes is ~50 min compared with 100 min for UVB-induced damage.[104] However, between 30 and 60 min post-UVB irradiation, the levels of strand breaks increase due to nucleotide excision repair.

4. Transcription Repair Coupling

DNA repair rates are heterogeneous throughout the genome; active genes are repaired far more efficiently compared with inactive ones.[105-106] Ruven *et al.* described the selective removal of CPDs from transcriptionally active genes in the epidermis of hairless mice.[107] Similarly, lesions in the template strand within a transcribed sequence are repaired more rapidly than lesions in the nontranscribed (coding) strand.[108] Such heterogeneity and preferential strand-specific repair may be of relevance in evolutionary terms as selective adaptation promotes cell survival.

There are many factors that govern repair rates,[109] such as the configuration of chromatin structure, accessibility to damage, level of CpG methylation, and the interaction with the nuclear matrix. In humans there appears to be preferential repair genes transcribed by RNA polymerase II.[110] The relationship between DNA excision repair and repair of transcribed strands has been investigated in both prokaryotic and eukaryotic systems. In humans the mechanistic details remain unclear. However, studies in *E. coli* reveal that a 130-kDa protein referred to as transcription-repair coupling factor (TRCF or MFD) is involved in the displacement of the stalled RNA pol, and the promotion of repair via binding to the damage recognition subunit (UvrA) of the excision nuclease.[111] Although the precise details are not known in humans, two gene products, CSA/ERCC8 and CSB/ERCC6, appear to be involved in the recognition and promotion of repair of transcription-blocking lesions. Humans defective in either TRC proteins appear to recruit XPA and TFIIH to the lesion site such that following excision and repair synthesis transcription can resume.[112]

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5. Mitochondrial Repair in UV-Induced Lesions

Human mitochondrial (mt) DNA comprises less than 1% of the total cellular genome. mtDNA consists of 16,569 nucleotides and encodes 37 gene products (2 rRNA molecules, 22 tRNA molecules, and 13 proteins), all essential for electron transport and oxidative phosphorylation. During their normal function, mitochondria are subject to constant attack from oxy-radicals and reactive oxygen species. Such oxidative stress together with other features, for example, their relaxed codon-anticodon pairing rule, are believed to contribute to a number of clinical manifestations.[113] The accumulation of mitochondrial mutations and deletions have long since been linked with the development of malignancy, neurodegenerative disorders,[114-115] as well as the progression of aging.[116]

The increasing mutation rate of mtDNA is believed to be linked to inefficient repair mechanisms and the lack of protective structures. To date, several repairs have been detected in mitochondria, these are uracil DNA glycosylase,[117] AP endonuclease,[118] and mtDNA polymerase γ. These enzymes appear to be transported through the membrane and therefore are not encoded in mtDNA.[51] With respect to UV-induced lesions in mtDNA, studies have shown that mitochondria are unable to repair pyrimidine dimers generated by high-energy far UV.[119,120] However, adducts such as 8-hydroxy-deoxyguanine resulting from visible, near UV damage, are repaired with a high degree of efficiency,[121] suggesting that mitochondria are better equipped for coping with oxidative stress.

V. CELLULAR RESPONSE TO DNA DAMAGE

The mechanisms of intracellular signaling and regulation of cellular response after exposure to DNA-damaging agents have been investigated actively over the last decade. Briefly, the induction of mammalian gene function can be broadly classified as early response genes, which are transcriptionally activated within minutes (such as the protooncogenes c-*fos* and c-*jun*) and the secondary response genes. In the UV response, these include proteins binding to DNA damage sites,[122] those affecting cell proliferation (e.g., GADD genes[123]), proteins involved in signal transduction, including protein kinase C,[124] the antioxidants heme oxygenase, and Mn SOD, and the tumor suppressor gene p53. These are summarized in Table 5.

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TABLE 5
Summary of Genes Activated in Mammalian Cells by UVR

Gene	Activity/function	Ref.
fos	Component of transcription factor AP-1	125
jun	Component of transcription factor AP-1	136
DNA damage binding protein	Unknown, possible role in repair	125a
Collagenase	Degradation of extracellular matrix; associated with invasive tumors	126
ICAM–1	Adhesion of leukocytes to activated endothelium, during activation flattening + extravasation	127
PKC	Ubiquitous intracellular second messenger	124
Cyclo-oxygenase	Involved in prostaglandin metabolism, and production of lipid mediators	128
Phospholipase A2	Synthesis of lipid messengers	129
Metallothionene	Metal ion binding protein, radical scavenger	130
Heme oxygenase	Degradation of released heme	131
p53	Tumor suppressor gene; cell cycle checkpoint control	150
WAF–1	A cyclin-dependent kinase inhibitor protein involved in cell cycle regulation	132
GADD 45	Suppresses cell growth, inhibits DNA replication	123

A. AP-1 Transcription Factor Expression

UV radiation can stimulate cell signaling by protein kinases, leading to the phosphorylation and activation of c-*fos* and c-*jun*. The c-*jun* protooncogene encodes a protein that can form a heterodimer with c-*fos* to

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yield the transcription factor AP-1. This protein forms an initiation complex with RNA polymerase and therefore has a transactivating role for adjacent gene expression.

Attempts to elucidate the signal pathways involved in c-*jun* expression following UV irradiation have shown that activation of membrane-associated Src tyrosine kinase is the earliest step for induction of c-*jun* by UV, followed by the activation of the GTP binding protein, p21 Ras, and Raf-1.[133] However, contradictory data suggest that UV initially elicits a signal from DNA damage, subsequently transducing the signal to the cytoplasm and ultimately activating Raf-1 and MAP-2 kinases.[134] In contrast, Coffer *et al.*[135] have examined the propagation of the UVC-induced signal leading to gene expression. Following c-*jun* expression, EGF and insulin receptors are activated by phosphorylation within 5 min, and this subsequently activates p21ras. A failure of the cells to respond to growth factors postirradiation suggests that receptor-mediated events regulate the response of mammalian cells to UV. Preformed complexes of AP-1 with the c-*jun* promoter mediate production of the immediate response gene, c-*jun*, due to phosphorylation of c-*jun* promotor at serines 63 and 73.[136]

Similarly, the induction of c-*fos* by UV in mammalian cells appears to require a membrane event,[125] which is then translocated to the nucleus. An elegant study by Gillardon *et al.*[137] demonstrated that the topical application of c-*fos* anti-sense oligo-deoxynucleotides (ODN's) inhibited c-*fos* activation in UVB-irradiated epidermal cells. This was associated with a significant suppression of PCNA expression (normally involved in DNA repair synthesis and replication). This may represent a transcriptional mechanism linking DNA damage and DNA repair, as the promoter of the mouse PCNA gene has been identified as a sequence relating to the consensus sequence for the transcription factor AP-1.

AP-1 binds selectively to promoter and enhancer sequences regulating gene expression and this has been described for the human metallothionein gene, collagenase, hemeoxygenase, and c-*fos*. The secondary response to UV thus can be mediated through direct binding of early response gene products to cis-acting elements in promoter regions of the secondary response genes.

B. NF-KB Expression

The protein NF-KB, which comprises a heterodimer of p50 and p65, has been termed an oxidative stress-responsive transcription factor.

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Normally present in the cytoplasm in association with an inhibitory factor IKB, NFKB becomes activated by ROS, and translocated to the nucleus where transcriptional activation of immune and acute phase proteins occurs.

A recent report by Vile *et al.*[138] has confirmed that despite extensive DNA damage induced by all wavelengths of UV radiation, the signal for NF-KB activation is membrane dependent. Furthermore, inhibition of membrane damage by α-tocopherol and butylated hydroxytoluene prevented NF-KB activation.This confirms the observations of Simon *et al.*[139] In addition, UV irradiation induces cytokine production, including IL-1, IL-6, and βFGF. As the 5′ flanking region of IL-6 contains a consensus NF-KB binding sequence, Simon *et al.*[139] investigated the effects of UVB (290 to 320 nm) on NF-KB-like binding activity in a human epidermal cancer cell line. These workers demonstrated that a sublethal dose of UVB leads to an increase in NF-KB binding independent of DNA damage and possibly acting via a membrane signaling pathway. The subsequent increase in cytokine release, which acts in an autocrine manner, results in gene transcription and mutation fixation.

Rho B is an immediate early response gene inducible by growth factors and UVB.[140] This GTP binding protein could rapidly control adaptive cellular responses by GTP hydrolysis. A putative scheme for control of the early responses is shown in Figure 3.

C. DNA Damage Recognition Proteins

The induction of novel proteins in response to DNA damage has been reported following radiation. While their functions are not well understood, it is postulated that they may serve a role in damage recognition and repair processes. These can be detected in UV-irradiated DNA by electrophoretic mobility shift assays, as proteins that reduce the migration of restricted DNA. Using the band shift assay, Vaisman and Chaney[122] have identified a nuclear protein extract from human carcinoma cell lines that selectively bind to UV-damaged dsDNA. Expression of this protein was found to be inhibited by actinomycin and cycloheximide, suggesting that induction of UV-DNA damage recognition protein requires *de novo* RNA and protein synthesis. This work supports earlier observations by Chu and Chang,[141] and Reardon *et al.*[142] Wakasugi *et al.*[143] have examined nuclear and cytoplasmic proteins from UV-treated HeLa cells that bind selectively to UV-damaged DNA. They have identified a 40-kDa polypeptide on

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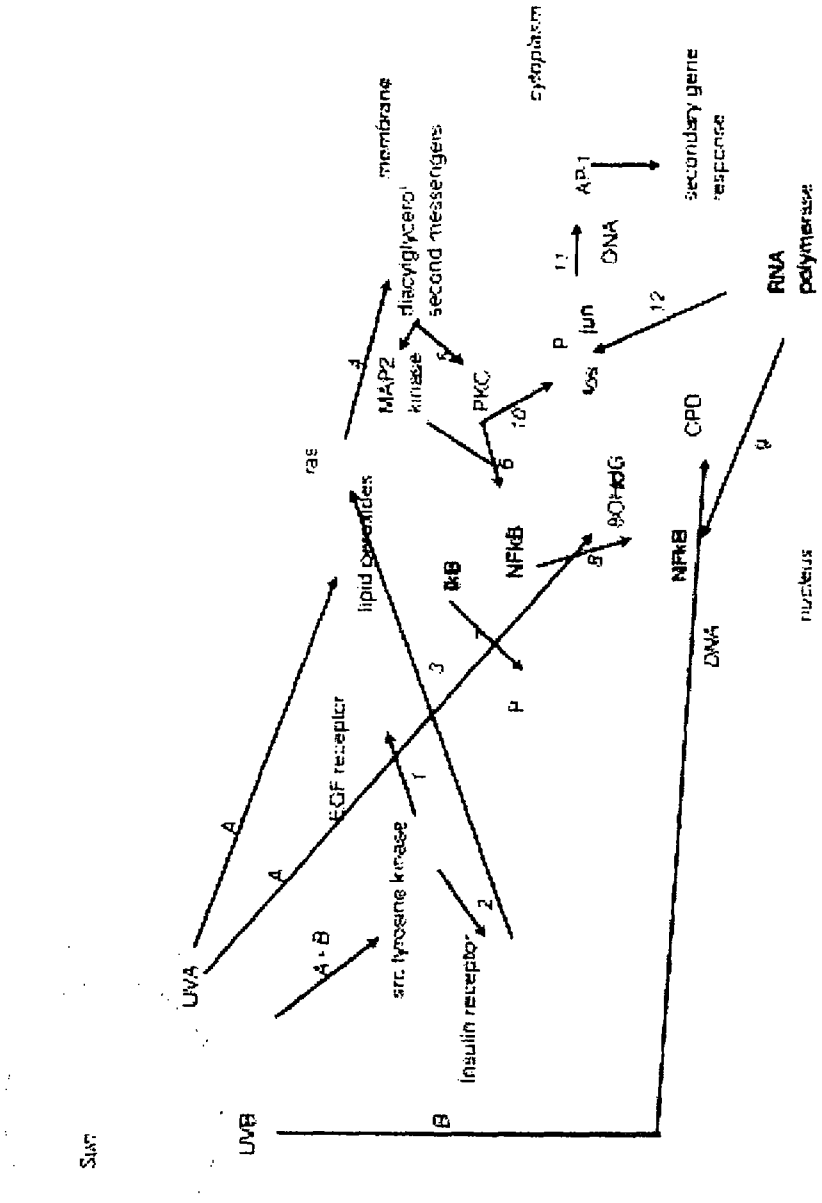

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FIGURE 3. A schematic illustration of the subcellular processes involved in UV-induced gene expression. (A) UVA radiation induces membrane lipid peroxidation, and 8-OHdG formation in DNA. (B) UVB radiation induces bulky DNA adducts, for example, CPD and in combination with UVA (A + B) mediates tyrosine kinase activation, which catalyzes phosphorylation of EGF receptor (1) and insulin receptor (2). Of the many intracellular responses to IGF receptor activation, diacylgycerol (DAG) is formed (4), which in turn activates protein kinase C (PKC (5)) while Ras becomes phosphorylated (3). Active PKC may catalyze phosphorylation and activation of c-*jun* promotor site (10), in addition to the phosphorylation of IKB and therefore activation of NFKB (6). In association with c-*fos* to form AP-1 (11), DNA-bound transcription factors can induce a gene response to UV following association with RNA polymerase (9, 12).

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SDS-PAGE that binds to irradiated dsDNA, whose induction kinetics correspond to the induction of the (6–4) photoproduct. Furthermore, removal of this photoproduct from irradiated DNA by photolyase diminished the binding of this protein, which has been identified since that time as glyceraldehyde 3-phosphate dehydrogenase.[144] Immunodetection of this protein may provide a simple procedure for the *in situ* detection of (6–4) photoproducts. Similar studies in a normal human fibroblast cell strain identified a novel DNA damage-binding activity that preferentially bound the (6–4) photoproduct in both double- and single-stranded oligonucleotides, rather than the cyclobutane dimer. An apparent molecular mass of 66 kDa was determined by southwestern analysis, consisting of two subunits ~ 22 kDa and 44 kDa.[145] As the binding activity of this protein was found to be significantly greater in G1 phase compared with S phase, these workers propose that the protein may function not only in repair but also in cell cycle or gene regulation.

D. p53 Expression

The tumor suppressor gene p53 maintains DNA integrity (1) by serving as a critical regulator of a G1 cell cycle checkpoint via WAF–1, (2) through GADD 45 that suppresses cell growth and inhibits replication[146] and (3) through apoptosis following UV-induced DNA damage. In addition, a possible role for p53 has been proposed in nucleotide excision repair where p53 may bind single-stranded DNA ends and catalyze DNA renaturation.[147] Many of the biological activities that have been ascribed to p53 are effected by its transactivational activity following binding to promoters that have a specific p53 binding motif.

Irradiation of mammalian cells with UV light results in a dose-dependent increase in p53, which is evident within 2 h.[148] Nelson and Kastan[149] have proposed that DNA strand breaks in cells exposed to UV are sufficient and probably necessary for the induction of p53 wild-type alleles. Further investigation by Liu *et al.*[150] into UVB-induced expression of p53 in mouse keratinocytes has demonstrated a 4- to 10-fold induction of the protein, peaking 5 h postirradiation. However, mRNA levels were unaffected and the protein half-life was extended ~7-fold, supporting the induction of p53 by UV as a posttranscriptional event. Using antibody 529, which has high recognition of cyclobutane dimers, we have identified an increase of 529 binding 3 h postirradiation in cultured, transformed fibroblasts (see Table 6), which correlated with an increase in p53 expression.[151] However, this does not establish a causal link. Scheidman and Landsberg[152]

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TABLE 6
Dose Dependence of DNA Damage and p53 Expression in SV40 Transformed Keratinocytes Following UVA Irradiation

UVA dose	Time post reintroduction of medium (hr)	p53 expression	529 binding
		Results are mean fluorescence values of n = 3 experiments	(SEM)
	0	74(26)	114(37)
0.5 J/cm²	1	87(12)	93(31)
	2	81(13)	67(15)
	3	130(9)	140(33)
	24	92(14)	62(34)
	0	74(23)	105(10)
1 J/cm²	1	92(6)	97(30)
	2	69(13)	77(18)
	3	119(18)	127(34)
	24	100(21)	89(26)

Note: Human SV 40 transformed keratinocytes were synchronized by serum deprivation and UVA irradiated. Cells were probed with an antibody to UV-DNA damage, 529 and a monoclonal anti-p53 (DO-7) that recognizes both native and mutated forms of the protein and detected using fluorescein-labeled secondary antibodies. Quantitation was by a Becton Dickinson FACScan flow cytometer, where results are as arbitrary fluorescence units.[151]

confirmed that UV irradiation leads to transient changes in the phosphorylation of p53.

Recently, Renzing *et al.*[153] have demonstrated that oxidative stress resulting from UVA exposure, but not DNA damage, is involved in p53 activation by inhibition of gene activation with *N*-acetyl cysteine that does not affect DNA damage. Rathmall *et al.*[154] have shown in fibroblasts from severe combined immunodeficient (SCID) mice, that the activation of p53 in response to UV-DNA damage is not due to signal transduction by DNA protein kinase. Taken together, these data indicate that UV-induced DNA damage alone does not activate p53. Figure 4 illustrates the effect of UV on the cell cycle mediated by p53.

Within this text, many cell models have been compared with respect to the molecular consequences of DNA damage. Yet, there is a major difference in the cellular response of keratinocytes and melanocytes to the effects of UV-induced DNA damage and ultimately in the development of cancer.[155] While keratinocytes are more prevalent in the epidermis, they

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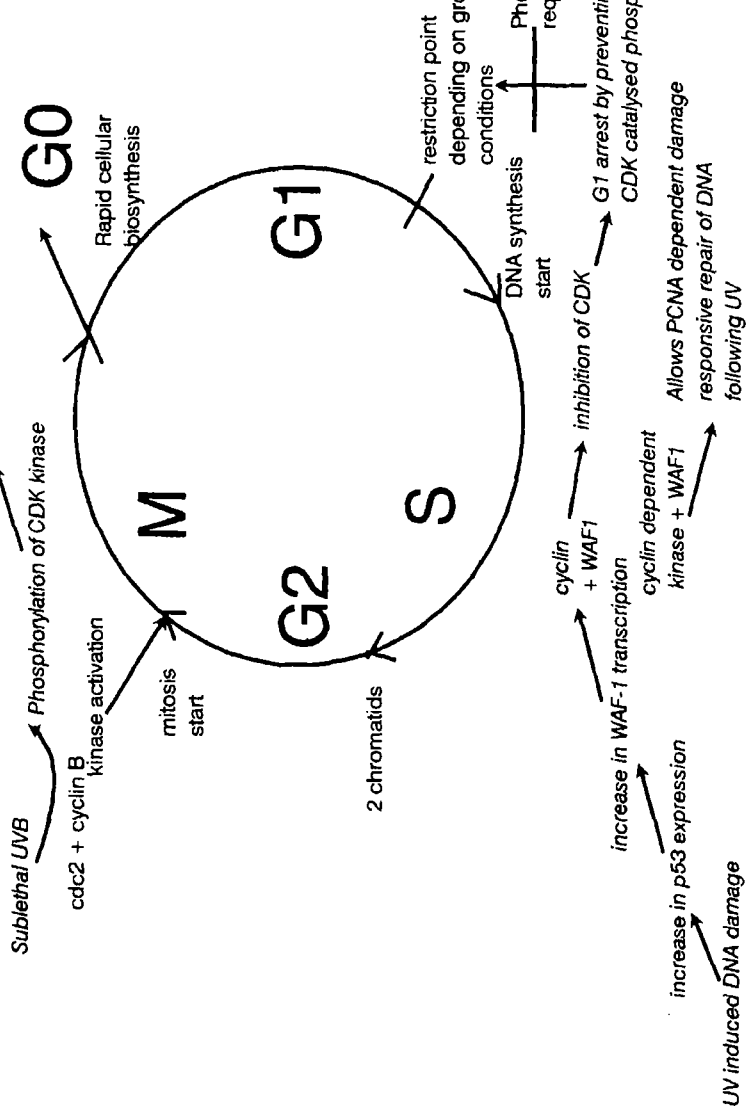

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FIGURE 4. In response to genotoxic stress such as UVR, cell cycle progression can be arrested at certain checkpoints in order to maintain DNA integrity. Regulation is achieved through the sequential activation of protein kinases, which consist of a regulatory subunit, a cyclin, and a cyclin-dependent kinase (CDK). At the G1/S interphase, following UV-induced DNA damage p53 is induced, WAF–1 levels increase and bind to cyclin, thereby preventing the action of CDK. This allows the PCNA-dependent damage-responsive repair to occur prior to replication. At the G2/M interface, a sublethal dose of UVB can induce phosphorylation and therefore inhibition of CDK, causing long-lasting cell cycle arrest.

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are organized for loss and replacement. In addition, keratinocytes are prone to undergo apoptosis. However, melanocytes have a limited capacity to regenerate damaged cells, and apoptosis appears to be restricted.[155] Thus, while UVA is important in the development of melanoma,[1] melanocytes appear resistant to the toxic effects of UVR[156] and DNA-damaged melanocytes may survive with mutation. The gene mutations most frequently associated with carcinogenesis appear to be within the Ras family and in p53 (see Section V).

E. Apoptosis

Cell death is no longer considered exclusively as an uncontrolled response to damage or disease (necrosis), but rather as an active process requiring protein synthesis, DNA degradation, and subsequent recognition and degradation by phagocytes.[157] p53-driven apoptosis provides a mechanism for the removal of cells whose DNA damage is irreparable.

An *in vitro* study by Malorni *et al.*[158] compared UVB- and UVA-induced apoptosis in cultured human keratinocytes. In the order of 60% of UVA-exposed cells and 90% of UVB-exposed cells displayed morphological characteristics of apoptosis within 24 h of exposure. The antioxidant vitamin E conferred significant protection against both UVA- and UVB-induced apoptosis, implicating ROS in the induction of cell damage by both UVA and UVB. Oxidative stress is recognized as an inducer of apoptosis,[159] and this is possibly through NF-KB activation[160] and signal transduction.

A more recent investigation into the effects of UV-dose on the induction of apoptosis has been undertaken by Cotton and Spandau.[161] These workers reported that while high UV doses induce apoptosis, lower doses induced repair. The cellular localization of p53 was also affected by UV dose; in apoptosing cells, p53 is located within cell surface blebs containing damaged DNA, whereas nuclear staining of p53 predominates in actively repairing cells.

Failure to apoptose and remove DNA-damaged cells may lead to fixation of mutations and ultimately cancer.

VI. PATHOLOGICAL EFFECTS OF UV-INDUCED DNA DAMAGE

The skin acts as a protective barrier against external insults and therefore is the primary target for UV irradiation effects. These can range from

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being acute inflammatory, self-resolving responses, to chronic invasive changes. Strong epidemiological evidence links UVR to the development of skin cancer.

A. Skin Cancer

Basal cell carcinoma (BCC) is the most prevalent malignant skin tumor (~80% of all skin cancers), arising from the basal epidermal layer cells that invade the underlying dermis. Squamous cell carcinoma (SCC) is the next most common malignant tumor, characterized by well-differentiated keratinocytes, whereas malignant melanoma (MM) is less frequent. UVR exposure is believed to be the most important etiological factor.

Carcinogenesis is a complex multistage process requiring the alteration of cellular DNA either as a result of chromosomal abberation or mutation. The DNA damage induced by UV light can contribute to cytotoxicity (Section E), block replication, and also give rise to mutation (e.g., misreading of modified sites by DNA polymerase), or by induction of recombinatorial events. Thymine glycol in DNA blocks replication by *E. coli* DNA polymerase I *in vitro*, but is only weakly mutagenic. However, 8-OHdG directs misincorporation of adenine by DNA polymerase *in vitro* and causes G-T transversions in *E. coli*. The mutations at dipyrimidine sites frequently show CC ⇒ TT double base changes and a highly frequent C ⇒ T substitution. Mutations associated with carcinogenesis commonly involve tumor suppressor genes and oncogenes. The p53 is found in most cells of the body, where it functions as a tumor suppressor protein. Many mutations have been reported over an extensive region of the gene, all of which cause its activation.

Examination of the mutation pattern in the p53 gene in BCC and SCC showed ~90% of mutations occurring at dipyrimidine sites.[162] In addition, a comparison of the effects of UV on normal skin demonstrated that 74% of sun-exposed normal skin contained p53 mutated at dipyrimidine sites, while only 5% mutation was observed in unexposed skin.[163] The majority of p53 point mutations are located at pyrimidine-pyrimidine sequences in over 90% of skin tumors. Berg *et al.*[164] have used a hairless mouse model to unequivocally demonstrate that the kinetics of constitutive p53 alteration are causally linked to chronic UVB exposure, and that this is a very early event in the induction of skin cancer.

Mutations in *ras* oncogenes have been detected in cultured cells of mouse skin tumors, induced by near-UV radiation, where mutations occurred at dipyrimidine sites.[165]

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Using a hairless mouse model, Berg *et al.*[166] have demonstrated that combined UVA and UVB is less effective than UVB alone in inducing pyrimidine dimers at equivalent carcinogenic doses of irradiation. This implies that other base lesions (possibly oxidative) are contributing to the development of cancer in UVA- and UVB-irradiated mice, and questions the relevance of analysing pyrimidine dimers alone as a carcinogenic risk measure. In addition, the suppression of the immune system by cellular DNA damage may also contribute to the development of cancer following UV exposure, by enabling developing tumors to escape immune surveillance.[167]

Investigations into correlation between mutation and melanoma are less conclusive. McGregor *et al.*[168] examined cutaneous melanocytic lesions for p53 immunoreactivity. Owing to the short half-life of p53, any immunoreactivity must be attributable to posttranslation modification or mutation. These workers reported a highly significant correlation between immunoreactivity and malignancy, where p53 immunoreactivity was observed in 63% of tumor specimens. Yamamoto *et al.*[169] examined p53 expression with respect to clinical stage in MM. While no relationship was observed in the early stages of disease, p53 expression was found to correlate with invasive and highly mitotic tumors, suggesting that p53 may have a role in malignant transformation. Hartmann *et al.*[170] confirmed these findings; from genomic sequencing of adjacent splice sites of p53 in 20 immunoreactive tumors, three C:G to T:A transitions and one CC to TT mutation were observed at dipyrimidine sites. These data suggest that although p53 mutations may be involved in some malignant melanomas, they do not play as large a role as in BCC and SCC.

Noz *et al.*[25] have examined nevus cells originating from dysplastic nevi and demonstrated that these cells had 65% higher induction of DNA strand breaks in response to UVB irradiation than in foreskin melanocytes. The reasons for the increased sensitivity of dysplastic nevi may relate to decreased protection or repair.

Few antioxidant intervention studies aimed at minimizing skin tumor development have been reported. Supplementation with dietary selenium (a cofactor for glutathione peroxidase) in mice did not exert any protective effect against tumor development during UV exposure. However, post-treatment those animals receiving (0.5 mg Se/Kg) showed a leveling off in tumor development compared with untreated controls.[171]

The presence of particular GST phenotypes may confer a protective role against skin cancer following UVR. Heagerty *et al.*[172] have suggested that the presence of GSTM1 may be protective against single or multiple

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BCC, based on a study of the GSTM1 gene locus in patients with cutaneous tumors, where GSTM1 null genotype was associated with increased tumor number. In contrast, Shanley *et al.*[173] did not observe an increased frequency of the GSTM1 null genotype using multiplex polymerase chain reaction in BCC or MM. However, this was a small study, and a much larger cross-sectional analysis of multiple cutaneous BCC has since confirmed the influence of GSTM1 and GSTT1 on tumor number and, longitudinally, on tumor accrual.[174]

The stringency of the DNA repair processes outlined in Section E indicates that inefficient repair capacity may be a risk factor for cancer development. Hall *et al.*[175] have investigated UV-induced DNA damage repair in BCC and SCC, but did not find a significant difference in overall repair capacity in these groups compared with controls. However, studies by Tornaletti and Pfeiffer[176] using LMPCR have identified mutation hot spots in p53 at nucleotide regions that are repaired slowly, suggesting that repair efficiency may affect the mutation spectrum within cancer-associated genes such as protooncogenes and tumor suppressor genes. Using a p53 transgenic mouse, Li *et al.*[177] have studied DNA repair efficiency and apoptosis in keratinocytes after UV irradiation. Mutant p53-transgenic mouse skin had reduced repair of UV-induced DNA damage *in vitro* and *in vivo*, while apoptosis was slightly increased. These results suggest that mutant p53 interacts with wild-type p53 present within the cells to interfere with UV induced-DNA damage repair but not apoptosis.

B. Xeroderma Pigmentosum

The link between defective DNA repair capacity and skin cancer is exemplefied by xeroderma pigmentosum. Xeroderma pigmentosum (XP), which is a rare hereditary syndrome associated with an increased (>1000 fold) cancer incidence for SCC, BCC, and MM. All cultured cells isolated from XP patients are hypersensitive to UV-induced killing and mutagenesis, and while there is heterogeneity in the genotype of the abnormality, 80% are defective in the nucleotide excision repair gene, XPA (see Section V). An additional form, the XP-variant, has defective postreplication repair.

Individuals with the XPA phenotype are equally inefficient in the repair of nuclear and Mt DNA damage, suggesting a similarity between the processes used to repair damage at the two sites.[178] However, Runger *et al.*[179] have demonstrated that differential DNA repair pathways exist in

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human cells for the repair of direct and indirect DNA damage based on observations within XP cells; all complementation groups show a reduced repair of UVB-induced DNA damage, whereas all groups except XP-C were effective in the repair of UVA-induced lesions. This capacity for mammalian cells to process UVA- and B-induced damage differently further complicates the assessment of UV exposure risk.

In order to further characterize the defect in XP cells, Abousekhra and Wood examined UV-irradiated cells for PCNA. Immunostaining for PCNA in XP-A and XP-G fibroblasts showed a complete absence of PCNA following UV irradiation. This indicates an absolute role for XP-A and XP-G in the incision step.[180]

Using reverse transcriptase PCR and single strand conformation polymorphism, Dumaz *et al.*[181] analyzed more than 40 XP skin tumors for mutations in the p53 gene. The authors reported that 40% contained at least one mutation in the p53 gene at dipyrimidine sites, particularly C-C. These are noted hot spots for p53 mutation that relate to unrepaired UV-induced lesions (e.g., pyrimidine dimers).

Studies on the *Ha-ras* gene by Daya-Grosjean *et al.*[182] demonstrated amplification and rearrangement of *Ha-ras* in 70% of XP tumors. Furthermore, a twofold increase in mutational frequency in *ras* was observed in skin tumors from XP when compared with equivalent tumors from otherwise healthy subjects.

C. Photosensitive Lupus

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of a variety of autoantibodies, particularly against DNA and nuclear components. For many SLE patients (~45%), cutaneous lesions are provoked by UV light.

It has been postulated that the persistence of UV-induced DNA damage caused by repair deficiencies in combination with immunoregulatory abnormalities may lead to the accumulation of DNA-containing immune complexes.[183] Rosenstein *et al.*[184] have examined DNA damage repair in a small study of SLE fibroblasts; while excision repair, pyrimidine dimer removal, and endonuclease III-sensitive sites appeared normal, the formation and maintenance of DPCs (possibly with repair proteins) and SSBs were reduced when compared with normal fibroblasts. An inability to repair lesions induced by UV light may result in prolonged presence of antigenic DNA, an increase in immune complexes and increased tissue damage in SLE.

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Emlen *et al.*[185] have identified an increased rate of apoptosis in lymphocytes from SLE patients, which may represent a mechanism by which nuclear DNA could be presented extracellularly. Furthermore, following UVB irradiation, SLE keratinocytes become apoptotic with Ro/SSA antigen expression in discrete surface blebs associated with sites of oxygen modification.[186]

Paradoxically, phototherapy by UVA may be of therapeutic benefit in SLE,[187] particularly in those with cutaneous lesions. The mechanism of this therapy requires further investigation.

CONCLUSION

Our understanding of the molecular effects of UVA and B radiation on cellular DNA has developed rapidly from the original observations of pyrimidine dimer formation following exposure to UVB. Many different lesions arising from both direct UV absorption and indirect photosensitisation reactions have been characterized, facilitated by the development of sensitive analytical and molecular biological tools for their evaluation.

The conservation of the genome despite UV-induced genotoxicity is achieved by a combination of antioxidant, detoxification, and repair processes. These areas are under intensive investigation and may not only provide clues as to mechanisms of disease but also may lead to the development of novel biomarkers for clinical chemistry and strategies for limiting the effects of UV on DNA, particularly with respect to conditions such as skin cancer and photosensitive lupus.

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REFERENCES

1. Setlow RB, Woodhead A. Temporal changes in the incidence of malignant melanoma — explanation from action spectrum. *Mutat Res* 1994; **307:** 365–74.

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2. Cadet J, Anselmino C, Douki T, et al. Photochemistry of nucleic acids in cells. *Photochem Photobiol* 1992; **15:** 277–98.

3. Ellison MJ, Childs JD. Pyrimidine dimers induced in *Escherichia coli* DNA by ultraviolet irradiation. *Photochem Photobiol* 1981; **34:** 465–9.

4. Coohill TP, Peak MJ Peak JG. The effects of UV wavelengths of radiation present in sunlight on human cells in vitro. *Photochem Photobiol* 1987; **46:** 1043–50.

5. Barak Y, Cohen-Fix O, Livneh Z. Deamination of cytosine-containing pyrimidine photodimers in UV irradiated DNA. Significance for UV light mutagenesis. *J Biol Chem* 1995; **270:** 24174–9.

6. Mitchell DL, Pfeiffer GP, Taylor JS, et al. Biological role of (6–4) photoproducts and cyclobutane dimers. In: Shima A, Ichihasi M, Fujiwara Y, Takebe H, Eds. *Frontiers of photobiology*. pp 337–344. Amsterdam: Elsevier Science, 1993.

7. Stewart MS, Cameron GS Pence BC. Antioxidant nutrients protect against UVB-induced oxidative damage to DNA of mouse keratinocytes in culture. *J Invest Dermatol* 1996; **106:** 1086–9.

8. Peak JG, Peak MJ. Comparison of initial yields of DNA to protein crosslinks and single strand breaks induced in cultured cells by far and near UV light, blue light and X-rays. *Mutat Res* 1991; **246:** 187–96.

9. Foote CS. Definition of type I and type II photosensitised oxidations. *Photochem Photobiol* 1991; **54:** 54–70.

10. Devasgayam TPA, Steenken S, Obendorf MSW, et al. Formation of 8-OHdG and generation of strand breaks at guanine residues by singlet oxygen. *Biochemistry* 1991; **30:** 6283–9.

11. Pflaum M, Boiteux S Epe B. Visible light generates oxidative DNA base modifications in high excess of strand breaks in mammalian cells. *Carcinogenesis* 1994; **15:** 297–300.

12. Fisher GJ, Land EJ. Photosensitisation of pyrimidines by 2-methylnapthoquinone in water: a laser flash photolysis study. *Photochem Photobiol* 1983; **37:** 27–32.

13. Tyrrell RM. Induction of pyrimidine dimers in bacterial DNA by 365 nm radiation. *Photochem Photobiol* 1973; **17:** 69–73.

14. Umlas ME, Franklin WA, Chan GL, et al. UV light irradiation of defined sequence of DNA under conditions of chemical photosensitisation. *Photochem Photobiol* 1985; **42:** 265–73.

15. Mori T, Matsunga T, Hirose T, et al. Establishment of a monoclonal antibody recognising UV light induced (6–4) photoproducts. *Mutation Res* 1988; **194:** 263–70.

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Downloaded By: [DNL] At: 09:13 23 June 2008

16. Peak MJ, Peak JG Canes BA. Induction of direct and indirect single strand breaks in human cell DNA by far and near UV radiations: action spectrum and mechanisms. *Photochem Photobiol* 1987; **45:** 381–7.

17. Blazek ER, Peak JG Peak MJ. Singlet oxygen induces frank strand breaks as well as alkali and piperidine labile sites in supercoiled plasmid DNA. *Photochem Photobiol* 1989; **49:** 607–13.

18. Roza L, Van Der Schans GP Lohman PHM. The induction and repair of DNA damage and its influence on cell death in primary human fibroblasts exposed to UV-A or UV-C irradiation. *Mutat Res* 1985; **146:** 89–98.

18a. Peak MJ, Pilas B, Dudek EJ, et al. DNA breaks caused by monochromatic 365 nm UVA radiation or hydrogen peroxide and their repair in human epitheliod xeroderma pigmentosum cells. *Photochem Photobiol* 1991; **54:** 197–203.

19. Gantt R, Jones GM, Stephens EV, et al. Visible light induced DNA crosslinks in cultures of mouse and human cells. *Biochim Biophys Acta* 1979; **565:** 231–40.

20. Murata-Kamiya N, Kamiya H, Iwamoto N, et al. Formation of glyoxal from DNA treated with oxygen free radicals. *Carcinogenesis* 1995; **16:** 2251–3.

21. Bhusate LL, Herbert KE, Scott DL, et al. Increased DNA strand breaks in mononuclear cells from patients with rheumatoid arthritis. *Ann Rheum Dis* 1992; **51:** 8–12.

22. Harris G, Cramp WA, Edwards JC, et al. Radiosensitivity of peripheral blood lymphocytes in autoimmune disease. *Int J Radiat Biol* 1985; **47:** 689–99.

23. Singh NP, McCoy MT, Tice RR, et al. A simple technique for quantitation of low levels of DNA damage in single cells. *Exp Cell Res* 1988; **175:** 184–91.

24. De With A, Leitz G Greulion KO. Ultraviolet B laser induced DNA damage in lymphocytes observed by single cell gel electrophoresis. *J Photochem Photobiol (B: Biology)* 1994; **24:** 47–53.

25. Noz KC, Bauwens M, Van Buul PPW, et al. Comet assay demonstrates a higher UVB sensitivity to DNA damage in dysplastic nevus cells and foreskin melanocytes. *J Invest Dermatol* 1996; **106:** 1198–202.

26. Speit G, Hartmann A. The contribution of excision repair to the DNA effects seen in the alkaline single cell gel test (Comet assay). *Mutagenesis* 1995; **10:** 555–9.

27. Mizuno T, Matsunaga T, Ihara M, et al. Establishment of a monoclonal antibody recognising cyclobutane type thymine dimers in DNA; a comparative study with 64M–1 antibody specific for (6–4) photoproducts. *Mutat Res – DNA Repair* 1991; **254:** 175–84.

28. Snopov SA, Berg RJW, Van Weelden H, et al. Molecular dosimetry by flow cytometric detection of thymine dimers in mononuclear cells from extracorporally UV-irradiated blood. *J Photochem Photobiol (B:Biol)* 1995; **28:** 33–7.

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29. Herbert KE, Mistry N, Griffiths HR, et al. Immunochemical detection of sequence specific modifications to DNA induced by UV light. *Carcinogenesis* 1994; **15:** 2517–21.

30. Berg RJW, de Gruijl FR, Rozal L, et al. Flow cytometric immunofluorescence assay for quantification of cyclobutylthymidine dimers in separate phases of the cell cycle. *Carcinogenesis* 1993; **14:** 103–6.

31. Hori M, Udono MU, Yoshida H, et al. Immunochemical detection of unrepaired cyclobutane-type pyrimidine dimers of DNAs extracted from skin tumours. *Arch Dermatol Res* 1992; **284:** 283–9.

32. Clingen PH, Arlett CF, Roza, et al. Induction of cyclobutane pyrimidine dimers, pyrimidine (6–4) pyrimidone photoproducts and Dewar isomers by natural sunlight in normal human mononuclear cells. *Cancer Res* 1995; **55:** 2245–8.

33. Chadwick CA, Potten CS, Nikaido O, et al. The detection of cyclobutane thymine dimers, (6–4) photoproducts and the Dewar photoisomers in sections of UV-irradiated human skin using specific antibodies and the demonstration of depth penetration effects. *J Photochem Photobiol (Biology B)* 1995; **28:** 163–70.

34. Floyd RA, West HS, Eneff KL, et al. Methylene blue plus light mediates 8OHdG formation in DNA. *Arch Biochem Biophys* 1989; **273:** 106–11.

35. Hattori Y, Nishigori C, Tanaka T et al. 8-hydroxy-2-deoxyguanosine is increased in epidermal cells of hairless mice after chronic UVB exposure. *J Invest Dermatol* 1996; **107:** 733–7.

36. Tornaletti S, Pfeiffer GP. UV light as a photofootprinting agent: modulation of UV-induced DNA damage by transcription factors bound at promotors of three genes. *J Mol Biol* 1995; **249:** 714–28.

37. Franklin WA, Haseltine WA. Removal of UV-light induced pyrimidine pyrimidone (6–4) photoproducts from *E. coli* DNA requires the uvrA, uvrB and uvrC gene products. *Proc Natl Acad Sci USA* 1984; **81:** 3821–24.

38. Glickman BW, Schaaper RM, Haseltine WA, et al. The (6–4) photoproduct is mutagenic in *E. coli*. *Proc Natl Acad Sci USA* 1986; **83:** 6945–9.

39. Hutchinson F, Yamamdo K, Stein J, Wood R. Effect of photoreactivation on mutagenesis of lamda phage by ultraviolet light. *J Mol Biol* 1988; **202:** 593–601.

40. Ramsey RS, Ho CH. Determination of pyrimidine dimers in DNA by HPLC/GC and electron capture detection. *Anal Biochem* 1989; **182:** 424–31.

41. Epe B, Henzl H, Adam W, et al. Endonuclease sensitive DNA modifications induced by acetone and acetophenone as photosensitiser. *Nucleic Acids Res* 1993; **21:** 863–9.

42. Doetsch PW, Zastawny TH, Martin AM, et al. Monomeric base damage products from adenine guanine and thymine induced by exposure to ultraviolet radiation. *Biochemistry* 1995; **34:** 737–42.

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43. Podmore ID, Cooke, ME, Herbert KE, et al. Quantitative determination of cyclobutane thymine dimers in DNA by stable isotope-dilution mass spectrometry. *Photochem Photobiol* 1996; **64:** 310–5.

44. Fischer-Nielsen A, Loft S, Gjervig Jenson K. 8OHdG in vitro: effects of glutathione, ascorbate and 5-aminosalicylate. *Free Radic Biol Med* 1992; **13:** 121–6.

45. Fischer-Nielson A, Loft IS Gjervig Jenson K. Effect of ascorbate and 5-amino salicylate on light induced 8OHdG formation in V79 Chinese hamster cells. *Carcinogenesis* 1993; **14:** 2431–3.

46. Fuchs J, Huflift ME, Rothfluss LM, et al. Acute effects of near UV and visible light on the cutaneous antioxidant defence system. *Photochem Photobiol* 1989; **50:** 739–44.

47. Epstein JH. Effects of β carotene on UV induced tumour formation in hairless mouse skin. *Photochem Photobiol* 1977; **25:** 211–3.

48. Matthews-Roth MM, Krinsky NI. Carotenoids affect development of UVB induced skin cancer. *Photochem Photobiol* 1987; **46:** 507–9.

49. Wei H, Cai Q Rahn RO. Inhibition of UV light and Fenton reaction induced oxidative DNA damage by the soybean isoflavone genistein. *Carcinogenesis* 1996; **17:** 73–77.

50. Kerb R, Brockmoller J. Reum T, et al. Deficiency in glutathione-*S*-transferase T1 and M1 as heritable factors of increased cutaneous UV sensitivity. *J Invest Dermatol* 1997; **108:** 229–32.

51. Bohr VA. DNA repair fine structure and its relations to genomic instability. *Carcinogenesis* 1995; **16:** 2885–92.

52. Tornaletti S, Pfeifer GP. Slow repair of pyrimidine dimers at *p53* mutation hotspots in skin cancer. *Science* 1994; **263:** 1436–40.

53. Tornaletti S, Pfeifer GP. UV damage and repair mechanisms in mammalian cells. *BioEssays* 1996; **18:** 221–8.

54. Vassuer F, Marlier-Facon C, Delaporte E, et al., Excision repair analysis and skin response to UV-B in young patients with basal cell carcinoma. *Nouv Dermatol* 1994; **13:** 321–8.

55. Wei Q, Matanoski GM, Farmer ER, et al. DNA repair and susceptibility to basal cell carcinoma: a case-control study. *Am J Epidemiol* 1994; **140:** 598–607.

56. Ahmed FE, Setlow RB, Grist E, et al. DNA damage, photorepair, and survival in fish and human cells exposed to UV radiation. *Environ Mol Mutagen* 1993; **22:** 18–25.

57. Carell T. Sunlight induced DNA lesions-Lesion structure, mutation characteristics and repair. *Chimia* 1995; **49:** 365–73.

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58. Kato Jr T, Todo T, Ayaki H, et al. Cloning of a marsupial DNA photolyase gene and the lack of related nucleotide sequences in placental mammals. *Nucleic Acids Res* 1994; **22:** 4119–24.

59. Ley RD. Photoreactivation in humans. *Proc Natl Acad Sci USA* 1993; **90:** 4337.

60. Sancar A. Structure and function of DNA photolyase. *Biochemistry* 1994; **33:** 2–9.

61. Kim ST, Malhotra K, Smith CA, et al. Characterization of (6–4)-photoproduct DNA photolyase. *J Biol Chem* 1994; **269:** 8535–40.

62. Todo T, Takemori H, Ryo H, et al. A new photoreactivating enzyme that specifically repairs ultraviolet light-induced (6–4) photoproducts. *Nature* 1993; **361:** 371–4.

63. Hsu DS, Zhao X, Zhao S, et al. Putative human blue-light photoreceptors hCRY1 and hCRY2 are flavoproteins. *Biochemistry* 1996; **35:** 13871–77.

64. Vanderspek PJ, Kobayashi K, Bootsma D, et al. Cloning, tissue expression, and mapping of a human photolyase homolog with similarity to plant blue-light receptors. Genomics 1996; 37(2): 177–82.

65. Setlow P. I will survive: protecting and repairing spore DNA. *J Bacteriol* 1992; **174:** 2737–41.

66. Grombacher T, Kaina B. Constitutive expression and inducibility of O^6-methylguanine-DNA methyltransferase and *N*-methylpurine-DNA glycosylase in rat liver cells exhibiting different status of differentiation. *Biochem Biophys Acta* 1995; **1270:** 63–72.

67. Sekiguchi M, Nakabeppu Y, Sakumi K, et al. DNA-repair methyltransferase as molecular device for preventing mutation and cancer. *J Cancer Res Clin Oncol* 1996; **122:** 199–206.

68. Seeberg E, Eide L Bjoras M. The pathway of base excision repair. *Trends Biochem Sci* 1995; **20:** 391–7.

69. Krokan HE, Standal R Slupphaug G. DNA glycosylases in the base excision repair of DNA. *Biochem J* 1997; **325:** 1–16.

70. Girard PM, Guibourt N Boiteux S. The Ogg1 protein of *Saccaromyces cerevisiae*: a 7,8-dihydro-8-oxoguanine DNA glycosylase/ AP lyase whose lysine 241 is a critical residue for catalytic activity. *Nucleic Acids Res* 1997; **25:** 3204–11.

71. Grollman AP, Moriya M. Mutagenesis by 8-oxoguanine: an enemy within. *Trends Biochem Sci* 1993; **9:** 246–9.

72. Nash HM, Bruner SD, Scharer OD, et al. Cloning of a yeast 8-oxoguanine DNA glycosylase reveals the existence of a base-excision DNA repair protein superfamily. *Current Biol* 1996; **6:** 968–80.

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73. Radicella JP, Dherin C, Desmaze C, et al. Cloning and characterization of *hOGG1*, a human homolog of the *OGG1* gene of *Saccharomyces cerevisiae*. *Proc Natl Acad Sci USA* 1997; **94:** 8010–15.

74. Roldan-Arjona T, Wei YF, Carter KC, et al. Molecular cloning and functional expression of a human cDNA encoding the antimutator enzyme 8-hydroxyguanine-DNA glycosylase. *Proc Natl Acad Sci USA* 1997; **94:** 8016–20.

75. Rosenquist TA, Zharkov DO Grollman AP. Cloning and characterization of a mammalian 8-oxoguanine DNA glycosylase. *Proc Natl Acad Sci USA* 1997; **94:** 7429–34.

76. Van der Kemp PA, Thomas D, Barbey R, et al. Cloning and expression in *Escherichia coli* of the OOG1 gene of *Saccharomyces cerevisiae*, which codes for a DNA glycosylase that excises 7,8-dihydro–8-oxoguanine and 2,6-diamino–4-hydroxy–5-*N*-methylformidopyrimidine. *Proc Natl Acad Sci USA* 1996; **93:** 5197–202.

77. Aspinwall R, Rothwell DG, Roldan-Arjona T, et al. Cloning and characterization of a functional human homologue of *Escherichia coli* endonuclease III. *Proc Natl Acad Sci USA* 1997; **94:** 109–14.

78. Doetsch PW, Zastawny TH, Martin AM, et al. Monomeric base damage products from adenine, guanine and thymine induced by exposure of DNA to ultraviolet radiation. *Biochemistry* 1995; **34:** 737–47.

79. Eide L, Bjoras M, Pirovano M, et al. Base excision of oxidative purine and pyrimidine DNA damage in *Saccharomyces cerevisiae* by a DNA glycosylase with sequence similarity to endonuclease III from *Escherichia coli*. *Proc Natl Acad Sci USA* 1996; **93:** 10735–740.

80. Hilbert TP, Boorstein RJ, Kung HC, et al. Purification of a mammalian homologue of *Escherichia coli* endonuclease III: identification of a bovine pyrimidine hydrate-thymine glycol DNA-glycosylase/AP lyase by irreversible cross linking to a thymine glycol-containing oligonucleotide. *Biochemistry* 1996; **35:** 2505–11.

81. Dizdaroglu M, Zastawny TH, Carmical JR, et al. A novel DNA N-glycosylase activity of *Escherichia coli* T4 endonuclease-V that excises 4,6-diamino–5-formamidopyrimidne from DNA, a UV-radiation-induced and hydroxyl radical-induced product of adenine. *Mutat Res* 1996; **362:** 1–8.

82. Purmal AA, Rabow LE, Lampman GW, et al. A common mechanism of action for the N-glycosylase/AP lyase from *E. coli* and T4. *Mutat Res* 1996; **364:** 193–207.

83. Savva R, McAuley, Heucht K, Brown T, et al. The structural basis of specific base excision repair by uracil-DNA glycosylase. *Nature* 1995; **373:** 487–93.

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Downloaded By: [DNL] At: 09:13 23 June 2008

84. Slupphaug G, Eftedal I, Kavli B, et al. Properties of a recombinant human uracil-DNA glycoyslase from the UNG gene and evidence that UNG encodes the major uracil-DNA glycoyslase. *Biochemistry* 1995; **34:** 128–38.

85. Demple B, Harrison L. Repair of oxidative damage to DNA: enzymology and biology. *Annu Rev Biochem* 1994; **63:** 915-48.

86. Sancar A. DNA repair in humans. *Annu Rev Gen* 1995; **29:** 60–105.

87. Shivji MKK, Kenny MK Wood RD. Proliferating cell nuclear antigen is required for DNA excision repair. *Cell* 1992; **69:** 367–74.

88. Singhal RK, Prasad R Wilson SH. DNA polymerase beta conducts the gap filling uracil-initiated base excision repair in a bovine testis nuclear extract. *J Biol Chem* 1995; **270:** 949–57.

89. de Murcia G, Menissier de Murcia J. Poly (ADP-ribose) polymerase: a molecular nick-sensor. *Trends Biochem Sci* 1994; **19:** 172–76.

90. Kupper JH, Van Gool L Burkle A. Molecular genetic systems to study the role of poly(ADP-ribosyl)ation in cellular response to DNA damage. *Biochimie* 1995; **77:** 450–5.

91. Frosina G, Fortini P, Rossi O, et al. 2 pathways for base excision-repair in mammalian cells. *J Biol Chem* 1996; **271(16):** 9573–78.

92. Huang JC, Hsu DS, Kazantsev A, et al. Substrate spectrum of human excinuclease-repair of abasic sites, methylated bases, mismatches and bulky adducts. *Proc Natl Acad Sci USA* 1994; **91:** 12213-17.

93. Reardon JT, Bessho T, Kung HC, et al. *In vitro* repair of oxidative DNA damage by human nucleotide excision repair system: possible explanation for neurodegeneration in Xeroderma pigmentosum patients. *Proc Natl Acad Sci USA* 1997; **94:** 9463–8.

94. Sancar A. Excision repair in mammalian cells. *J Biol Chem* 1995; **270:** 15915–8.

95. Bessho T, Sancar A, Thompson LH, et al. Reconstitution of human excision nuclease with recombinant XPF-ERCC1 complex. *J Biol Chem* 1997; **272:** 3833–7.

96. Brookman KW, Lamberdin JE, Thelen MP, et al. ERCC4 (XPF) encodes a human nucleotide excision-repair protein with eukaryotic recombination homologs. *Mol Cell Biol* 1996; **16:** 6553–62.

97. Matsunaga T, Mu D, Park CH, et al. Human DNA repair excision nuclease analysis of the roles of the subunits involved in dual incisions by using anti-XPG and anti-ERCC1 antibodies. *J Biol Chem* 1995; **270:** 20862–9.

98. Mu D, Hsu D, Sancar A. Reaction mechanism of human DNA repair excision nuclease. *J Biol Chem* 1996; **271:** 8285–94.

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Downloaded By: [DNL] At: 09:13 23 June 2008

99. Park CH, Bessho T, Matsunaga T, et al. Purification and characterization of the XPF-ERCC1 complex of human DNA-repair excision nuclease. *J Biol Chem* 1995; **270:** 22657–60.

100. Reardon JT, Mu D Sancar A. Overproduction, purification and characterization of the XPC subunit of the human DNA-repair excision nuclease. *J Biol Chem* 1996; **271:** 19451–6.

101. Lindahl T, Sedgwick B, Sekiguchi M, et al. Regulation and expression of the adaptive response to alkylating agents. *Annu Rev Biochem* 1988; **57:** 133–57.

102. Kim J, Patel D Choi B. Contrasting structural impacts induced by *cis-syn* cyclobutane dimer and (6–4) adduct in DNA duplex decamers: Implications in mutagenesis and repair activity. *Photochem Photobiol* 1995; **62:** 44–50.

103. Young AR, Cahdwick CA, Harrison G, et al. The *in situ* repair kinetics of thymine dimers and 6–4 photoproducts in human skin types I and II. *J Invest Dermatol* 1996; **106:** 1307–13.

104. Henriksen EK, Moan J, Kaalhus O, et al. Induction and repair of DNA damage in UV irradiated human lymphocytes. Spectral differences and repair kinetics. *J Photochem Photobiol* 1996; **32:** 19–48.

105. Bohr VA, Smith CA, Okumoto DS, et al. DNA repair in an active gene: removal of pyrimidine dimers from DHFR gene of CHO cells is much more efficient then in the genome overall. *Cell* 1985; **40:** 359–69.

106. Madhani HD, Bohr VA Hanawalt PC. Differential DNA repair in transcriptionally active and inactive proto-oncogenes: *c-adl* and *c-mos*. *Cell* 1986; **45:** 417–23.

107. Ruven HJT, Berg RJW, Seelken CMJ, et al. UV induced cyclobutane pyrimidine dimers are selectively removed from transcriptionally active genes in the epidermis of hairless mice. *Cancer Res* 1993; **53:** 1642–5.

108. Friedberg EC. Relationships between DNA repair and transcription. *Annu Rev Biochem* 1996; **65:** 15–42.

109. Hanawalt PC. Transcription-coupled repair and human disease. *Science* 1994; **266:** 1457–8.

110. Hanawalt PC. DNA repair comes of age. *Mutat Res* 1995; **336:** 101–13.

111. Selby CP, Sancar A. Molecular mechanisms of transcription-repair coupling. *Science* 1993; **260:** 53–8.

112. Sancar A. DNA excision repair. *Annu Rev Biochem* 1996; **65:** 43–81.

113. Lestienne P, Bataille N. Mitochondrial DNA alterations and genetic diseases: a review. *Biomed Pharmacother* 1994; **48:** 199–214.

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Downloaded By: [DNL] At: 09:13 23 June 2008

114. Beal MF, Hyman BT Koroshetz W. Do defects in mitochondrial energy metabolism underlie the pathology of neurodegenerative diseases? *Trends Neurosci* 1993; **16(4):** 125–31.

115. Schapira AHV. Nuclear and mitochondrial genetics in Parkinson's disease. *J Med Genet* 1995; **32:** 411–4.

116. Bohr VA, Anson M. DNA damage, mutation and fine structure DNA repair in aging. *Mutat Res* 1995; **338:** 25–34.

117. Anderson CT, Friedberg EC. The presence of nuclear and mitochondrial uracil DNA glycosylase in extracts of human KB cells. *Nucleic Acids Res* 1980; **8:** 875–88.

118. Tomkinson AB, Bonk RT Linn S. Mitochondrial endonuclease activates for apurinic/apyrimidinic sites in DNA from mouse cells. *J Biol Chem* 1988; **263:** 12532-37.

119. Clayton DT, Doda JN Friedberg EC. The absence of a pyrimidine dimer repair mechanism in mammalian mitochondria. *Proc Natl Acad Sci USA* 1974; **71:** 2777–81.

120. LeDoux SP, Wilson EJ, Beecham EJ, et al. Repair of mitochondrial DNA after various types of DNA damage in Chinese hamster ovary cells. *Carcinogenesis* 1992; **13:** 1967-73.

121. Driggers WJ, LeDoux SP Wilson GL. Repair of oxidative damage within the mitochondrial DNA of RINr 38 cells. *J Biol Chem* 1993; **268:** 22042–5.

122. Vaisman A, Chainey SG. Induction of UV-damage recognition protein by cisplatin treatment. *Biochemistry* 1995; **34:** 105 -14.

123. Hollander MC, Alamo I, Jackman J, et al. Analysis of mammalian gadd45 gene and its responses to DNA damage. *J Biol Chem* 1993; **268:** 24385–93.

124. Matsui MS, DeLeo VA. Induction of protein kinase C activity by UV. *Carcinogenesis* 1990; **11:** 229–34.

125. Devary Y, Rosette C, Di Donata JA, et al. NFκB activation by UV light is not dependent on a nuclear signal. *Science* 1993; **261:** 1442–5.

125a. Hirschfield S, Levine AS, Ozatao K, et al. A constitutive damage specific DNA binding protein is synthesised at higher levels in UV irradiated primate cells. *Mol Cell Biol* 1990; **10:** 2041–8.

126. Scharffetter K, Wiaschek M, Hogg A, et al. UVA irradiation induces collagenase in human dermal fibroblasts in vitro and in vivo. *Arch Dermatol Res* 1991; **283:** 506–11.

127. Krutman J, Kock A, Schauer E, et al. TNF β and ultraviolet radiation are potent regulators of human keratinocytes ICAM–1 expression. J Invest Dermatol 1990; **95:** 127-31.

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Downloaded By: [DNL] At: 09:13 23 June 2008

128. Hanson DL, DeLeo VA. Long wave Ultraviolet irradiation stimulates arachidonic acid release and cyclo-oxygenase activity in mammalian cells in culture. *Photochem Photobiol* 1989; **49:** 423–30.

129. Hanson DL, De Leo VA. Long wave ultraviolet light induces phospholipase activation in cultured human epidermal keratinocytes. *J Invest Dermatol* 1990; **95:** 158–63.

130. Angel P, Poling A Mallick M. Induction of metallothionein and other mRNA species by carcinogens and tumour promotors in primary human skin fibroblasts. *Mol Cell Biol* 1986; **6:** 1760–6.

131. Keyse SM, Tyrrell RM. Haem oxygenase is the major 32 kDa stress protein induced in human skin fibroblasts by ultraviolet A radiation, hydrogen peroxide and sodium arsenite. *Proc Natl Acad Sci USA* 1989; **86:** 99–103.

132. Medrano EE, IM S, Yang F, et al. Ultraviolet B light induces G1 arrest in human melanocytes by prolonged inhibition of retinoblastoma protein phosphorylation associated with long-term expression of the p21 (Waf-1/SDI-1, Cip-1) protein. *Cancer Research* 1995; **55:** 4047–52.

133. Devary Y, Gottlieb RA, Smeal T, et al. The mammalian UV response is triggered by activation of Src tyrosine kinases. *Cell* 1992; **71:** 129–57.

134. RadlerPohl A, Sachsenmaier C Gebel S. UV activation of AP-1 involves obligatory extranuclear steps including Raf-1 kinase. *EMBO J* 1993; **12:** 1005–12.

135. Coffer PJ, Burgering BMT, Pepplenbosch MP, et al. UV activation of receptor tyrosine kinase activity. *Oncogene* 1995; **11:** 561–9.

136. Rozek D, Pfeiffer GP. In vivo protein-DNA interactions at c-jun promotor: preformed complexes mediate the UV response. *Mol Cell Biol* 1993; **13:** 5490–9.

137. Gillardon F, Moll I Uhlmann E. Inhibition of c-fos expression in UV irradiated epidermis by topical application of antisense oligodeoxyribonucleotides suppresses activation of proliferating cell nuclear antigen. *Carcinogenesis* 1995; **16:** 1853–6.

138. Vile GF, Tanew Hiffschaw A Tyrrell RM. Activation of NFkB in human skin fibroblasts by the oxidative stress generated by UVA radiation. *Photochem Photobiol* 1995; **62:** 463–8.

139. Simon MM. UVB light induces NFkB activity independently of DNA damage in cell free cytosolic extracts. *J Invest Dermatol* 1994; **102:** 422.

140. Fritz G, Kaina B Aktories K. The ras-related small GTP binding protein Rho B is immediate-early inducible by DNA damaging treatments. *J Biol Chem* 1995; **270:** 25172–7.

141. Chu G, Chang E. Cisplatin-resistant cells express increased levels of a factor that recognises damaged DNA. *ProcNatl Acad Sci USA* 1988; **87:** 3324–7.

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Downloaded By: [DNL] At: 09:13 23 June 2008

142. Reardon JT, Nichols AF, Keeney S, et al. Comparative analysis of binding of human damaged DNA-binding protein (XPE) and *E. coli* damage recognition protein (UvrA) to the major ultraviolet photoproducts: T[c,s]T, T[t,s]T, T[6–4]T, and T[Dewar]T. *J Biol Chem* 1993, **268:** 21301-8.

143. Wakasugi M, Abe Y Yoshida Y. Purification of a novel UV-damaged DNA binding protein specific for (6–4) photoproducts. *Nucleic Acids Res* 1996; **24:** 1099–104.

144. Wakasugi M. PhD Thesis, Kanazawa University 1996.

145. Ghosh R, Peng CH Mitchell DL. Evidence for a novel DNA damage binding protein in human cells. *Proc Natl Acad Sci USA* 1996; **83:** 6945–49.

146. Smith ML, Chen IT Zhan Q. Interactions of the p53 regulated protein gadd45 with PCNA. *Science* 1994; **266:** 1376.

147. Bakalkin G, Yakovleva T, Selivanova G, et al. p53 binds single stranded DNA ends and catalyses DNA renaturation and strand transfer. *Proc Natl Acad Sci USA* 1994; **91:** 413–7.

148. Perry ME, Piette J, Zawadzki JA, et al. The mdm–2 gene is induced in response to UV light in a p53 dependent manner. *Proc Natl Acad Sci USA* 1993; **90:** 11623–7.

149. Nelson WG, Kastan MB. DNA strand breaks: the DNA template alteration that trigger p53 dependent DNA damage response pathways. *Mol Cell Biol* 1994; **14:** 1815–23.

150. Liu M, Dhanwada KR, Birt DF, et al. Increase in p53 protein half life in mouse keratinocytes following UV-B irradiation. *Carcinogenesis* 1994; **15:** 1089–92.

151. Cooke MS, Finnegan MT, Herbert KE, et al. Cell cycle and dose dependence of DNA damage and p53 expression. *Biochem Soc Trans* 1995; **23:** 481s.

152. Scheidman KH, Landsberg G. UV irradiation leads to transient changes and stability of the tumour suppressor gene p53. *Int J Oncol* 1996; **9:** 1277–85.

153. Renzing J, Hansen S Lane DP. Oxidative stress is involved in the UV activation of p53. *J Cell Sci* 1996; 1105–12.

154. Rathmall WK, Kaufman WK, Hurt JC, et al. DNA dependent protein kinase is not required for accumulation of p53 or cell cycle arrest after DNA damage. *Cancer Res* 1997; **57:** 68–74.

155. Camplejohn RS. DNA damage and repair in melanoma and non-melanoma skin cancer. *Cancer Surv* 1995; **26:** 193–206.

156. De Leeuw SM, Janssen S, Simons JW, et al. UV action spectrum for the clone forming ability of cultured human melanocytes and keratinocytes. *Photochem Photobiol* 1994; **59:** 430–6.

157. Wyllie AH. Apoptosis. *Br J Cancer* 1993; **67:** 205–8.

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158. Marloni W, Stratface E, Donelli G, et al. UV induced cytoskeletal damage, surface blebbing and apoptosis. *Eur J Dermatol* 1996; **6:** 414–20.

159. Buttke TM, Sanstrom PA. Oxidative stress as a mediator of apoptosis. *Immunology Today* 1994; **15:** 7–10.

160. Schreck R, Grassman R, Fleckenstein B, et al. Antioxidants selectively suppress activation of NFKB by human T cell leukemia virus type I Tax protein. *J Virol* 1992; **66:** 6288–93.

161. Cotton DJ, Spandau DF. Ultraviolet B-radiation does influences the induction of apoptosis and p53 in human keratinocytes. *Radiat Res* 1997; **147:** 148–55.

162. Brash DE, Rudolph JA, Simon JA, et al. A role for sunlight in skin cancer: UV induced p53 mutations in squamous cell carcinoma. *Proc Natl Acad Sci USA* 1991; **88:** 10124–8.

163. Nakazawa H, English D, Randell PL, et al. UV and skin cancer; specific p53 gene mutation in normal skin as a biologically relevant measurement. *Proc Natl Acad Sci USA* 1994; **91:** 360–4.

164. Berg RJW, Van Kranen HJ, Rebel HG, et al. Early p53 alterations in skin carcinogenesis by UVB irradiations: immunohistochemical detection of mutant p53 protein in clusters of preneoplastic epidermal cells. *Proc Natl Acad Sci USA* 1996; **93:** 274–8.

165. Nishigori C, Wang S, Miyakoshi J, et al. Mutations in ras genes in cells cultured from mouse and skin tumours induced by ultraviolet irradiation. *Proc Natl Acad Sci USA* 1994; **91:** 7189–93.

166. Berg DE, Rudolph JA, Simon JA, et al. Substitution of equally carcinogenic UVA for UVB irradiations lowers epidermal thymine dimer levels during skin cancer induction in hairless mice. *Carcinogenesis* 1995; **16:** 2455–9.

167. Hurks HMH, out-Luiting C, Vermeer BJ, et al. The action spectra for UV-induced suppression of MLR and MECLR show that immunosuppression is mediated by DNA damage. *Photochem Photobiol* 1995; **62:** 449–53.

168. McGregor JM, Yu CCW, Dublin EA, et al. p53 Immunoreactivity in human malignant melanoma and dysplastic naevi. *Br J Dermatol* 1993; **128:** 606–11.

169. Yamamoto M, Takahashi H, Saitoh K, et al. Expression of p53 protein in malignant melanoma as a prognostic indicator. *Arch Dermatol Res* 1995; **287:** 146–51.

170. Hartmann A, Blaszyk H, Cunninghamn JS, et al. Overexpression and mutations of p53 in metastatic malignant melanoma. *Int J Cancer* 1996; **67:** 313–7.

171. Pence BC, Delver E Dunn BM. Effects of dietary selenium on UVB-induced carcinogenesis and epidermal antioxidant status. *J Invest Dermatol* 1994; **102:** 759–61.

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Downloaded By: [DNL] At: 09:13 23 June 2008

172. Heagerty AHM, Fitzgerald D, Smith A, et al. Glutathione-S-transferase GSTM1 phenotypes and protection against cutaneous tumours. *Lancet* 1994; **343:** 266–8.

173. Shanley SM, Chenevix T, Rench G, et al. Glutathione-*s*-transferase GSTM1 null genotype is not over represented in Australian patients with nevoid basal cell carcinoma syndrome or sporadic melanoma. *Carcinogenesis* 1995; **16:** 2003–4.

174. Lear JT, Heagerty AHM, Smith A, et al. Multiple cutaneous basal carcinomas: glutathione-S-transferase (GSTM1, GSTT1) and cytochrome p450 (CYP2D6, CYP1A1) polymorphisms influence tumour numbers and accrual. *Carcinogenesis* 1996; **17:** 1891–6.

175. Hall J, English DR, Artuso M, et al. DNA repair capacity as a risk factor for non-melanocytic skin cancer - - a molecular epidemiological study. *Int J Cancer* 1994; **58:** 179–84.

176. Tornaletti S, Pfeiffer GP. Slow repair of pyrimidine dimers at p53 mutation hotspots in skin cancer. *Science* 1994; **263:** 1436–40.

177. Li G, Mitchell DL, Ho VC, et al. Decreased DNA repair but normal apoptosis in UV-irradiated skin of p53 transgenic mice. *Am J Pathol* 1996; **148:** 1113–23.

178. Driggers WJ, Grishko VI, LeDoux SP, et al. Defective repair of oxidative DNA damage in the mitochondrial DNA of a xeroderma pigmentosum cell line. *Cancer Res* 1996; **56:** 1262–6

179. Runger TM, Epe B Moller K. Repair of UVB and singlet oxygen induced DNA damage in xeroderma pigmentosum cells. *J Invest Dermatol* 1995; **104:** 68–73.

180. Abboussekhra A, Wood RD. Detection of nucleotide excisions in human fibroblasts by immunostaining for PCNA. *Exp Cell Res* 1995; **221:** 326–32.

181. Dumaz N, Drougard C, Sarasin A, et al. Specific UV-induced mutation spectrum in the p53 genes of skin tumours from DNA repair deficient xeroderma pigmentosum patients. *Proc Natl Acad Sci USA* **90:** 10529–33.

182. Daya Grosjean L, Robert C, Drugard C, et al. High mutation frequency in ras genes of skin tumours isolated from DNA repair deficient xeroderma pigmentosum patients. *Cancer Res* 1993; **53:** 1625–9.

183. Lunec J, Herbert KE, Blount S et al. 8OHdG: a marker of oxidative damage in SLE. *FEBS Lett* 1994; **348:** 131–8.

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184. Rosenstein BS. Rosenstein RB Zamansky GB. Repair of DNA damage induced in Systemic Lupus Erythematosus skin fibroblasts by simulated sunlight. *J Invest Dermatol* 1992; **98:** 469–74.

185. Emlen W, Niebur J Kedera R. Accelerated in vitro apoptosis of lymphocytes from patients with systemic lupus erythematosus. *J Immunol* 1994; **152:** 3685.

186. Casciola-Rosen LA, Anhalt G Rosen A. Autoantigens targetted in SLE are clustered in two populations of surface structures on apoptotic keratinocytes. *J Exp Med* 1994; **179:** 1317–30.

187. Cohen MR, Isenberg DA. UV irradiation in Systemic Lupus Erythematosus: friend or foe. *Br J Rheum* 1996; **35:** 1002–7.

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EUROPEAN COMMISSION
HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL

Directorate C - Public Health and Risk Assessment
C7 - Risk assessment

SCIENTIFIC COMMITTEE ON CONSUMER PRODUCTS

SCCP

Opinion on

Biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes.

Adopted by the SCCP
during the 8th plenary of 20 June 2006

TABLE OF CONTENTS

1. BACKGROUND

The main source of exposure to ultraviolet radiation (UVR) is the sun, but for some individuals substantial exposure occurs from artificial sources including sunbeds for cosmetic purposes, industrial lamps, arc welding and medical UVR therapies.

There is evidence that UVR can cause damage to health.

In the context of a notification under the safeguard procedure in accordance with Article 9 of the Low Voltage Directive (LVD) 73/23/EEC[1], a shortcoming in the European harmonised standard EN 60335-2-27:1997[2] has been brought to the attention of the European Commission by the Spanish authorities.

The LVD, a harmonisation Directive based on Article 95 of the EC Treaty, regulates the placing on the market of electrical appliances with a voltage rating between 50 and 1000 V (AC) and 75 and 1500 V (DC) with respect to health and safety. According to Article 95(3) of the EC Treaty[3] the LVD takes as its basis a high level of protection. Electrical appliances that comply with European harmonised standards under the LVD are presumed to comply with the corresponding essential health and safety requirements of the LVD.

The above mentioned shortcoming in the European harmonised standard EN 60335-2-27:1997, which has been reported to the European Commission, relates to the fact that the standard does not entirely cover the health and safety aspects which have to be considered during the design phase of the electrical appliance. In particular, it does not provide limit values on the maximum effective irradiance of UV radiation for the types of tanning devices that are covered by the scope of the standard.

In reaction to the notification and after consultation of governmental experts of Member States in the LVD ADCO[4] working group the Commission Services decided to request a scientific opinion from the "Non-Food Scientific Committees".

The scientific opinion will be used when preparing a Commission mandate to the European standardisation organisations regarding:

- the revision of the above mentioned standard EN 60335-2-27:1997;
- drafting or revising product related standards covering risks associated with the exposure of persons to ultraviolet radiation (UVR).

[1] Council Directive 73/23/EEC of 19 February 1973 relating to electrical equipment designed for use within certain voltage limits (OJ L 77, 26.3.1973); Directive as amended by Directive 93/68/EEC (OJ L 220, 30.8.1993)

[2] EN 60335-2-27:1997 "Safety of household and similar electrical appliances - Part 2-27: Particular requirements for appliances for skin exposure to ultraviolet and infrared radiation"

[3] Article 95 of the EC Treaty see: www.europa.eu.int/eur-lex/en/treaties/selected/livre221.html

[4] "Administrative co-operation" working group in the area of the LVD, consisting of the Market Surveillance representatives from all Member States and the European Commission

2. TERMS OF REFERENCE

The scientific committee is requested to answer the following questions in relation to the sunbeds for cosmetic purposes:

1. What are the general health and safety implications (negative and positive) relating to the exposure of persons to ultraviolet radiation (UVR)[5]?

2. What are the differences between risks associated with exposure of persons to natural UVR and those risks from artificial UVR? What are the differences regarding the health and safety risks with respect to exposure of persons to UVA, UVB and UVC radiation respectively?

3. Is the total dose value of UVR the only effective health and safety parameter with regard to the risks associated with exposure of persons to both natural and artificial UVR? What is the validity of the Bunsen-Roscoe law[6] over the range of irradiances and wavelengths associated with exposure of persons to both natural and artificial UVR?

4. What are the specific health and safety implications (negative and positive) relating to the exposure of persons to UVR from tanning devices for cosmetic purposes?

5. Are limit values necessary for the irradiance of UVR from artificial sources, in particular from tanning devices for cosmetic purposes, with respect to health and safety? Is it necessary to give different values for the irradiance of UV-A, UV-B and UV-C radiation respectively? If so, please specify the limit values for the irradiance of artificial UVR above which adverse health effects will occur. What are the uncertainties of these limit values?

6. Please specify the limit values of total dose of artificial UV-A, UV-B and UV-C radiation above which adverse health effects will occur, taking into account skin phototype, intensity of exposure, duration of exposure and associated uncertainties.

Supporting documents

- Spanish formal objection against European harmonised standard EN 60335-2-27
- ICNIRP statement (2003) (http://www.icnirp.org/documents/sunbed.pdf)
- WHO guidance brochure: artificial tanning sunbeds (2003) (http://www.who.int/uv/publications/en/sunbeds.pdf)
- ESA (European Sunlight Association) Position paper
- ESA (European Sunlight Association) frequently asked questions (http://www.europeansunlight.org/test/esa/html/faq.htm)
- NRPB: Health effects from Ultraviolet Radiation V13 No.1 2002 (http://www.nrpb.org/publications/documents_of_nrpb/pdfs/doc_13_1.pdf)
- NRPB: Advice on Protection Against Ultraviolet Radiation V13 No.3 2002 (http://www.nrpb.org/publications/documents_of_nrpb/pdfs/doc_13_3.pdf)

[5] The International Commission on Illumination (CIE) defines ultraviolet radiation (UVR) as optical radiation between 100 and 400 nm. The spectral region is divided into three photo-biological spectral regions: UVC (100-280 nm), UVB (280-315 nm) and UVA (315-400 nm).

[6] The Bunsen-Roscoe law (law of reciprocity) states that a certain biological effect is directly proportional to the total energy dose irrespective of the administered regime. Dose is the product of intensity and the duration of exposure. (Bunsen R, Roscoe HE, Photochemische Untersuchungen, Poggendorff's Annalen 1855: 96: 373-394, 1857: 100: 43-88 and 481-516, 1857: 101:235-263, 1859: 108: 193-273.).

- SSK: Schutz des Menschen vor den Gefahren der UV-Strahlung in Solarien (http://www.ssk.de/2001/ssk0101w.pdf)
- Scientific investigations from ECOFYS
- Other documents

National and international organisations contributing to the discussion

- ICNIRP - International Commission on Non-Ionizing Radiation Protection (http://www.icnirp.org)
- WHO - World Health Organization (http://www.who.int)
- IARC - International Agency for Research on Cancer (http://www.iarc.fr)
- UNEP - United Nations Environment Programme (http://www.unep.org/PDF/Solar_Index_Guide.pdf)
- NRPB - National Radiological Protection Board (UK) (http://www.nrpb.org)
- SSK – Strahlenschutzkommission (Germany) (http://www.ssk.de)
- IMM – Institute of Environmental Medicine (Sweden) (http://www.imm.ki.se)
- EPA - U.S. Environmental Protection Agency (US) (http://www.epa.gov)
- FDA - U. S. Food and Drug Administration (US) (http://www.fda.gov)
- NIES - National Institute for Environmental Studies (JP) (www@nies.go.jp)
- List of experts provided by ESA (European Sunlight Association)

3. OPINION

The cosmetic purpose of using a sunbed is to achieve a tan. The tanning effect has been demonstrated and quantified in a study that followed a Food and Drug Administration (FDA) protocol (Caswell, 2000) with 3 weekly exposures for 8 weeks. A significant tanning effect was evident after 6 exposures and the level of tan increased steadily over the 8-week assessment period. Another study, with twice weekly exposure for 6 weeks, demonstrated tanning (Ruegemer et al, 2002).

Commercial sunbeds were developed in the 1970s and came into widespread use in the 1990s. Thus, the full health effects of artificial tanning are not yet known. It will take several years before the real picture of the role of the sunbeds in inducing skin cancer becomes fully apparent, due to the long induction period of this disease.

In this Opinion, the term "sunbed" refers to all types of UV tanning devices for cosmetic purposes.

The six questions raised in the Terms of Reference have also been addressed by van der Leun and Forbes (2005).

1. What are the general health and safety implications (negative and positive) relating to the exposure of persons to ultraviolet radiation (UVR)?

1.1 Negative Effects

1.1.1 Acute

Skin

Exposure of the skin to solar UVR (~ 295 – 400 nm) results in inflammation (erythema/sunburn) that is usually maximal about 24 hours later (Farr et al, 1988). This response is primarily induced by its UVB component (~295-315nm) (see section 2(b).1) and is associated with increased blood flow (Young et al, 1985), increased sensitivity to thermal and mechanical stimuli (Harrison et al, 2004), a dermal inflammatory infiltrate (Gilchrest et al, 1983; Hawk et al, 1988) and the presence of apoptotic keratinocytes know as sunburn cells (Sheehan and Young, 2002). Individual sensitivity to erythema can be assessed by determining the minimal erythema dose (MED) that increases with skin type as shown in Table 1 but MED is not predictive of skin type because there is considerable variation of MED within different white skin types (Harrison and Young, 2002). Within a few days of exposure to solar UVR delayed melanogenesis (tanning) occurs that is dependent on skin type and like erythema is primarily caused by UVB. This results from the synthesis of melanin in melanocytes: specialized pigment producing cells in the epidermis that transfer melanin to keratinocytes. Many people expose themselves to UVR, either from the sun or sunbeds, for the sole purpose of obtaining a tan that becomes more intense with repeated exposure. This repeated exposure also results in thickening of the epidermis, especially the *stratum corneum*, the outermost dead layer, which results in the skin feeling dry. The UVA content of solar UVR makes a relatively small contribution to erythema and tanning (see section 2(b).1). A UVB tan is photoprotective against erythema but the level of photoprotection is modest and equivalent to a sunscreen with a sun protection factor (SPF) of 2-3 (Agar and Young, 2005). However, tans primarily induced by UVA are not photoprotective against erythema

(Gange et al, 1985). UVR exposure, in particular UVA, results in transient immediate pigment darkening (IPD) the function of which is not known (Routaboul et al, 1999).

Table 1: A classification of skin phototypes based on susceptibility to sunburn in sunlight, together with indicative MEDs that might be expected following UV exposure on unacclimatized skin

Skin Photo Type	Sunburn Susceptibility	Tanning Ability	Classes Of Individuals	No. in SED[§] for 1 minimal erythema dose (MED)
I II	High High	None Poor	Melano-compromised	1 - 3
III IV	Moderate Low	Medium Dark	Melano-competent	3 - 7
V VI	Very low Extremely low	Natural brown skin Natural black skin	Melano-protected	7 - >12

[§] The unit of erythemal radiation is the Standard Erythema Dose (SED), where 1 SED is equivalent to an erythemal effective radiant exposure of 100 Jm^{-2} (CIE 1998). It requires an exposure of about 3 SED to produce just minimal erythema in the unacclimatized white skin of the most common northern European skin types (Harrison & Young 2002). An exposure of 5-8 SED will result in moderate sunburn and 10 SED or more can result in a painful, blistering sunburn.

Solar UVR exposure can aggravate certain skin diseases such as lupus erythematosus and pemphigus (Morison et al, 1999) and induce skin photosensitivity with commonly used UVR-absorbing systemic drugs and topically encountered chemicals (Ferguson et al, 1999). Furthermore, there is a wide range of acquired and genetic UVR and visible radiation photodermatoses that are beyond the scope of this document.

Exposure of the skin to UVR can suppress cell-mediated immunity when assessed with the sensitisation (Kelly et al, 2000) and the elicitation arms (Moyal and Fourtanier, 2003) of the contact hypersensitivity (CHS) response. A single sub-erythemal exposure of solar simulating radiation (SSR) suppresses the induction (sensitisation) arm of the CHS response in skin types I/II (Kelly et al, 2000) but erythemal exposure is necessary to suppress the elicitation arm (Moyal and Fourtanier, 2003). Suppression of cell-mediated immunity is thought to play a role in UVR-induced skin cancer and infectious diseases, e.g. Herpes simplex infections.

The clinical effects of UVR exposure, whether acute or long-term, are underpinned by many molecular and cellular events (Matsumura and Ananthaswamy, 2002). UVR-induced damage to epidermal DNA, especially cyclobutane pyrimidine dimers (CPD), is thought to be responsible for many adverse effects of solar UVR, including immunosuppression, and can be demonstrated in the skin immediately after exposure to erythemal and sub-erythemal UVR (Young et al, 1998). DNA integrity is maintained by complex repair processes and the p53 mediated elimination of damaged cells by apoptosis (sunburn cell formation). Failure of these processes is though to result in skin cancer (Matsumura and Ananthaswamy, 2002). Membrane as well as DNA effects also contribute to UVR-induced skin damage. The relevant cell surface or cytoplasmic chromophores are currently unknown. There is considerable evidence that the photoisomerization of stratum corneum trans-urocanic acid (UCA) to the cis-form also plays an important role in immunosuppression. Exposure to erythemal UVR or repeated sub-erythemal UVR results in a loss of epidermal antigen presenting Langerhans cells (Novakovic et al, 2001).

Eye

The eye is a complex multi-layered organ that receives visible radiation on its retina. The intermediate layers attenuate UVR to different degrees and thereby protect the retina from UV photodamage. The outermost cornea absorbs UVC and a substantial amount of UVB, which is further attenuated by the lens and the vitreous humor in front of the retina. UVA is less well attenuated by the cornea but is attenuated by the internal structures so it does not reach the retina (Sliney, 2001; Roberts, 2001; Johnson, 2004).

The only acute clinical effect of UVR on the eye is photokeratitis that is also known as snow blindness or welder's flash (Sliney, 2001; Roberts, 2001; Johnson, 2004). This is a painful transient inflammatory condition caused by UVC and UVB-induced damage to the corneal epithelium. Typically it appears 6-12 hours after exposure and resolves, within 48 hours. In some ways it can be regarded as sunburn of the eye.

1.1.2 Chronic

Skin Cancer

An IARC monograph on solar and ultraviolet radiation classified solar radiation as "carcinogenic" to humans (Group 1) and UVA and UVB and the use of sunbeds as "probably carcinogenic" to humans (Group 2A)(IARC, 1992).

Non-melanoma

Solar exposure is recognized as the main environmental factor in the development of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) that form the great majority of skin cancers (IARC, 1992). These lesions result in a high level of morbidity with only occasional mortality from infrequent metastatic SCC. UVR is also associated with actinic keratoses (AK) that may be regarded as precancerous lesions for SCC.

The evidence for UVR in these lesions has been primarily ecologic (reviewed by Armstrong and Kricker, 2001), supported by mouse studies in the case of SCC (de Gruijl, 1995). More recently, a role for UVR has been supported by the presence of UVR "signature mutations" in tumours (Brash et al, 1996). Skin type is an important determinant of BCC and SCC risk with skin types I and II at greater risk than skin types III and IV, with the lowest risk being in skin types V and VI. SCC is associated with chronic UVR exposure and is more common in people with outdoor occupations. There is evidence that BCC is associated with intermittent exposure (Kricker et al, 1995). Many cancer registers do not record BCC and SCC. Melanoma has been registered for many years and there is evidence that the incidence rate is increasing substantially in Europe (Boyle et al, 2004). Data from the skin cancer registry in Trentino, Italy showed incidence rates of 88 per 100,000 for BCC and 29 per 100,000 for SCC in the period 1993-1998 in comparison to 14 per 100,000 for melanoma (Boi et al, 2003).

Melanoma

Though much less common than BCC and SCC, melanoma is the main cause of death from skin cancer. There were an estimated 35,000 cases of melanoma diagnosed in Europe in 2000 with 9000 deaths (Boyle et al, 2004). Sun exposure is established as the major environmental determinant of melanoma (IARC, 1992; Donawho et al, 1994; Armstrong and Kricker, 1993) and the risk of melanoma depends on the interaction between environmental exposures and the genes which determine susceptibility. Melanoma is rare in black skinned peoples (Parkin et al, 1997).

There is no doubt that skin colour and sun exposure are potent determinants of risk of melanoma. World incidence figures show that the risk to individuals is greatest where pale skinned peoples live at low latitudes such as Australia and New Zealand (Parkin et al, 1997; Bulliard, 2000). In areas of the world where dark and pale skinned peoples live at high UV exposure levels, such as Hawaii, then the risk to pale skinned people is much greater than for their darker skinned neighbours (Chuang et al, 1999). Within Europe there is variation in incidence which reflects the interaction between skin colour and latitude as the peak incidence is in the north, in countries such as Sweden, where fair skinned peoples live an outdoor life and have access to sunny holidays in the south, or Switzerland where fair skinned peoples live at high altitude (Parkin et al, 1997). So, in the period 1996-8 the incidence rates (European Standardised Rates) in women were reported to be 17 per 100,000 in Switzerland, 6 per 100,000 in Spain and 16 per 100,000 in Sweden (de Vries and Coebergh, 2004).

Broadly, it would be reasonable to conclude that the risks of melanoma are so low in black-skinned peoples that sun protection advice should be directed only towards white-skinned peoples. The difficulty here is that skin colour is a continuous rather than a discontinuous variable. Some Asian peoples have quite a high tendency to burn and within white skinned peoples there is variation in susceptibility to sunburn and to melanoma which is related to skin colour and whether there are freckles or not. Data from many case control studies have established that phenotypic characteristics associated with vulnerability to the sun are risk factors for melanoma. Gandini et al (2005a) recently summarized these in a meta-analysis of 60 such studies. Her overall conclusions were that skin type I (versus IV) was associated with a relative risk (RR) of 2.1 for melanoma (95% CI 1.7-2.6), where skin type I, is skin which always burns and never tans and skin type IV is skin which never burns. A high density of freckles was associated with a RR=2.1 (95% CI 1.8-2.5), eye colour (Blue vs. Dark: RR=1.5, 1.3-1.7) and hair colour (Red vs. Dark: RR=3.6, 2.6-5.4). Hence, whatever the ethnic origin of Europeans, in terms of skin type, health advice about skin cancer should be directed to those individuals with a tendency to burn rather than to tan, those who have freckles and those with fair (particularly red) hair. It is clear from the level of these risk factors that the relative risk is significant but the absolute risk associated with these phenotypic characteristics is relatively small in European countries with incidence rates of between 5 and 17 per 100,000 per annum (European Standardised Rates) (de Vries and Coebergh, 2004). The prevalence of individuals with these risk factors will vary considerably between populations. In a study of healthy women in the UK, 8% had red hair and 6% had very high freckle scores on the back (Bertram et al, 2002).

Risk of melanoma is also greater in patients with larger numbers of melanocytic naevi whether banal or clinically atypical, where an atypical naevus is defined as a mole 5mm or greater in diameter, with an irregular or ill-defined edge and variable pigmentation. Numerous case-control studies have addressed this, and a second meta-analysis by Gandini et al (2005b) showed that the number of common naevi was confirmed as an important risk factor for melanoma with a substantially increased risk associated with the presence of 101-120 naevi compared with <15 (pooled Relative Risk (RR) = 6.9; 95% Confidential Interval (CI): 4.6, 10.3) as was the number of atypical naevi (RR = 6.4 95%; CI: 3.8, 10.3; for 5 versus 0). Twin studies have provided strong evidence that naevus number is genetically determined (Wachsmuth et al, 2001; Zhu et al, 1999; Easton et al, 1991) and the association of the phenotype with melanoma risk therefore implies the presence of naevus genes, which are also low penetrance melanoma susceptibility genes. Thus, persons with this atypical naevus phenotype have an increased risk of melanoma, which is significantly higher than that associated with red hair or freckles. The prevalence of this

phenotype also varies between populations but was reported in 2% of individuals in the UK (Bataille et al, 1996).

The phenotypes described above are genetically determined and therefore it is not surprising that family history is a risk factor for melanoma. Familial melanoma was reported in the 19th century in the UK (Norris, 1820), and a strong family history of melanoma is the most potent risk factor for melanoma (Kefford et al, 1999). Any family history of melanoma is associated with a doubling of risk for close relatives. A study from the Utah population database estimates risk to first-degree relatives of melanoma cases to be 2.1 (95% CI 1.4-2.9). A similar study from the Swedish Cancer Registry estimated the standardized incidence ratio for melanoma to be 2.4 (95% CI 2.1-2.7) for offspring if one parent had a melanoma, 3.0 (95% CI 2.5-3.5) for an affected sibling and 8.9 (95% CI 4.3-15.3) if a parent and a sibling were both affected. The highest ratio was 61.8 (95% CI 5.8-227.2) for offspring when a parent had multiple melanomas (Hemminki et al, 2003). Such patterns of risk are indicative of a significant hereditary component, which is most probably inherited as an autosomal dominant trait with incomplete penetrance. The risk of melanoma increases with age although in Europe the age distribution curve is relatively flat and in Europe the incidence is commonly higher in women than in men (Parkin et al, 1997).

Sun exposure is clearly the major environmental risk factor for melanoma as discussed above. A third meta-analysis reported by Gandini et al (2005c) has supported the conclusions of many individual case-control studies that intermittent sun exposure remains the most predictive environmental risk factor for melanoma (random effects model RR=1.6 (95% CI 1.3-2.0) and that sunburn, especially in childhood is a significant risk factor, although there was much heterogeneity between studies. A random effects model suggested a highly significant effect for sunburn at any age (RR=2.0 95% CI 1.7-2.4). The pooled analysis provided no evidence for a causal effect of chronic sun exposure on melanoma risk, RR=1.0 (95% CI 0.9-1.0). Further evidence for a role of sun exposure in melanoma comes from penetrance studies for the melanoma susceptibility gene CDKN2A in which there was evidence for an interaction between susceptibility genes and latitude of residence so that penetrance was highest in families with germline CDKN2A mutations living in Australia when compared with those in Europe (Bishop et al, 2002).

A meta-analysis, incorporating latitude, showed that phenotypic indicators of excessive sun exposure (representing gene/environment interaction) in fair-skinned individuals are risk factors for melanoma (Gandini et al, 2005a). Pre-malignant and malignant lesions were associated with a RR=4.3 (2.8-6.6) and actinic damage indicators with a RR=2.0 (1.2-3.3). This is of note despite the lack of epidemiological evidence from case-control studies for chronic sun exposure as a risk factor for melanoma.

In summary, there is strong evidence that excessive sun exposure is causal for melanoma. Evidence persists that the exposure pattern is important, e.g. intermittent, although the observation in some studies that actinic skin damage is a risk factor provides some evidence that chronic over-exposure is also causal in some patients. The evidence is also strong that excessive sun exposure increases the risk of melanoma in those with a strong family history. There is an emerging view, based upon epidemiological and biological studies that there may be more than one route to melanoma: one associated with low or intermittent sun exposure and for which numerous naevi is a risk factor and another with chronic over exposure (Whiteman et al, 2003). All of the risk factors quoted above are independent risk factors in individual case control studies

and therefore the presence of multiple risk factors in an individual increases the relative risk of melanoma.

Health education is postulated to be most effective when targeted at those at greatest risk. Thus, UVR risk communication to European citizens is probably best directed at those with established risk factors (e.g. family history, fair skin and multiple naevi). There is a need to communicate these complex issues to the European citizen in a way that is easily understood.

Photoageing

Exposure of the skin to UVR results in UVR-induced skin ageing known as photoageing, which is very evident, when one compares normally sun-exposed (face) and sun-protected (buttock) sites. Clinical symptoms of photoageing include wrinkling, laxity and disturbances of the distribution of pigmentation (Glogau, 1996). Photoageing is thought to at least partially arise from the induction of matrix metalloproteinases (MMPs) that degrade collagen, the major structural protein of the dermis (Fisher et al, 2002). Photoageing, assessed by elastosis, is an indicator of non-melanoma skin cancer risk (Kricker et al, 1991).

Effects on the Eye

There is epidemiological evidence that solar UVR exposure increases the risk of cataracts of the lens, anterior lens capsular change and pterygium (Johnson, 2004). *In vivo* and *ex vivo* acute studies on mammalian lens (Pitts et al, 1977; Merriam et al, 2000; Oriowo et al, 2001) and a chronic *in vivo* study (Jose and Pitts, 1985) have indicated that the UVB part of the solar spectrum is most likely to be responsible for any long term effects that solar UVR has on the lens. There is also epidemiological evidence that solar UVR exposure results in ocular melanoma, especially from a study in Australia (Vajdic et al, 2002) that showed that choroid and ciliary body melanoma were positively associated with time outdoors on weekdays with OR up to 1.8 (95% CI 1.1 – 2.8) and $p = 0.01$ for trend. Unlike melanoma of the skin there is no latitude gradient for ocular melanoma (Vajdic et al, 2003), which may be because UVR dose to the eye is probably determined by UVR exposure from horizon sky that is less affected by latitude.

1.2 Positive Effects

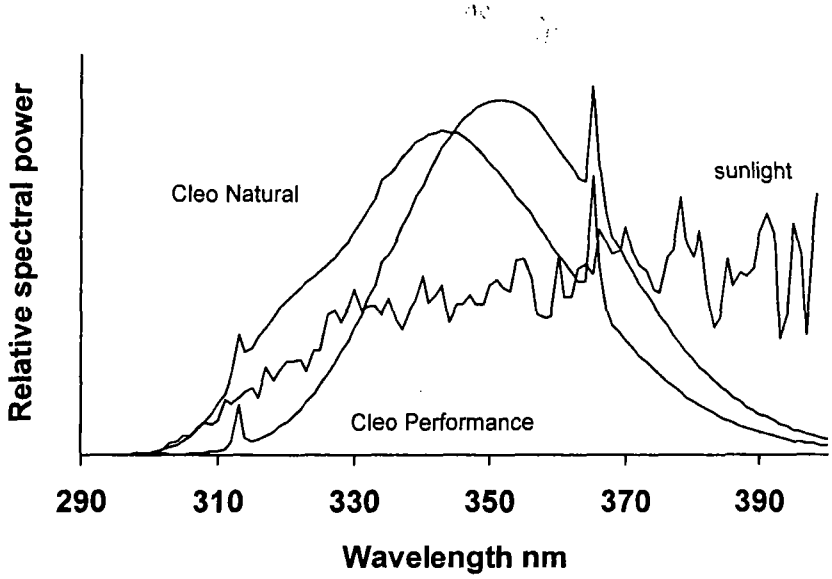
Exposure to solar UVB initiates the synthesis of vitamin D, in the skin, that is vital for musculo-skeletal health (Vieth, 2005) and there is evidence that large numbers of people are vitamin D insufficient (Holick, 2005). Rickets, widespread in industrialized cities in 19th century Europe, is being increasingly diagnosed in ethnic minority populations in Northern and Southern Europe and can be attributed to vitamin D deficiency (Pedersen, 2003; Yeste and Carrascossa, 2003; Ladhani et al, 2004; Mallet et al, 2004). There is also emerging evidence, as yet mainly ecologic (i.e. by association), that vitamin D is important in other aspects of health such the prevention of autoimmune disorders (Ponsonby et al, 2005) and several internal malignancies (Berwick and Kesler, 2005; Giovannucci et al., 2006). There are also recent data suggesting that vitamin D may be important in improving outcome from cancer (Chen and Holick, 2003; Zhou et al, 2005). Exposure to the sun may therefore have widespread beneficial effects but it seems likely that these beneficial effects would also be produced by increased oral intake of vitamin D. However,

the role of vitamin D in non-skeletal health, along with its association with UVR exposure remains a very controversial area and more data are needed for informed discussion.

2(a) What are the differences between risks associated with exposure of persons to natural UVR and those risks from artificial UVR?

There are no physical differences in type of radiation between natural and artificial UVR *per se*. However, there are important differences in the spectral distribution and absolute and relative irradiances of UVR from the sun and artificial sources, and between different artificial sources as shown in Figure 1. There is no standard solar spectrum because this varies with factors such as season, latitude and time of day. From a physical standpoint, the UV emission from sun is primarily within the UVA range. Artificial emission spectra are different from solar emission spectra from a physical point of view.

It is relatively easy to compare the acute risks of exposure to natural and artificial UVR, which are similar, the details of which are discussed in Section 4. It is much more difficult to compare chronic effects which, in the sun, also depend on patterns of exposure.



¶ Measured in Melbourne (38° S) at solar noon on 17 January 1990. Measurements were made at the Australian Radiation Laboratory with a Spex 1680B double monochromator with a resolution of 1 nm

Figure 1 Emission spectra of solar UVR and two tanning lamps (i) Cleo natural and (ii) Cleo performance

Data on the risk of skin cancer associated with artificial UVR sources (see Section 4) are few compared with those related to sun exposure. Furthermore the tanning device studies are often uninformative because of small numbers of cases and controls, and low usage of the devices. There are also great difficulties in collecting adequate exposure data because of recall bias and lack of user knowledge of the type of UVR emitted by the devices. Many studies therefore have recorded only whether a tanning device has been used "ever" or "never" so that the power to address dose or age effects is limited.

Furthermore, tanning device users are often those who sunbathe frequently and it is likely that case-control studies are seriously confounded. There are some data published on the effects of medical use of artificial UVR sources. Although the UVR dose is considerably lower than that to which users of tanning devices are potentially exposed, such studies do have the merit of much more accurate dosage estimation.

Photo(chemo)therapy is used in the treatment of skin diseases. The use of psoralen plus UVA (PUVA) to treat psoriasis is known to cause skin cancer (Stern and Laird, 1994) but PUVA is mechanistically quite different from UVA and UVB and therefore is not relevant to the current discussion. In the PUVA cohort study reported by Stern from the United States, there was no discernable additional effect of exposure to UVB (Stern and Laird, 1994). In a study of psoriatics treated with coal tar and UVB in the 1950s followed up for 25 years there was no demonstrable increased risk of skin cancer but the numbers treated were relatively small (280) (Pittelkow et al, 1981). In an even smaller study of 195 German psoriatics treated with broadband (n=69) or narrow band UVB (n= 126) from 1994 to 2000 only one skin cancer had occurred by 2004. This was an *in situ* melanoma which developed in the same year that narrow band UVB therapy was begun (Weischer et al, 2004). A study in Scotland with a median follow up period of 4 years has shown a small increase in BCC after treatment with narrow band UVB phototherapy (Man et al, 2005).

Overall, the risks of skin cancer from the medicinal use of artificial UVR (in the absence of photosensitizers) appear to be small but the data are few and the dose to which the patients are exposed tends to be significantly smaller than users of commercial sunbeds are potentially exposed to. It is likely, from our knowledge of skin cancer and solar UVR, that the skin cancer risk attributable to artificial UVR will be greater in those who are genetically susceptible such as the fair skinned.

Household lights emit significant amounts of UVR (Sayre et al, 2004) and several case-control studies have addressed risk for melanoma associated with such exposure. The earliest study suggested an elevated risk associated with exposure to fluorescent lights at work (Beral et al, 1982) but all subsequent studies failed to identify such a risk (Osterlind et al, 1988; Rigel et al, 1983; Walter et al, 1992; Holly et al, 1995).

2(b) What are the differences regarding the health and safety risks with respect to exposure of persons to UVA, UVB and UVC radiation respectively?

Coblentz introduced the concept of the spectral regions UVA, UVB and UVC at the Second International Congress on Light in Copenhagen in 1932. These regions were determined by the transmission properties of three common glass filters; a barium-flint filter defined the UVA (315-400nm); a barium-flint-pyrex filter the UVB (280-315nm); and a pyrex filter defined the

UVC (wavelengths shorter than 280nm). So the basis of these divisions has its grounding in physics, and not biology, although these definitions have been very useful in biology. Although these are the official designations of the Commission Internationale de l'Éclairage (CIE), other authorities, especially in the biological and clinical sciences, use different definitions such as UVA (320-400nm), UVB (290-320nm) and UVC (190-280nm). More recently, the terms UVA-I (340-400nm) and UVA-II (315-340nm) have come into use because of a better understanding of mechanistic differences between UVB and UVA. Mechanistically, UVA-II is similar to UVB in which the target molecule (e.g. DNA) is directly altered by its absorption of UVR energy. In contrast, UVA-I reactions tend to cause indirect damage to target molecules via reactive oxygen species (ROS) generated by UVR absorption by other molecules.

2(b).1 Acute Effects

The wavelength dependency of a given photobiological effect is demonstrated by its action spectrum, which depends on a variety of factors but is based on the absorption spectrum of the chromophore (UVR absorbing biomolecule) and the optical properties of the skin. Action spectroscopy and studies with different broad-spectrum sources show that UVB is much more effective than UVA for most acute endpoints studied in human skin. This includes erythema (Anders et al, 1995; CIE 1998; Young et al, 1998), delayed pigmentation (Parrish et al, 1982), DNA photodamage (Young et al, 1998) and UCA photoisomerization (McLoone et al, 2005). In general, UVB is 3 to 4 orders of magnitude more effective per unit physical dose (J/cm^2) than UVA, but this difference depends on the specific wavelengths/wavebands being compared. Action spectra for immunosuppression in human skin are not available. UVB is known to be immunosuppressive but the role of UVA is still not clear (Phan et al, 2006). The action spectrum for IPD shows that UVA is more effective than UVB (Irwin et al, 1993).

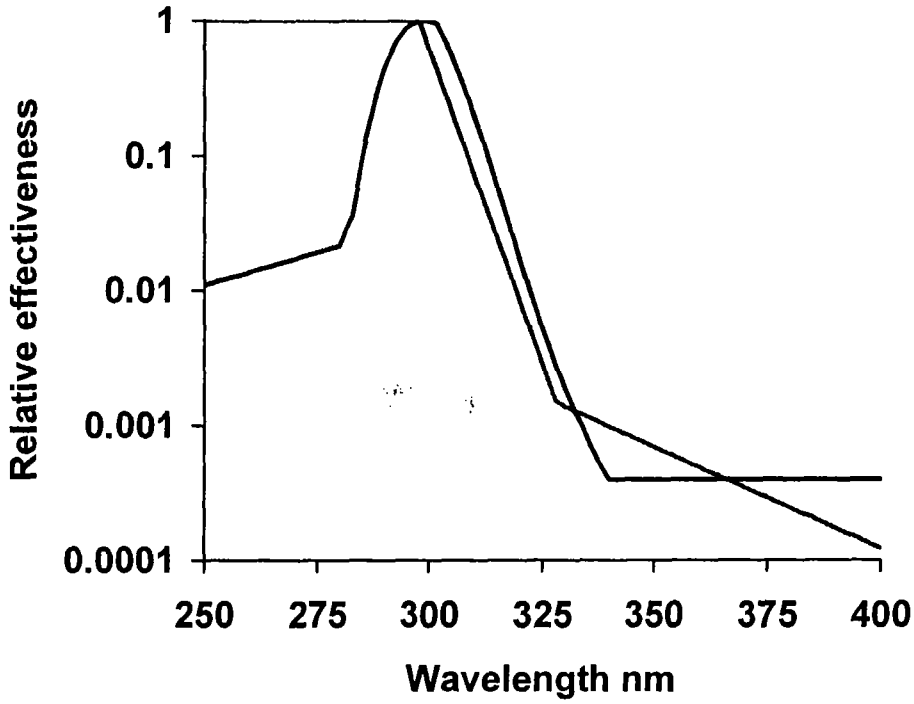
UVC is not an issue for terrestrial solar UVR because it is completely absorbed by the ozone layer. In any case, UVC is strongly attenuated by chromophores in the upper epidermis (Young, 1997) and UVC-induced DNA damage in the dividing basal layer of human epidermis is not readily detected (Campbell et al, 1993; Chadwick et al, 1995) which may explain why the dose response curve for UVC erythema in human skin is very much less steep than for UVB (Diffey and Farr, 1991). It is unlikely that UVC from artificial sources presents an acute or long-term hazard to human skin. However, UVC is likely to cause acute photokeratitis.

Wavelength dependency is crucial in determining the biological effect of a given spectral region of a UVR source. For example, the 0.8% UVB content of a tanning lamp accounted for 75% of the CPD (cyclobutane pyrimidine dimers) that it induced in human keratinocytes *in vitro* (Woollons et al, 1999). Thus action spectra are essential as weighting functions to determine the biological effects of different broad-spectrum UVR emission spectra (see Section 5). Emission spectra without relevant action spectrum weighting are of very limited value in risk assessment. Action spectra are only valid if there is no interaction between different spectral regions. However, there is evidence that such interactions do occur at the cellular level (Schieke et al, 2005).

2(b).2 Chronic Effects

The wavelength dependencies for skin cancer (SCC) and photoageing (elastosis) have been determined in hairless mouse models (de Gruijl, 1995; Kligman and Sayre, 1991) and these studies have shown action spectra similar to that for human erythema (CIE, 1998; Young et al, 1998). Figure 2 shows the action spectra for human erythema and non-melanoma skin cancer (SCC) (CIE 1998, 2000) and it can be seen that these are very similar, especially in the solar UVB and UVA-II (315-340nm) ranges. Thus, one might conclude that erythema, primarily caused by UVB, can be regarded as a surrogate risk factor for SCC and photoageing. There is no animal model for UVR-induced BCC.

Figure 2: The CIE (1987) reference action spectrum for erythema in human skin (red) and the estimated CIE (2000) action spectrum for human squamous cell carcinoma (blue) based on mouse studies



Sunburn, an important risk factor for melanoma, has therefore implicated UVB in its pathogenesis (Wang et al, 2001). The incidence of melanoma, as well as BCC and SCC, is very high in xeroderma pigmentosum (XP) with defective excision repair of UVB-type DNA damage, e.g CPD. The wavelength dependency for melanoma however is not yet established because of the lack of a good animal model (Noonan et al, 2003). Melanomas have proved extremely difficult to induce by UVR alone in mice. Wavelength dependency has been determined in a fish model (*Xiphophorus*) (Schartl et al, 1997) the value of which is limited because its melanoma-like lesions arise from the dermis instead of the epidermis and fish are phylogenetically very different from humans. Studies in these fish however showed that visible and UVA radiation, as well as UVB (Setlow et al, 1993) induced lesions that raised concern that UVA might be causal for human melanoma as well or instead of UVB. A mammalian opossum model also developed

melanoma-like lesions after broad-band UVA exposure but with low potency compared to broad-band UVB (Robinson et al, 2000). A mouse model was described in 2003 (the hepatocyte growth factors/scatter factor transgenic mouse) in which melanomas with a strong epidermal component were induced (Nonnan et al, 2003). Neonatal UV irradiation was necessary and sufficient to induce melanoma although adult irradiation increased the number of lesions. In 2004 the same group reported studies using the mouse in which UVB but not UVA induced melanoma, providing perhaps more persuasive evidence that UVB exposure is causal rather than UVA (De Fabo et al, 2004).

Studies of somatic mutations in a variety of genes have been reported in the search for evidence to support a role for UVB exposure. Genes such as p53 have, however, failed to show the characteristic UVB signature C to T transitions and CC to TT mutations, providing additional concern that UVB may not be the only causal waveband. Recently, mutations in BRAF (downstream of RAS) were found in a majority of naevi and melanoma. The dominant point mutation (T1796A) is not characteristic of UVB radiation, but this does not exclude a causal role for UVR (de Gruijl, 2003).

It is more difficult to determine UVA induced mutagenesis because DNA does not significantly absorb UVA at doses obtained with solar exposure. It is thought that UVA induced mutagenesis is mainly mediated by photosensitising reactions that generate reactive oxygen species. In one system it was suggested that T to G transversions are typical of UVA induced damage (Drobetsky et al, 1995) but in another G to T transversions were seen as well as small tandem base deletions (Pfeifer et al, 2005). There is no consensus on UVA signature somatic mutations in tumours. Furthermore, it is possible that UVA may have an indirect adverse effect on the micro-environment in the dermis and dermo-epidermal junction by inducing growth factor release which may have a proliferative effect on melanocytes (Brenner et al, 2005).

In summary, UVB is likely to be the main cause of photoageing and SCC. Sunburn, a marker for excessive UVR exposure, is a risk factor for melanoma. UVB is the main cause of sunburn but this does not necessarily mean that it is the prime cause of melanoma, the spectral dependence of which remains unknown. The conservative approach is to restrict UVB and UVA exposure in susceptible phenotypes until wavelength dependency is established. UVC exposure is unlikely to cause acute or long-term damage to the skin but can cause severe acute damage to the eye and should not be permitted at all from any tanning device.

3 (a) Is the total dose value of UVR the only effective health and safety parameter with regard to the risks associated with exposure of persons to both natural and artificial UVR? (b) What is the validity of the Bunsen-Roscoe law over the range of irradiances and wavelengths associated with exposure of persons to both natural and artificial UVR?

Experiments in which the photoresponse of a material is investigated as a function of radiant flux (dose rate or irradiance) are commonly called *reciprocity law experiments*. Bunsen and Roscoe (1859) are credited with conducting the first reciprocity law experiments. Reciprocity holds in photobiology when the observable response depends only on the total administered radiant exposure (commonly referred to as *dose*) and is independent of the two factors that determine total dose, that is, irradiance and exposure time.

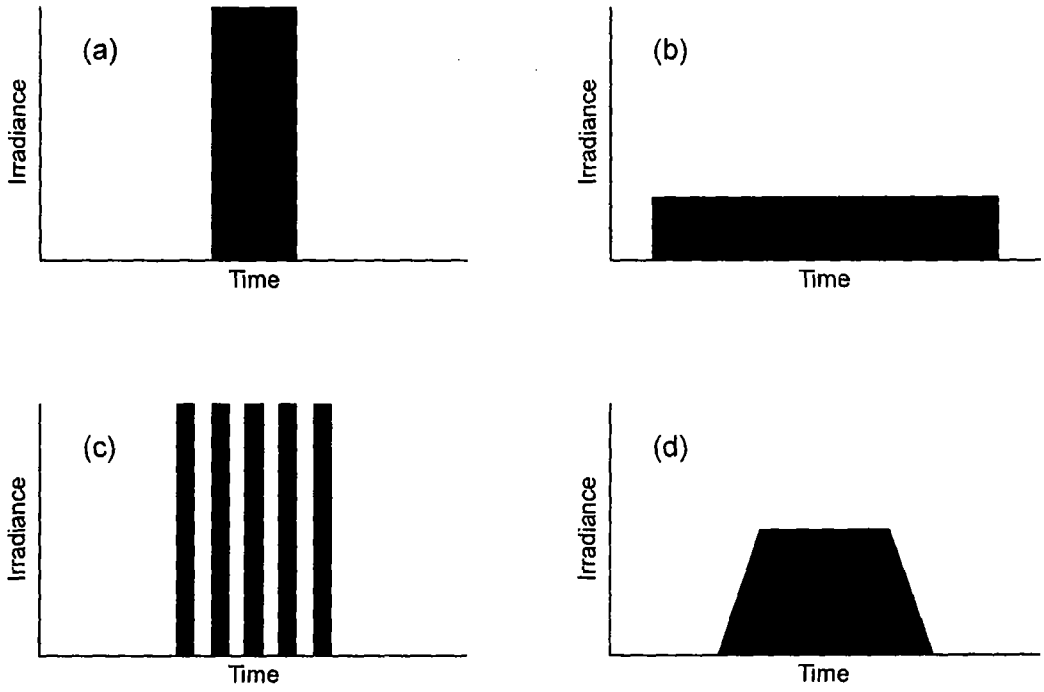
Since the reciprocity law only depends on total dose, its validation for a particular end-point can have many experimental manifestations. Assuming that the reciprocity law is valid, then each manifestation should be equivalent to the others as long as the integrated total dose is the same. Thus, when the reciprocity law is obeyed, the same photobiological response is observed when specimens receive the same integrated total dose regardless as to whether the exposure is performed:

a) At a high irradiance for a short period of time.
b) At a low irradiance for a long period of time.
c) By repeatably switching a light source on-or-off and controlling both the on-off frequency of the light and the length of time that the light remains in the on-state and the off-state. Experiments in which the light is turned on-and-off at an extremely high frequency are called *flash photolysis experiments*, while experiments in which the light is turned on-and-off at a low frequency are called *intermittency experiments*.
d) By ramping the irradiance to a high level, holding the flux for a specified period of time, and then ramping it back down to a lower level or any variant of these stress regimes.

These exposure regimes, depicted graphically in Fig 3, are adapted from a similar representation given by Forbes et al (1979).

Figure 3: A selection of irradiance *vs* exposure time regimes for testing the law of reciprocity in which the integrated areas (i.e. dose) for each exposure regime are identical. When the reciprocity law is obeyed, the photoresponse for each of these exposure regimes is the same.

A summary of reciprocity experiments carried out in human and mouse skin are reviewed by Martin et al (2003). In every case, reciprocity for erythema was shown to hold. Of particular relevance to sunbed use, where exposure times will vary between a few minutes up to half-an-hour or so depending on the power and spectral output of the lamps, Meanwell & Diffey (1989) showed that exposure to polychromatic radiation for time periods ranging from 1s to 1h induced degrees of delayed erythema ranging from minimal to marked that depended only on dose and not dose rate. These findings both support and extend those of previous studies in which the end point was confined to minimal erythema.



(a) High UVR intensity over short period
(b) Low UVR intensity over long period
(c) High UVR intensity in short bursts
(d) Gradual increase, holding and decrease of UVR intensity

On the other hand, Table 2 shows that reciprocity has been shown not to hold in UV-induced mice skin carcinogenesis where, in general, for a fixed dose of UV radiation the carcinogenic effectiveness in mice skin increases as the irradiance decreases or is fractionated (van der Leun et al 2005).

Although reciprocity has been shown to hold for erythema, different skin types respond differently to repeated daily sub-erythemal doses of simulated solar UVR. In sun-sensitive skin types II these have a cumulative effect such that a frank erythema becomes evident after 2-3

exposures of 0.65MED (Sheehan et al, 2002). Whereas in sun-tolerant skin type IV, this accumulation is not observed which suggests much better resolution of acute UVR damage.

Table 2: UVR reciprocity studies in human and mouse skin. Mouse tumorigenesis studies are for SCC

Response	Source	Spectrum	Irradiation	Range in irradiance	Reciprocity?	Reference
Human skin						
Erythema	Mercury	Monochromatic	Continuous	4	Y	Hausser 1927
Erythema	Mercury	Monochromatic	Continuous	?	Y	Hausser 1928
Erythema	Mercury	Monochromatic	Continuous	8	Y	Luchiesh 1930
Erythema	Mercury	Monochromatic	Continuous	4	Y	Coblentz 1932
Erythema	Mercury	Monochromatic	Continuous	20	Y	Blum 1946
Erythema	Mercury	Monochromatic	Flash	200	Y	Schmidt 1963
Erythema	Mercury	Monochromatic	Continuous	10^3	Y	Park 1984
Erythema	Xenon	Monochromatic	Intermittent	?	Y	Everett 1969
Erythema	Xenon	Monochromatic	Continuous	?	Y	Everett 1969
Erythema	Xenon	Polychromatic	Continuous	10^3	Y	Meanwell 1989
Erythema	Laser	Monochromatic	Flash	3	Y	Parrish 1976
Erythema	Laser	Monochromatic	Continuous	10^4	Y	Anderson 1980
Langerhans cell depletion	Xenon	Monochromatic	Continuous	10	Y	Murphy et al, 1993
Mice skin						
Tumorigenesis	Mercury	Polychromatic	Continuous	12	N	Blum 1941
Tumorigenesis	Mercury	Polychromatic	Intermittent	4	N	Blum 1942
Tumorigenesis	Mercury	Polychromatic	Intermittent	4	N	Bain 1943
Tumorigenesis	Xenon	Monochromatic	Intermittent	3	N	Forbes 1979
Tumorigenesis	Fluorescent	Polychromatic	Continuous	5	N	Forbes 1981
Tumorigenesis	Fluorescent	Polychromatic	Continuous	8	N	de Gruijl 1983
Immunosuppression	Fluorescent	Polychromatic	Intermittent	1	Y	DeFabo 1979
Immunosuppression	Fluorescent	Polychromatic	Continuous	10	Y	DeFabo 1980
Immunosuppression	Fluorescent	Polychromatic	Continuous	10	Y	Noonan 1981

4 What are the specific health and safety implications (negative and positive) relating to the exposure of persons to UVR from tanning devices for cosmetic purposes?

4.1 Negative Effects

4.1.1. Acute and non skin cancer effects

The use of tanning devices has been associated with acute adverse reactions such as a form of skin fragility known as pseudoporphyria (Murphy et al, 1990; Weiss and Jung, 1990) and lentigines (Salisbury et al, 1989; Kadunce et al, 1990) that have been noted in case reports. There have also been case reports of induction (Fruchter and Edoute, 2004) and exacerbation (Stern and Docken, 1986) of systemic lupus erythematosus.

There is a risk of phototoxic reactions with people using certain medications (Bisland, 1990) or applying topical aromatherapy products, such as bergamot oil, that contain photosensitising chemicals (Kaddu and Wolf, 2001) or eating plants that contain such chemicals (Ljunggren, 1990).

Devices with a higher UVB/UVA ratio or a high UVB irradiance will be more effective at tanning and will require a shorter exposure time. However, this also increases the likelihood of a burn (doses > 1 MED) because there is a lower margin of error in the determination of exposure time (see Section 5). Burns have also been reported due to equipment failure (Eltigani and Mathews, 1994).

Studies in the late 1980s showed that the use of tanning devices has an adverse effect on human immune function (Hersey et al, 1987; Rivers et al, 1989). More recently, Whitmore and Morison (2000) reported that 10 full-body exposures over a two-week period suppressed immunity as assessed by the induction and elicitation arms of the contact hypersensitivity response (CHS). These authors also studied the effect of 10 full-body tanning exposures in 11 volunteers and, not surprisingly, reported the presence of CPD and p53 protein expression in keratinocytes *in vivo* (Whitmore et al, 2001). One study used a Cleo Natural source (see Figure 1) to assess the immunological effects of repeated whole-body sub-erythemal exposure (1.2 SED) on 165 skin types II and III for up to 30 consecutive days (Narbutt et al, 2005). The results showed a cumulative UVR dose-dependent reduction of the primary allergic response and the elicitation arm of the CHS response and suggest that there is no adaptation to these immunological responses.

Comment on UVA-induced immunosuppression
The role of UVB in immunosuppression is well established in mice and humans. The role of UVA is much less clear. Much of the evidence for the role of UVA in humans has come from sunscreen studies in which the addition of UVA filters has been shown to improve immunoprotection (Fourtanier et al 2005). In mice, there is evidence that UVA abrogates UVB-induced immunosuppression (Tyrrell and Reeve, 2006) but there is evidence of a positive interaction of UVB and UVA in human immunosuppression (Poon et al, 2005), i.e. the combined effect is greater than the sum of the parts. It should be noted that immunosuppression is a complex issue and that the above brief comments are a necessary simplification.

4.1.2 Chronic
Skin Cancer

Non-melanoma
Very few studies have been done on the relationship between sunbed use and non-melanoma skin cancer risk. Two hospital-based case-control studies in Ireland, in the mid to late 1980s, did not show any relationship between the use of tanning devices and non-melanoma skin cancer (O'Loughlin et al, 1985; Herity et al, 1989). A similar conclusion, at about the same time, was reached by Bajdik et al (1996) in British Columbia, Canada, who evaluated 406 controls (population based) against 180 SCC cases and 226 BCC cases. About 10% of each group had "ever" used a sunlamp. The adjusted OR for BCC and SCC for "ever" having used a sunlamp were 1.2 (0.7-2.2) and 1.4 (0.7-2.7) respectively, which are clearly non-significant. One small study from 2002, using the "generalized estimating equation method" reported no significant effect of tanning devices for BCC, even though the total lifetime exposure to tanning devices

was almost twice as high in patients compared with controls (Boyd et al, 2002). In the same year, Karagas et al (2002) assessed the relationship between use of tanning devices and BCC and SCC in a population-based case control study. In this study there was greater use of tanning devices ranging from 9.2% (male controls) to 28.4% (female patients). The OR for BCC and SCC were 1.5 (1.1-2.1) and 2.5 (1.7-3.8) respectively and adjustment for a variety of factors made no difference to these results. The results of Karagas et al (2002) indicated that the use of tanning devices is a risk factor for non-melanoma skin cancer.

Melanoma

Sunbed usage has increased considerably in recent years (Rafnsson et al, 2004) but the data on melanoma risk are scanty. There are a number of case-control studies but the details on exposure for the majority was small and all, as case-control studies, were subject to bias of recall and the effect of confounders. There is a single cohort study (Verierod et al, 2003) in which risk of melanoma was addressed.

A number of case-control studies reported no evidence of sunbed use as a risk factor for melanoma (Osterlind et al, 1988; Holly et al, 1995; Westerdal et al, 1994; Zanetti et al, 1988; Chen et al, 1998; Dunn-Lane et al, 1993; Naldi et al, 2000; Bataille et al 2004, 2005). The majority of these studies were, however, small and the prevalence of sunbed usage in cases and controls was very low. Others were supportive of weak evidence or evidence in "at risk" groups (Walter et al, 1990; Westerdahl et al, 2000). Walter et al (1990) showed some suggestion of a trend to increased risk of melanoma with longer duration of use. In the study by Westerdahl et al (2000) an increased risk of melanoma was demonstrated only for use of sunbeds before the age of 35 years (OR, 2.3; CI, 1.2–4.2). Swerdlow et al (1988) showed a significantly increased risk for any use of sunbeds OR 2.94 (95% CI 1.4-6.17) with a significant trend for increased duration of use. Autier et al (1994) showed little evidence of risk overall when corrected for skin type etc but did show evidence of increased risk for usage of sunbeds for 10 hours or more, when burning was reported after use of the sunbed or when the users reported use of the sunbed to tan.

The only cohort study to address risk associated with solaria followed more than 100,000 Norwegian and Swedish women for an average of 8 years, and 187 melanomas developed. This study identified use of a solarium for 1 or more times per month as a risk factor for melanoma. When the exposures occurred between the ages of 20 – 29 years the adjusted relative risk was 2.58 (95%CI 1.48-4.50). Among women who had used a solarium once or more per month, in at least one of the three decades between ages 10 and 39, the adjusted relative risk of melanoma compared to women that had never or rarely used a solarium during these three decades, was 1.55 (95%CI 1,4-2.32) (Veierød et al, 2003). This is probably the most persuasive evidence for a role for sunbeds in causing melanoma but the data are as yet relatively weak and support the view only that frequent use is deleterious.

Gallagher et al (2005) carried out a meta-analysis of 9 case-control studies and the one cohort study and came to the conclusion that sunbed use significantly increased the risk of melanoma with an OR of 1.25 (1.1-1.5) "ever" versus "never" used. This increased to 1.69 (1.3 –2.2) using the metric "first exposure as a young adult".

Photoageing
There seems to be no published literature on the photoageing effects of sunbed use but this would be expected from the long-term use of sunbeds because photoageing is associated with solar exposure (Fisher et al, 2002). Some studies have looked at the effect of repeated sub-erythemal exposure of UVB and UVA in human skin and reported some changes that are associated with photoageing (Lavker et al, 1995a, 1995b; Lavker and Kaidby, 1997).

As with the sun, tanning devices emit infrared radiation (IR: 760nm to 1mm). The effects of IR on skin are poorly understood but *in vitro* studies suggest that it may play a role in photoageing, which has been suggested by animal studies (Schieke et al, 2003).

Effects on the eye
Four studies have assessed the relationship between sunbed use and ocular melanoma and found varying degrees of association Tucker et al, 1985; Seddon et al, 1990; Holly et al, 1996). The most recent study (Vajdic et al, 2004) provides "moderately strong" evidence, with several metrics, that sunbed use results in ocular melanoma, after adjustment for confounding factors including exposure to solar radiation. The OR for use (never vs ever) was 1.7 (95% CI 1.0 – 2.8) and 2.4 (95% CI 1.0 – 6.1) for first use under 21 years. There was a significant trend ($p = 0.04$) for duration of use. This study also suggested a protective effect from wearing goggles with an OR = 2.2 (95% CI 0.5 - 9.7) in those who did not always wear goggles but this was not significant ($p = 0.3$).

4.2 Positive Effects

Vitamin D status
Tanning with UVB-emitting sunbeds would be expected to improve vitamin D status and this has been reported in a recent study (Tangpricha et al, 2004) that showed that people who used a sunbed at least once a week for at least 6 months had a mean serum concentration of 25 hydroxyvitamin D (25(OH)D) of 115.5 ± 8.0 (SEM) nmol/L compared with the controls who had levels of 60.3 ± 3.0 nmol/L ($P < 0001$). The tanners also had significantly higher hipbone mineral density. However, this study has several flaws; (i) it relied on recall of sunbed use without establishing serum 25(OH)D before sunbed use, (ii) the tanning group had much greater sunlight exposure and (iii) there was a much greater proportion of white-skinned people in the tanning group. Furthermore, there were no data on the spectral output of the tanning devices used.

Feel good factor
Many people claim to feel better after sunbed use (Diffey 1986) but studies using primarily UVA emitting sunbeds showed that mood effects could not be attributed to circulating serotonin or melatonin (Gambichler et al, 2002a) or opioid peptides (Gambichler et al, 2002b). The possible role of UVB-induced keratinocyte-derived β-endorphin (Gilchrest et al, 1996) has yet to be investigated.

5. (a) Are limit values necessary for the irradiance of UVR from artificial sources, in particular from tanning devices for cosmetic purposes, with respect to health and safety? (b) Is it necessary to give different values for the irradiance of UVA, UVB and UVC radiation respectively? (c) If so, please specify the limit values for the irradiance of artificial UVR above which adverse health effects will occur. What are the uncertainties of these limit values?

From the above discussion on reciprocity, it is clear that acute clinical effects resulting from sunbed use (i.e. erythema) are likely to depend only on total dose and not dose rate. It is not possible to make any statements on the risk of skin cancer, especially melanoma. Since all tanning devices emit a broad UVR spectrum, the spectral profile of which determines the device's effectiveness to elicit clinical effects, it is irrelevant to specify irradiance limits in different spectral wavebands, especially since the spectral regions UVA, UVB and UVC were originally based on the optical properties of different glasses (see section 2b). A more appropriate way to speak of tanning devices than using the terms UVA, UVB and UVC is to compare their erythemal power, as a percentage of total UVR power, with sunlight. This is expressed mathematically as:

$$100 \times \sum_{290}^{400} E(\lambda).\varepsilon(\lambda).\Delta\lambda / \sum_{290}^{400} E(\lambda).\Delta\lambda$$

$E(\lambda)$ is the relative spectral power distribution of the UV source and $\varepsilon(\lambda)$ is the erythemal effectiveness of radiation of wavelength λ nm (CIE 1998). An example of this calculation is given in Appendix A. For the 3 sources illustrated in the Figure 1, the erythemally effective percentages are 0.44%, 0.51% and 0.13% and for summer sunlight, the "Cleo Natural" and "Cleo Performance" lamps, respectively. Clearly, the "Cleo Natural" lamp more closely resembles sunlight "biologically" than the "Cleo Performance" lamp.

In specifying an upper limit of irradiance, the important quantity is the erythemally-weighted irradiance, obtained by weighting each spectral irradiance component of the lamp by its relative effectiveness to induce erythema and summing over all wavelengths present in the source spectrum (see equation above). To minimise the risk of timing errors, which might result in "sunburn" it is desirable that the prescribed sunbed exposure session should be no less than 10 minutes. The avoidance of "sunburn" may also reduce the risk of melanoma.

Depending on an individual's phototype, the exposure in SED during this 10-minute period should not exceed the subject's estimated indicative MED (see Table 1). The maximum erythemal-weighted irradiance should not exceed 11 SED/h (0.3 W/m^2). This is equivalent to a UV index (UVI) of 12, which WHO describes as "extreme". A noon UVI of 12 would be typical in summer in Darwin, Australia (13°S) and Colombo, Sri Lanka (13°N).

The main conclusion from this analysis is that the erythemally weighted properties of a given sunbed emission spectrum (as demonstrated in Appendix A) are more important than its physical properties *per se*. This is because UVB is orders of magnitude more erythemogenic than UVA (as shown in Figure 2) which, as shown in Figure 1, is the main UVR component of sunlight and

tanning device spectra. At present, certainty can only be reasonably assured for acute effects such as erythema.

6 Please specify the limit values of total dose of artificial UVA, UVB and UVC radiation above which adverse health effects will occur, taking into account skin phototype, intensity of exposure, duration of exposure and associated uncertainties.

The clinical effects of UVR exposure can be either *deterministic*, where the magnitude of the effect is related to exposure and a threshold dose is possible, or *stochastic,* in which the probability of the effect is related to exposure and there is no threshold dose. Erythema is an example of a deterministic effect with a threshold and SCC is a stochastic effect without a threshold.

There is no need to specify total dose separately for UVA, UVB and UVC for the reasons given in Section 5. It is not possible to specify uncertainties for long-term effects.

For a single exposure on a sunbed it is important to avoid marked or severe erythema but necessary (for the desired cosmetic effect) to receive a sufficient UVR dose to stimulate melanogenesis. Experience has shown that an exposure at or just below that to induce a just perceptible MED 8 to 24 hours after exposure approximates the optimum.

A classification of skin phototypes based on susceptibility to sunburn in sunlight (WHO 2003), together with indicative MEDs that might be expected following exposure on unacclimatized skin, is given in Table 1. Depending on an individual's phototype, the exposure in SED on any single occasion should not exceed their estimated indicative MED.

With a stochastic effect like SCC skin cancer there is no threshold dose below which the effect will not occur. Consequently, any recommendation about a limit value of total dose accumulated over a specific time period (e.g. year, lifetime) is arbitrary and subjective. A limit of 20 sessions per year (equivalent to an exposure of approximately 40 SED or 20 MED in melano-compromised individuals) was proposed by the British Photodermatology Group (BPG) in 1990 (Diffey *et al* 1990) and was subsequently adopted by the UK Health & Safety Executive (HSE 1995).

The International Electrotechnical Commission (1995) recommends that the maximum annual exposure should not exceed an erythemal-weighted dose of 15 kJ/m^2 (150 SED), equivalent to around 50 MED in white-skinned people. Not surprisingly, it is this higher limit adopted by The Sunbed Association in the UK in their code of practice for operators (TSA 2004). A pragmatic defence of the limit of 20 sessions per year is that it discourages people from purchasing sunbeds to use at home where the temptation to use them several times a week or for prolonged time during a single tanning session is evident.

Other agencies have simply advised against sunbed use and not specified an "acceptable" maximum annual usage (AGNIR 2002; WHO 2003; ICNIRP 2003).

Estimates have been made of the risk of basal and squamous cell skin cancers arising from sunbed use (AGNIR 2002) and what constitutes an "acceptable" risk is a matter of judgment. For most people, who may use sunbeds 10 or 20 times a year for 10 years or so in young adulthood,

the estimated additional lifetime risk of non-melanoma skin cancer, compared with non-users, is up to 10% (AGNIR 2002).

Case-control studies, particularly more recent ones, have generally found an association between sunbed use and melanoma (Young 2004) with an odds ratio of around 1.5 (Veierød et al. 2003). In communicating this risk to policy makers (Heller *et al* 2003), it may be helpful to estimate the potential number of cases and deaths prevented each year in a population if sunbeds were eliminated. These are given in Table 3 for the UK, where the relative risk of incidence and mortality of sunbed users is taken to be 1.5 relative to non-users. The figure of 1.5 is used for illustrative purposes since different studies have yielded different relative risks (Young 2004) and so the population impacts in Table 3 should be treated with caution (B. Diffey). Melanoma incidence and mortality data refer to the year 2002 (Cancer Research UK, 2005).

Sex	Millions in UK Population in 2002	Melanoma per 10^5		% using sunbeds	Relative risk of incidence & mortality	Population attributable risk	No. affected in 2002?		Estimated population impact (no. people) by eliminating sunbeds	
		Incidence	Mortality				Incidence	Mortality	Incidence	Mortality
Male	28.7	11.2	3.0	5	1.5	0.024	3193	874	78	21
Female	30.3	13.7	2.5	9	1.5	0.043	4128	770	179	33
						Total	**7321**	**1644**	**257**	**54**

Table 3 Non-use of tanning devices might have resulted in about 54 fewer deaths from melanoma in 2002 than the 1644 that were observed in the UK

An alternative approach to estimating the mortality associated with sunbeds is through modelling population exposure to both sunlight and sunbeds, assuming that the patterns of exposure from these two sources are equally carcinogenic, that the melanomas that result are equally fatal, and that the fraction of deaths due to sunbed use is equal to the population exposure from sunbeds expressed as a fraction of the total population exposure from sunlight and sunbeds. Using this approach Diffey (2003) estimates the mortality due to sunbed use each year in the UK is around 100, with a range of about 50 to 200. The estimates from this approach and that illustrated in Table 3 are not inconsistent given the many uncertainties and assumptions involved. If it is assumed that the use of sunbeds increased the risk of melanoma by 50%, the additional lifetime risk of dying from melanoma will be of the order $1x10^{-3}$. From the above discussion it is clear that there is no limit value of total dose of artificial UVR below which adverse health effects will not occur and that any limit is subjective and arbitrary.
Based on data available the risk of developing skin cancer in connection with the use of sunbeds is high in comparison to the "acceptable" risk of developing cancer from other consumer products (WHO, in press).

4. COMMENTS RECEIVED DURING THE PUBLIC CONSULTATION

23 comments were received mainly from public health bodies and the sunbed industry. Some from public health bodies felt the SCCP committee had not sufficiently emphasized the health risks of sunbed use and those from industry felt that we had made too much of these risks. Some comments from public health bodies were accompanied with their own documents on the risks of UVR including that from sunbeds. There were several comments on vitamin D, some stating that there was no evidence of benefits other than for skeletal health and others stating that these benefits were better established than we had stated. Overall, there were many comments on detail, some of which have been addressed but none of which alters the overall conclusions of the SCCP committee.

There were a few common themes in the comments that we have specifically addressed:

- The erythemally weighted irradiance limit that was originally given was too high and we have now reduced this to $0.3 W/m^2$ which is in accord with other bodies
- There was no discussion on the effects of UVR on melanoma of the eye. This has now been addressed along with the inclusion of a study that shows a relationship between sunbed use and melanoma of the eye.
- The lack of inclusion of CIE action spectra that have now been included in Figure 2.

Comments received:

- Afsse (Agence Française de Sécurité Sanitaire Environnementale), InVS (Institut de Veille Sanitaire), afssaps (Agence Française de Sécurité Sanitaire des Produits de Santé)
- Afsset (Agence Française de Sécurité Sanitaire de l'Environnement et de Travail)
- BEUC, the European Consumers' Organisation
- The British Medical Association
- Cancer Research UK
- Dr. Jean-Pierre Cesarini, France
- Charité – Medical University, Germany
- Ir. G. Crevecoeur, Belgium
- Dr. Jan C. van der Leun (Ecofys BV, the Netherlands) and Dr. Paul Donald Forbes (Toxarus, Inc., USA)
- European Sunlight Association, Belgium
- EUROSKIN (European Society of Skin Cancer Prevention), Germany
- Gezondheidsraad / Health Council of the Netherlands
- UK Health Protection Agency
- Dr. Ph. Autier, France
- Bayerisches Staatsministerium für Umwelt, Germany
- Dr. Nji Ousseni, France
- State Non-Food Products Inspectorate, Lithuania
- Public Health Authority, Slovakia
- Nordic Radiation Protection and Health Authorities
- Dr. Alexander Steinmann, Germany
- SUNARC, USA

- Dr. Paul Donald Forbes (Toxarus, Inc., USA)
- Hospital Universitario de la Princesa, Spain

5. CONCLUSION

Question 1: What are the general health and safety implications (negative and positive) relating to the exposure of persons to ultraviolet radiation (UVR)[7]?

- Clinically relevant UV-radiation is UVB (280 – 315 nm) and UVA (315-400 nm)
- Solar UVB (~295 – 315nm) is primarily responsible for inducing erythema (sunburn) and tanning
- UVA has similar acute clinical effects to UVB if the physical doses (J/cm^2) given are approximately 1000 times greater
- Human skin may be phenotypically classified into phototypes I – VI which are determined by acute sensitivity to sunlight, melanin content and tanning ability
- Solar exposure is associated with basal cell carcinoma, squamous cell carcinoma and malignant melanoma.
- The risk of a given type of skin cancer is influenced by patterns of UVR exposure
- Phototype is a good indicator of skin cancer risk which reflects acute sensitivity to sunlight with phototype I being the most sensitive and phototype VI being the most resistant
- Moles and freckles are good indicators of susceptibility to malignant melanoma
- Moles and freckles are independent risk factors for skin cancer
- UVR is immunosuppressive in humans, the consequences of which are unknown but may be important in skin cancer and infectious diseases
- Public health messages should be directed to those people at greatest risk of skin cancer in order to promote behaviour which is appropriate to the balance of risk
- Solar UVR, especially UVB, causes photokeratitis (snow blindness) of the eye and increases a cataract formation.
- There is evidence that solar UVR exposure is associated with ocular melanoma

Question 2: What are the differences between risks associated with exposure of persons to natural UVR and those risks from artificial UVR? What are the differences regarding the health and safety risks with respect to exposure of persons to UVA, UVB and UVC radiation respectively?

- There are no intrinsic differences between the physical and biological properties of natural and artificial UVR but there are differences in spectral profile that may have biological consequences

[7] The International Commission on Illumination (CIE) defines ultraviolet radiation (UVR) as optical radiation between 100 and 400 nm. The spectral region is divided into three photo-biological spectral regions: UVC (100-280 nm), UVB (280-315 nm) and UVA (315-400 nm).

- It is relatively easy to compare the acute effects of natural and artificial UVR but much more difficult to compare the long-term effects.
- UVR, with and without photosensitizers, is used in the phototherapy of skin diseases and skin cancer is an accepted risk in such treatment
- Wavelength dependency (action spectrum) studies show that UVB is the most harmful part of the solar UVR spectrum for both acute and long term term-effects but wavelength dependency data on UVA are more limited than for UVB
- We lack data to make conclusive statements on the wavelength dependency of melanoma

Question 3: Is the total dose value of UVR the only effective health and safety parameter with regard to the risks associated with exposure of persons to both natural and artificial UVR? What is the validity of the Bunsen-Roscoe law[8] over the range of irradiances and wavelengths associated with exposure of persons to both natural and artificial UVR?

- The reciprocity law applies for human erythema
- There are no quantitative human data for long-term effects but patterns of exposure may be important, especially for melanoma (see Question 1) that suggests a failure of the reciprocity law

[8] The Bunsen-Roscoe law (law of reciprocity) states that a certain biological effect is directly proportional to the total energy dose irrespective of the administered regime. Dose is the product of intensity and the duration of exposure. (Bunsen R, Roscoe HE, Photochemische Untersuchungen, Poggendorff's Annalen 1855: 96: 373-394, 1857: 100: 43-88 and 481-516, 1857: 101:235-263, 1859: 108: 193-273.).

Question 4: What are the specific health and safety implications (negative and positive) relating to the exposure of persons to UVR from tanning devices for cosmetic purposes?

- There are some case reports for adverse clinical effects (other than skin cancer) from sunbed use but it is not possible to estimate the frequency of these
- Several studies, and a meta-analysis, have shown a significant association between sunbed use and malignant melanoma. Typically, the risk for developing melanoma in relation to the use of sunbeds is around 1.5.
- Sunbed use can result in the desired cosmetic outcome which is tanning
- There is no evidence to support a pharmacological basis for the "feel good" factor of sunbed use
- Use of sunbeds that contain UVB may enhance vitamin D status but there are few data available on this relationship. The emission spectrum of the source is likely to be important
- There is some evidence that sunbed use is associated with ocular melanoma

Question 5: Are limit values necessary for the irradiance of UVR from artificial sources, in particular from tanning devices for cosmetic purposes, with respect to health and safety? Is it necessary to give different values for the irradiance of UV-A, UV-B and UV-C radiation respectively? If so, please specify the limit values for the irradiance of artificial UVR above which adverse health effects will occur. What are the uncertainties of these limit values?

- The biological consequences of a given sunbed emission spectrum are much more relevant than its specific irradiances within different wavebands which were originally defined by physical rather than biological parameters
- A biologically effective dose can be obtained by weighting a given emission spectrum with a relevant action spectrum
- This weighting should be done with the human erythema action spectrum, which is similar to the tanning action spectrum and the estimated human action spectrum for squamous cell carcinoma. This gives an erythemally weighted irradiance of the emission spectrum of the sunbed as demonstrated in Appendix A
- The maximum erythemally weighted irradiance should not exceed 0.3W/m2, or 11 standard erythema doses (SED) per hour. This is equivalent to tropical sun, which the WHO terms extreme.
- Certainty can only be reasonably assumed for acute effects

Question 6: Please specify the limit values of total dose of artificial UV-A, UV-B and UV-C radiation above which adverse health effects will occur, taking into account skin phototype, intensity of exposure, duration of exposure and associated uncertainties.

- There is no need to specify different dose limits for UVB and UVA for the same reasons given in Question 5. However, there is no justification for the presence of UVC in tanning devices.
- The dose limits for adverse acute effects are dealt with in Question 5. In the context of risk assessment, it is not possible to give dose limits for skin cancer because of lack of

human dose-response data. However, SCC is a stochastic effect for which there is no assumed threshold dose. Any annual dose limits given are arbitrary

- The human erythema action spectrum is similar to the estimated human SCC action spectrum based on mouse data. This may also represent the wavelength dependency for human BCC. However, we lack mammalian data on the wavelength dependency of malignant melanoma. Broad spectrum studies in mice indicate that as with non melanoma skin cancer, UVB is much more important than UVA
- The important biological risk factors for malignant melanoma are age, sex (in some populations), skin phenotype (in particular types I and II), moles, freckles and family history. Behavioural/environmental risk factors include intermittent sunburning UVR exposure, especially in youth.
-

Overall Conclusion

UVR tanning devices were not in widespread use before the 1990-s and the full health effects of their use are not yet known. It will take several years before the real picture of the role of the UVR tanning devices in inducing skin cancer becomes fully apparent. This is due to the long induction period of the cancer.

The SCCP is of the opinion that the use of UVR tanning devices to achieve and maintain cosmetic tanning, whether by UVB and/or UVA, is likely to increase the risk of malignant melanoma of the skin and possibly ocular melanoma.
People with known risk factors for skin cancer, especially malignant melanoma, should be advised not to use UVR tanning devices. Specifically, these are (i) skin phototypes I and II and the presence of freckles, (ii) atypical and/or multiple moles and (iii) a family history of melanoma. Eye protection from UVB and UVA should be worn if sunbeds are used.

Risk of melanoma seems to be particularly high when using sunbeds at a young age. Thus UVR tanning devices should not be used by individuals under the age of 18 years.

6. MINORITY OPINION

Not applicable

7. GLOSSARY

AK – actinic keratosis
BCC – basal cell carcinoma
BPG – British Photodermatology Group
CHS – contact hypersensitivity
CI – confidential interval
CIE - Commission Internationale de l'Éclairage
CPD – cyclobutane pyrimidine dimers

IARC – International Agency for Research on Cancer
IPD – immediate pigment darkening
IR – infrared radiation
LVD - Low Voltage Directive
MED – minimal erythema dose
MMP – matrix metalloproteinases
PUVA – psoralen plus UVA
OR – odds ratio
RR – relative risk
ROS – reactive oxygen species
SCC – squamous cell carcinoma
SCCP – Scientific Committee on Consumer Products
SED – standard erythema dose
SPF – sun protection factor, based on UVB absorbance
SSR – solar simulating radiation
UCA – urocanic acid
UVA –Ultraviolet radiation with wavelengths 380–315 nm
UVA-I –Ultraviolet radiation with wavelengths 340-400m
UVA-II –Ultraviolet radiation with wavelengths 315-340nm
UVB - Ultraviolet radiation with wavelengths 315–280 nm
UVC - Ultraviolet radiation with wavelengths < 280 nm
UVR - ultraviolet radiation
XP – xeroderma pigmentosum

8. REFERENCES

Agar, N. and A. R. Young. Melanogenesis: a photoprotective response to DNA damage? Mutat. Res. 571:121-132, 2005.

AGNIR. Advisory Group on Non-ionising Radiation Health. Effects from Ultraviolet Radiation. Documents of the NRPB, 2002, 13 (1)

Anders A, Altheide HJ, Knalmann M, Tronnier H: Action spectrum for erythema in humans investigated with dye lasers. Photochem Photobiol 61:200-205 (1995).

Anderson RR, Parrish JA. A survey of the acute effects of UV lasers on human and animal skin, in: R. Pratesi, C.A. Sacchi (Eds.), Lasers in Photomedicine and Photobiology, Springer, New York, 1980, p. 109

Armstrong, B.K. and A. Kricker, How much melanoma is caused by sun exposure? Melanoma Res, 1993. 3(6): p. 395-401.

Autier, P., et al., Cutaneous malignant melanoma and exposure to sunlamps or sunbeds: an EORTC multicenter case-control study in Belgium, France and Germany. EORTC Melanoma Cooperative Group. Int J Cancer, 1994. 58(6): p. 809-13.

Bain JA, Rusch HP. Carcinogenesis with ultraviolet radiation of wavelength 2800–3400 Å. Cancer Res 1943; 3: 425

Bajdik, C. D., R. P. Gallagher, G. Astrakianakis, G. B. Hill, S. Fincham and D. I. McLean. Non-solar ultraviolet radiation and the risk of basal and squamous cell skin cancer. Br. J. Cancer 73:1612-1614, 1996.

Bataille, V., et al., Risk of cutaneous melanoma in relation to the numbers, types and sites of naevi: a case-control study. Br J Cancer, 1996. 73(12): p. 1605-11.

Bataille, V., et al., Exposure to the sun and sunbeds and the risk of cutaneous melanoma in the UK: a case-control study. Eur J Cancer, 2004. 40(3): p. 429-35.

Bataille, V., et al., A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. Eur J Cancer, 2005. 41(14): p. 2141-9.

Beral, V., et al., Malignant melanoma and exposure to fluorescent lighting at work. Lancet, 1982. 2(8293): p. 290-3.

Bertram, C.G., et al., An Assessment of the CDKN2A Variant Ala148Thr as a Nevus/Melanoma Susceptibility Allele. J Invest Dermatol, 2002. 119(4): p. 961-965.

Berwick, M. and D. Kesler. Ultraviolet Radiation Exposure, Vitamin D, and Cancer. Photochem. Photobiol. 2005 vol. 18, n° 6, pp. 1262-1266

Bilsland, D. and W. S. Douglas. Sunbed pseudoporphyria induced by nalidixic acid. Br. J. Dermatol. 123:547, 1990.

Bishop, D.T., et al., Geographical variation in the penetrance of CDKN2A mutations for melanoma. J Natl Cancer Inst, 2002. 94(12): p. 894-903

Blum HF, Kirby-Smith JS, Grady HG. Quantitative induction of tumors in mice with ultraviolet radiation. J Natl Cancer Inst 1941; 2: 259

Blum HF, Grady HG, Kirby-Smith. Relationships between dosage and rate of tumor induction by ultraviolet radiation. J Natl Cancer Inst 1942; 3: 91

Blum HF, Terus WS. Inhibition of the erythema of sunburn by large doses of ultraviolet radiation. Am J Physiol 1946; 146: 97

Boi, S., M. Cristofolini, R. Micciolo, E. Polla and P. P. Dalla. Epidemiology of skin tumors: data from the cutaneous cancer registry in Trentino, Italy. J. Cutan. Med. Surg. 7:300-305, 2003.

Boyd, A. S., Y. Shyr and L. E. King, Jr. Basal cell carcinoma in young women: an evaluation of the association of tanning bed use and smoking. J. Am. Acad. Dermatol. 46:706-709, 2002.

Boyle, P., J. F. Dore, P. Autier and U. Ringborg. Cancer of the skin: a forgotten problem in Europe. Ann. Oncol. 15:5-6, 2004.

Brash, D. E., A. Ziegler, A. S. Jonason, J. A. Simon, S. Kunala and D. J. Leffell. Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. J. Investig. Dermatol. Symp. Proc. 1:136-142, 1996.

Brazerol, W.F., et al., Serial ultraviolet B exposure and serum 25 hydroxyvitamin D response in young adult American blacks and whites: no racial differences. J Am Coll Nutr, 1988. 7(2): p. 111-8.

Brenner, M., et al., Differential expression of melanoma-associated growth factors in keratinocytes and fibroblasts by ultraviolet A and ultraviolet B radiation. Br J Dermatol, 2005. 153(4): p. 733-9.

Bulliard, J.L., Site-specific risk of cutaneous malignant melanoma and pattern of sun exposure in New Zealand. Int J Cancer, 2000. 85(5): p. 627-32.

Bunsen RW, Roscoe HE. Photochemische untersuchungen. Ann Phys 1859; 108: 193

Campbell, C., A. G. Quinn, B. Angus, P. M. Farr and J. L. Rees. Wavelength specific patterns of p53 induction in human skin following exposure to UV radiation. Cancer Res. 53:2697-2699, 1993.

Cancer Research UK, http://info.cancerresearchuk.org/cancerstats/, accessed [January][2006].

Caswell, M. The kinetics of the tanning response to tanning bed exposures. Photodermatol. Photoimmunol. Photomed. 16:10-14, 2000.

Chadwick, C. A., C. S. Potten, O. Nikaido, T. Matsunaga, C. Proby and A. R. Young. The detection of cyclobutane thymine dimers, (6-4) photolesions and the Dewar photoisomers

in sections of UV-irradiated human skin using specific antibodies, and the demonstration of depth penetration effects. J. Photochem. Photobiol. B 28:163-170, 1995.

Chen, Y.T., et al., Sunlamp use and the risk of cutaneous malignant melanoma: a population-based case-control study in Connecticut, USA. Int J Epidemiol, 1998. 27(5): p. 758-65.

Chuang, T.Y., et al., Melanoma in Kauai, Hawaii, 1981-1990: the significance of in situ melanoma and the incidence trend. Int J Dermatol, 1999. 38(2): p. 101-7.

CIE: Erythema reference action spectrum and standard erythema dose. CIE S 007/E ed (Commission Internationale de l' É clairage, Vienna 1998).

CIE Standard. Erythema reference action spectrum and standard erythema dose. CIE S 007/E-1998. Vienna: Commission Internationale de l'Éclairage, 1998

CIE: Action spectrum for photocarcinogenesis (non-melanoma skin cancers), CIE 132/2; TC 6-32 ed (Commission Internationale de l' Éclairage, Vienna 2000).

Coblentz WW, Stair R, Hogue JM. The spectral erythemic reaction of the untanned human skin to ultra-violet radiation. Bur Stand J Res 1932; 8: 541 (Research Paper No. 433)

Dawson-Hughes, B., Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. Am J Clin Nutr, 2004. 80(6 Suppl): p. 1763S-6S.

DeFabo EC, Kripke ML. Dose–response characteristics of immunologic unresponsiveness to UV-induced tumors produced by UV irradiation of mice. Photochem Photobiol 1979; 30: 385

DeFabo EC, Kripke ML. Wavelength dependence and dose-rate independence of UV radiation induced suppression of immunologic unresponsiveness of mice of a UV-induced fibrosarcoma. Photochem Photobiol 1980; 32: 183

DeFabo, E.C., et al., Ultraviolet B but not ultraviolet A radiation initiates melanoma. Cancer Res, 2004. 64(18): p. 6372-6.

de Gruijl FR, van der Leun JC. Effect of chronic UV exposure on epidermal transmission in mice. Photochem Photobiol 1982; 36: 433

de Gruijl, F. R. Action spectrum for photocarcinogenesis. Recent Results Cancer Res. 139:21-30, 1995.

de Gruijl, F.R., IL-40 UV Carcinogenesis and Melanocytes. Pigment Cell Res, 2003. 16(5): p. 591.

de Vries, E. and Coebergh, J.W. Cutaneous malignant melanoma in Europe. European J Cancer. 2004, 40:2355-2366

Diffey, B. L. Use of UV-A sunbeds for cosmetic tanning. Br. J. Dermatol. 115:67-76, 1986.

Diffey, B. L. and P. M. Farr. Sunbed lentigines. Br. Med. J. (Clin. Res. Ed) 296:1468, 1988.

Diffey BL, Farr PM, Ferguson J, Gibbs NK, de Gruijl FR, Hawk JLM, Johnson BE, Lowe G, MacKie RM, McKinlay AF, Moseley H, Murphy GM, Norris PG, Young AR. Tanning with ultraviolet A sunbeds. Br Med J 1990; 301: 773-4

Diffey, B. L. and P. M. Farr. Quantitative aspects of ultraviolet erythema. *Clin. Phys. Physiol Meas.* 12:311-325, 1991.

Diffey BL. A quantitative estimate of melanoma mortality from ultraviolet A sunbed use in the UK. Br J Dermatol 2003; 149: 578-581

Donawho, C.K., P. Wolf, and M.L. Kripke, Enhanced development of murine melanoma in UV-irradiated skin: UV dose response, waveband dependence, and relation to inflammation. Melanoma Research, 1994. 4: p. 93-100.

Drobetsky, E.A., J. Turcotte, and A. Chateauneuf, A role for ultraviolet A in solar mutagenesis. Proc Natl Acad Sci U S A, 1995. 92(6): p. 2350-4.

Dunn-Lane, J., et al., A case control study of malignant melanoma. Ir Med J, 1993. 86(2): p. 57-9.

Easton, D., et al., Genetic susceptibility to naevi- a twin study. Br J Cancer, 1991. 64: p. 1164-1167

Eltigani, E. and R. N. Matthews. An unusual cause of sunbed burns. Burns 20:87-88, 1994.

Everett MA, Sayre RM, Olson RL. Physiologic response of human skin to ultraviolet light. in: F. Urbach (Ed.), The Biologic Effects of Ultraviolet Radiation, Pergamon Press, New York, 1969, p. 181.

Farr, P. M., J. E. Besag and B. L. Diffey. The time course of UVB and UVC erythema. *J. Invest Dermatol.* 91:454-457, 1988.

Ferguson J. Druge and chemical photosensitivity. In: Photodermatology, Hawk JLM (ed) London: Arnold, 1999, pp. 155-169.

Fisher, G. J., S. Kang, J. Varani, Z. Bata-Csorgo, Y. Wan, S. Datta and J. J. Voorhees. Mechanisms of photoaging and chronological skin aging. Arch. Dermatol. 138:1462-1470, 2002.

Forbes PD, Davies RE, Urbach F. Aging, environmental influences, and photocarcinogenesis. J Invest Dermatol 1979; 73: 131

Forbes PD, Blum HF, Davies RE. Photocarcinogenesis in hairless mice dose–response and the influence of dose-delivery. Photochem Photobiol 1981; 34: 361

Fruchter, O. and Y. Edoute. First presentation of systemic lupus erythematosus following ultraviolet radiation exposure in an artificial tanning device. Rheumatology. (Oxford) 44:558-559, 2005.

Gallagher, R. P., J. J. Spinelli and T. K. Lee. Tanning beds, sunlamps, and risk of cutaneous malignant melanoma. Cancer Epidemiol. Biomarkers Prev. 14:562-566, 2005.

Gandini, S., et al., Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer, 2005Sep;41 (14): 2040-59

Gandini, S., et al., Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer, 2005b. 41(1): p. 28-44.

Gandini, S., et al., Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer, 2005c. 41(1): p. 45-60.

Gambichler, T., A. Bader, M. Vojvodic, F. G. Bechara, K. Sauermann, P. Altmeyer and K. Hoffmann. Impact of UVA exposure on psychological parameters and circulating serotonin and melatonin. BMC. Dermatol. 2:6, 2002a.

Gambichler, T., A. Bader, M. Vojvodic, A. Avermaete, M. Schenk, P. Altmeyer and K. Hoffmann. Plasma levels of opioid peptides after sunbed exposures. Br. J. Dermatol. 147:1207-1211, 2002b.

Gange, R. W., A. D. Blackett, E. A. Matzinger, B. M. Sutherland and I. E. Kochevar. Comparative protection efficiency of UVA- and UVB-induced tans against erythema and formation of endonuclease-sensitive sites in DNA by UVB in human skin. J. Invest Dermatol. 85:362-364, 1985.

Gilchrest, B. A., N. A. Soter, J. L. Hawk, R. M. Barr, A. K. Black, C. N. Hensby, A. I. Mallet, M. W. Greaves and J. A. Parrish. Histologic changes associated with ultraviolet A--induced erythema in normal human skin. J. Am. Acad. Dermatol. 9:213-219, 1983.

Gilchrest, B. A., H. Y. Park, M. S. Eller and M. Yaar. Mechanisms of ultraviolet light-induced pigmentation. Photochem. Photobiol. 63:1-10, 1996.

Glogau, R. G. Aesthetic and anatomic analysis of the aging skin. Semin. Cutan. Med. Surg. 15:134-138, 1996.

Harrison, G. I. and A. R. Young. Ultraviolet radiation-induced erythema in human skin. Methods 28:14-19, 2002.

Harrison, G. I., A. R. Young and S. B. McMahon. Ultraviolet radiation-induced inflammation as a model for cutaneous hyperalgesia. J. Invest Dermatol. 122:183-189, 2004.

Hausser KW, Vahle W. Sunburn and suntanning. Wiss Veröffnugnen Siemens Konzern 1927; 6: 101–120

Hausser KW, Vahle W. Die Abhängigkeit des Lichterythems und der Pigmentbildung von der Schwingungszahl (Wellenlänge) der erregenden Strahlung. Strahlentherapie 1928; 13: 41

Hawk, J. L., G. M. Murphy and C. A. Holden. The presence of neutrophils in human cutaneous ultraviolet-B inflammation. Br. J. Dermatol. 118:27-30, 1988.

Health & Safety Executive, Controlling the health risks from the use of UV tanning equipment. ING(G)209 10/95, 1995

Heller RF, Buchan I, Edwards R et al. Communicating risks at the population level: application of population impact numbers. Br Med J 2003; 327: 1162-5

Hemminki, K., H. Zhang, and K. Czene, Familial and attributable risks in cutaneous melanoma: effects of proband and age. J Invest Dermatol, 2003. 120(2): p. 217-23.

Herity, B., G. O'Loughlin, M. J. Moriarty and R. Conroy. Risk factors for non-melanoma skin cancer. Ir. Med. J. 82:151-152, 1989.

Hersey, P., M. MacDonald, C. Burns, S. Schibeci, H. Matthews and F. J. Wilkinson. Analysis of the effect of a sunscreen agent on the suppression of natural killer cell activity induced in human subjects by radiation from solarium lamps. J. Invest Dermatol. 88:271-276, 1987.

Holick, M. F. The vitamin d epidemic and its health consequences. J. Nutr. 135:2739S-2748S, 2005.

Holly EA, Aston DA, Char DH, Kristiansen JJ, Ahn DK: Uveal melanoma in relation to ultraviolet light exposure and host factors. Cancer Res 50:5773-5777 (1990).

Holly, E.A., et al., Cutaneous melanoma in women. I. Exposure to sunlight, ability to tan, and other risk factors related to ultraviolet light. Am J Epidemiol, 1995. 141(10): p. 923-33.

IARC. Solar and ultaviolet radiation (Internatinal Agency for Research on Cancer, Lyon) (1992).

ICNIRP International Commission on Non-Ionizing Radiation Protection. Health Issues of Ultraviolet Tanning Appliances Used for Cosmetic Purposes. Health Physics 2003; 84: 119-127.

IEC International Electrotechnical Commission. Safety of household and similar electrical appliances. Part 2: Particular requirements for appliances for skin exposure to ultraviolet and infrared radiation. Geneva:IEC, 1995, 335-2-27.

Irwin, C., A. Barnes, D. Veres and K. Kaidbey. An ultraviolet radiation action spectrum for immediate pigment darkening. Photochem. Photobiol. 57:504-507, 1993.

Johnson, G. J. The environment and the eye. Eye 18:1235-1250, 2004.

Jose, J. G. and D. G. Pitts. Wavelength dependency of cataracts in albino mice following chronic exposure. Exp. Eye Res. 41:545-563, 1985.

Kaddu, S., H. Kerl and P. Wolf. Accidental bullous phototoxic reactions to bergamot aromatherapy oil. J. Am. Acad. Dermatol. 45:458-461, 2001.

Kadunce, D. P., M. W. Piepkorn and J. J. Zone. Persistent melanocytic lesions associated with cosmetic tanning bed use: "sunbed lentigines". J. Am. Acad. Dermatol. 23:1029-1031, 1990.

Karagas, M. R., V. A. Stannard, L. A. Mott, M. J. Slattery, S. K. Spencer and M. A. Weinstock. Use of tanning devices and risk of basal cell and squamous cell skin cancers. J. Natl. Cancer Inst. 94:224-226, 2002.

Kefford, R.F., et al., Counseling and DNA testing for individuals perceived to be genetically predisposed to melanoma: A consensus statement of the Melanoma Genetics Consortium. J Clin Oncol, 1999. 17(10): p. 3245-51.

Kelfkens G, van Weelden H, de Gruijl FR, van der Leun JC. The influence of dose rate on ultraviolet tumorigenesis. J Photochem Photobiol B: Biology 1991, 10, 41-50

Kelly, D. A., A. R. Young, J. M. McGregor, P. T. Seed, C. S. Potten and S. L. Walker. Sensitivity to sunburn is associated with susceptibility to ultraviolet radiation-induced suppression of cutaneous cell-mediated immunity. J. Exp. Med. 191:561-566, 2000.

Kligman, L. H. and R. M. Sayre. An action spectrum for ultraviolet induced elastosis in hairless mice: quantification of elastosis by image analysis. Photochem. Photobiol. 53:237-242, 1991.

Kricker, A., B. K. Armstrong, D. R. English and P. J. Heenan. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer--a case-control study. Int. J. Cancer 48:650-662, 1991.

Kricker, A., B. K. Armstrong, D. R. English and P. J. Heenan. Does intermittent sun exposure cause basal cell carcinoma? a case-control study in Western Australia. Int. J. Cancer 60:489-494, 1995.

Ladhani S, Srinivasan L, Buchanan C, Allgrove J: Presentation of vitamin D deficiency. Arch Dis Child 89:781-784 (2004).

Lavker, R. M., D. A. Veres, C. J. Irwin and K. H. Kaidbey. Quantitative assessment of cumulative damage from repetitive exposures to suberythemogenic doses of UVA in human skin. Photochem. Photobiol. 62:348-352, 1995a.

Lavker, R. M., G. F. Gerberick, D. Veres, C. J. Irwin and K. H. Kaidbey. Cumulative effects from repeated exposures to suberythemal doses of UVB and UVA in human skin. J. Am. Acad. Dermatol. 32:53-62, 1995b.

Lavker, R. and K. Kaidbey. The spectral dependence for UVA-induced cumulative damage in human skin. J. Invest Dermatol. 108:17-21, 1997.

Ljunggren, B. Severe phototoxic burn following celery ingestion. Arch. Dermatol. 126:1334-1336, 1990.

Luchiesh M. Artificial Sunlight, New York: Van Nostrand, 1930, p. 77.

Mallet E, Gaudelus J, Reinert P, Le Luyer B, Lecointre C, Leger J, Loirat C, Quinet B, Benichou JJ, Furioli J, Loeuille GA, Roussel B, Larchet M, Freycon F, Vidailhet M, Varet I: [Symptomatic rickets in adolescents]. Arch Pediatr 11:871-878 (2004).

Man, I., I. K. Crombie, R. S. Dawe, S. H. Ibbotson and J. Ferguson. The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: early follow-up data. Br. J. Dermatol. 152:755-757, 2005.

Martin JW, Chin JW, Nguyen T. Reciprocity law experiments in polymeric photodegradation: a critical review. Progress in Organic Coatings 2003; 47: 292–311

Matsumura, Y. and H. N. Ananthaswamy. Short-term and long-term cellular and molecular events following UV irradiation of skin: implications for molecular medicine. *Expert. Rev. Mol. Med.* 2002:1-22, 2002.

McLoone, P., E. Simics, A. Barton, M. Norval and N. K. Gibbs. An action spectrum for the production of cis-urocanic acid in human skin in vivo. J. Invest Dermatol. 124:1071-1074, 2005.

Meanwell EF, Diffey BL. Reciprocity of ultraviolet erythema in human skin. Photodermatology 1989; 6: 146-148

Merriam, J. C., S. Lofgren, R. Michael, P. Soderberg, J. Dillon, L. Zheng and M. Ayala. An action spectrum for UV-B radiation and the rat lens. Invest Ophthalmol. Vis. Sci. 41:2642-2647, 2000.

Morison WL, Towne LE and Honig B. The photoaggravated dermatoses. In: Photodermatology, Hawk JLM (ed) (London: Arnold, 1999, pp. 199-212 .

Moyal, D. D. and A. M. Fourtanier. Efficacy of broad-spectrum sunscreens against the suppression of elicitation of delayed-type hypersensitivity responses in humans depends on the level of ultraviolet A protection. Exp. Dermatol. 12:153-159, 2003.

Murphy, G. M., J. Wright, D. S. Nicholls, P. H. McKee, A. G. Messenger, J. L. Hawk and G. M. Levene. Sunbed-induced pseudoporphyria. Br. J. Dermatol. 120:555-562, 1989.

Murphy GM, Norris PG, Young AR, Corbett MF, Hawk JL: Low-dose ultraviolet-B irradiation depletes human epidermal Langerhans cells. Br J Dermatol 129:674-677 (1993).

Naldi, L., et al., Sunlamps and sunbeds and the risk of cutaneous melanoma. Italian Group for Epidemiological Research in Dermatology. Eur J Cancer Prev, 2000. 9(2): p. 133-4.

Narbutt J, Lesiak A, Skibinska M, Wozniacka A, van Loveren H, Sysa-Jedrzejowska A, Lewy-Trenda I, Omulecka A, Norval M: Suppression of contact hypersensitivity after repeated exposures of humans to low doses of solar simulated radiation. Photochem Photobiol Sci 4:517-522 (2005).

Noonan FP, DeFabo EC, Kripke ML. Suppression of contact hypersensitivity by UV radiation and its relationship to UV-induced suppression of tumor immunity. Photochem Photobiol 1981; 34: 683.

Noonan, F.P., et al., Animal models of melanoma: an HGF/SF transgenic mouse model may facilitate experimental access to UV initiating events. Pigment Cell Res, 2003. 16(1): p. 16-25.

Norris, W., A case of fungoid disease. Edinb Med Surg J, 1820. 16: p. 562-565.

Novakovic, L., S. Lee, G. E. Orchard, J. M. Sheehan, A. R. Young and S. L. Walker. Effects of solar-simulated radiation dose fractionation on CD1a+ Langerhans cells and CD11b+ macrophages in human skin. Br. J. Dermatol. 145:237-244, 2001.

NRPB: Health effects from Ultraviolet Radiation V13 No.1 2002

Odeka E, Tan J: Nutritional rickets is increasingly diagnosed in children of ethnic origin. Arch Dis Child 90:1203-1204 (2005).

O'Loughlin, C., M. J. Moriarty, B. Herity and L. Daly. A re-appraisal of risk factors for skin carcinoma in Ireland. A case control study. Ir. J. Med. Sci. 154:61-65, 1985.

Oriowo, O. M., A. P. Cullen, B. R. Chou and J. G. Sivak. Action spectrum and recovery for in vitro UV-induced cataract using whole lenses. Invest Ophthalmol. Vis. Sci. 42:2596-2602, 2001.

Ortonne, J. P. The effects of ultraviolet exposure on skin melanin pigmentation. J. Int. Med. Res. 18 Suppl 3:8C-17C, 1990.

Osterlind, A., et al., The Danish case-control study of cutaneous malignant melanoma. II. Importance of UV-light exposure. Int J Cancer, 1988. 42(3): p. 319-24.

Park YK, Gange RW, Levins PC, Parrish JA. Low and moderate irradiances of UVB and UVC irradiation are equally erythemogenic in human skin. Photochem Photobiol 1984; 40: 667

Parkin, D., et al., Cancer Incidence in Five Continents. IARC Scientific Publications No 143, Lyon, International Agency for Research on Cancer, 1997. II.

Parrish JA, Anderson RR, Ying CY, Pathak MA. Cutaneous effects of pulsed nitrogen gas laser irradiation. J Invest Dermatol 1976; 67: 603

Parrish, J. A., K. F. Jaenicke and R. R. Anderson. Erythema and melanogenesis action spectra of normal human skin. Photochem. Photobiol. 36:187-191, 1982.

Pedersen P, Michaelsen KF, Molgaard C: Children with nutritional rickets referred to hospitals in Copenhagen during a 10-year period. Acta Paediatr 92:87-90 (2003).

Pfeifer, G.P., Y.H. You, and A. Besaratinia, Mutations induced by ultraviolet light. Mutat Res, 2005. 571(1-2): p. 19-31.

Phan, T. A., G. M. Halliday, R. S. Barnetso and D. L. Damian. Spectral and dose dependence of ultraviolet radiation-induced immunosuppression. *Front Biosci.* 11:394-411, 2006.

Pittelkow, M.R., et al., Skin cancer in patients with psoriasis treated with coal tar. A 25-year follow-up study. Arch Dermatol, 1981. 117(8): p. 465-8.

Pitts, D. G., A. P. Cullen and P. D. Hacker. Ocular effects of ultraviolet radiation from 295 to 365 nm. Invest Ophthalmol. Vis. Sci. 16:932-939, 1977.

Ponsonby, A. L., R. M. Lucas and d. M. van, I. A potential role for UVR and Vitamin D in the induction of Multiple Sclerosis, Type 1 Diabetes, Rheumatoid Arthritis. Photochem. Photobiol. 2005.

Rafnsson, V., et al., Risk factors for malignant melanoma in an Icelandic population sample. Prev Med, 2004. 39(2): p. 247-52.

Rigel, D.S., et al., Relationship of fluorescent lights to malignant melanoma: another view. J Dermatol Surg Oncol, 1983. 9(10): p. 836-8.

Rivers, J. K., P. G. Norris, G. M. Murphy, A. C. Chu, G. Midgley, J. Morris, R. W. Morris, A. R. Young and J. L. Hawk. UVA sunbeds: tanning, photoprotection, acute adverse effects and immunological changes. Br. J. Dermatol. 120:767-777, 1989.

Roberts, J. E. Ocular phototoxicity. J. Photochem. Photobiol. B 64:136-143, 2001.

Robinson, E.S., et al., The Monodelphis melanoma model: initial report on large ultraviolet A exposures of suckling young. Photochem Photobiol, 2000. 71(6): p. 743-6.

Routaboul, C., A. Denis and A. Vinche. Immediate pigment darkening: description, kinetic and biological function. Eur. J. Dermatol. 9:95-99, 1999.

Ruegemer, J., B. Schuetz, K. Hermann, R. Hein, J. Ring and D. Abeck. UV-induced skin changes due to regular use of commercial sunbeds. Photodermatol. Photoimmunol. Photomed. 18:223-227, 2002.

Salisbury, J. R., H. Williams and A. W. du Vivier. Tanning-bed lentigines: ultrastructural and histopathologic features. J. Am. Acad. Dermatol. 21:689-693, 1989.

Sayre, R.M., J.C. Dowdy, and M. Poh-Fitzpatrick, Dermatological risk of indoor ultraviolet exposure from contemporary lighting sources. Photochem Photobiol, 2004. 80: p. 47-51.

Schartl, A., et al., Analysis of genetic factors and molecular mechanisms in the development of hereditary and carcinogen-induced tumors of Xiphophorus. Recent Results Cancer Res, 1997. 143: p. 225-235.

Schieke, S.M., Schroeder P and Krutmann J. Cutaneous effects of infrared radiation: from clinical observations to molecular response mechanisms. Photodermatol. Photoimmuno. Photomed. 2003, 19: 228-234

Schieke, S. M., K. Ruwiedel, H. Gers-Barlag, S. Grether-Beck and J. Krutmann. Molecular crosstalk of the ultraviolet a and ultraviolet B signaling responses at the level of mitogen-activated protein kinases. J. Invest Dermatol. 124:857-859, 2005.

Schmidt K. Zur Hauterythemwirkung von UV-Blitzen. Stahlentherapie 1963; 124: 127

Seddon JM, Gragoudas ES, Glynn RJ, Egan KM, Albert DM, Blitzer PH: Host factors, UV radiation, and risk of uveal melanoma. A case-control study. Arch Ophthalmol 108:1274-1280 (1990).

Setlow, R.B., et al., Wavelengths effective in induction of malignant melanoma. Proc Natl Acad Sci USA, 1993. 90: p. 6666-6670.

Sheehan, JM. and A. R. Young. The sunburn cell revisited: an update on mechanistic aspects. Photochem. Photobiol. Sci. 1:365-377, 2002.

Sheehan JM, Cragg N, Chadwick CA, Potten CS, Young AR: Repeated ultraviolet exposure affords the same protection against DNA photodamage and erythema in human skin types II and IV but is associated with faster DNA repair in skin type IV. J Invest Dermatol 118:825-829 (2002).

Sliney, D. H. Photoprotection of the eye - UV radiation and sunglasses. J. Photochem. Photobiol. B 64:166-175, 2001.

Stern, R. S. and W. Docken. An exacerbation of SLE after visiting a tanning salon. *JAMA* 255:3120, 1986.

Stern, R.S. and N. Laird, The carcinogenic risk of treatments for severe psoriasis. Photochemotherapy Follow-up Study. Cancer, 1994. 73(11): p. 2759-64.

Swerdlow, A.J., et al., Fluorescent lights, ultraviolet lamps and risk of cutaneous melanoma. British Medical Journal, 1988. 297: p. 647-650.

Tangpricha, V., A. Turner, C. Spina, S. Decastro, T. C. Chen and M. F. Holick. Tanning is associated with optimal vitamin D status (serum 25-hydroxyvitamin D concentration) and higher bone mineral density. Am. J. Clin. Nutr. 80:1645-1649, 2004.

The Sunbed Association. Code of practice for operators, Chesham: The Sunbed Association, 2004

Tucker MA, Shields JA, Hartge P, Augsburger J, Hoover RN, Fraumeni JF, Jr.: Sunlight exposure as risk factor for intraocular malignant melanoma. N Engl J Med 313:789-792 (1985).

Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken J, Giles GG, Armstrong BK: Sun exposure predicts risk of ocular melanoma in Australia. Int J Cancer 101:175-182 (2002).

Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken J, Giles GG, Armstrong BK: Incidence of ocular melanoma in Australia from 1990 to 1998. Int J Cancer 105:117-122 (2003).

Vajdic CM, Kricker A, Giblin M, McKenzie J, Aitken JF, Giles GG, Armstrong BK: Artificial ultraviolet radiation and ocular melanoma in Australia. Int J Cancer 112:896-900 (2004).

Van der Leun, J.C. and P.D. Forbes. Ultraviolet tanning equipment: six questions. Photodermatol Photoimmunol Photomed, 2005. 21: p. 254-9

Veierod, M.B., et al., A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant melanoma in women. J Natl Cancer Inst, 2003. 95(20): p. 1530-8.

Vieth, R. The role of vitamin D in the prevention of osteoporosis. Ann. Med. 37:278-285, 2005.

Wachsmuth, R.C., et al., Heritability and gene-environment interactions for melanocytic nevus density examined in a U.K. adolescent twin study. J Invest Dermatol, 2001. 117(2): p. 348-52.

Walter, S.D., et al., The association of cutaneous malignant melanoma with the use of sunbeds and sunlamps. Am J Epidemiol, 1990. 131(2): p. 232-43.

Walter, S.D., et al., The association of cutaneous malignant melanoma and fluorescent light exposure. Am J Epidemiol, 1992. 135(7): p. 749-62.

Wang, S.Q., et al., Ultraviolet A and melanoma: a review. J Am Acad Dermatol, 2001. 44(5): p. 837-46.

Weischer, M., et al., No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. Acta Derm Venereol, 2004. 84(5): p. 370-4.

Weiss, J. and E. G. Jung. [Solarium pseudoporphyria. Report of a case and review of the literature]. Hautarzt 41:671-674, 1990.

Westerdahl, J., et al., Use of sunbeds or sunlamps and malignant melanoma in Southern Sweden. 1994. 140: p. 691-699.

Westerdahl, J., et al., Risk of cutaneous malignant melanoma in relation to use of sunbeds: further evidence for UV-A carcinogenicity. Br J Cancer, 2000. 82(9): p. 1593-9.

Whiteman, D.C., et al., Melanocytic nevi, solar keratoses, and divergent pathways to cutaneous melanoma. J Natl Cancer Inst, 2003. 95(11): p. 806-12.

Whitmore, S. E. and W. L. Morison. The effect of suntan parlor exposure on delayed and contact hypersensitivity. Photochem. Photobiol. 71:700-705, 2000.

Whitmore, S. E., W. L. Morison, C. S. Potten and C. Chadwick. Tanning salon exposure and molecular alterations. J. Am. Acad. Dermatol. 44:775-780, 2001.

WHO World Health Organization. Artificial tanning sunbeds - risks and guidance. Geneva, 2003

WHO World Health Organization. Principles for modelling dose-response for the risk assessment of chemicals. Environmental Health Criteria XXX, In press.

Woollons, A., C. Kipp, A. R. Young, C. Petit-Frere, C. F. Arlett, M. H. Green and P. H. Clingen. The 0.8% ultraviolet B content of an ultraviolet A sunlamp induces 75% of cyclobutane pyrimidine dimers in human keratinocytes in vitro. Br. J. Dermatol. 140:1023-1030, 1999.

Yeste D, Carrascosa A: [Nutritional rickets in childhood: analysis of 62 cases]. Med Clin (Barc) 121:23-27 (2003).

Young, A. R., R. H. Guy and H. I. Maibach. Laser Doppler velocimetry to quantify UV-B induced increase in human skin blood flow. Photochem. Photobiol. 42: 385-390, 1985.

Young, A. R. Chromophores in human skin. Phys. Med. Biol. 42: 789-802, 1997.

Young, A. R., C. A. Chadwick, G. I. Harrison, O. Nikaido, J. Ramsden and C. S. Potten. The similarity of action spectra for thymine dimers in human epidermis and erythema suggests that DNA is the chromophore for erythema. J. Invest Dermatol. 111: 982-988, 1998.

Young AR. Tanning devices – fast track to skin cancer? Pigment Cell Res 2004; 17: 2-9

Zanetti, R., et al., [A case-control study of melanoma of the skin in the province of Torino, Italy]. Rev Epidemiol Sante Publique, 1988. 36(4-5): 309-17

Zhu, G., et al., A major quantitative-trait locus for mole density is linked to the familial melanoma gene CDKN2A: a maximum-likelihood combined linkage and association analysis in twins and their sibs. Am J Hum Genet, 1999. 65(2): 483-92.

9. ACKNOWLEDGEMENTS

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10. APPENDIX A: TECHNIQUE FOR DETERMINING THE ERYTHEMAL-WEIGHTED IRRADIANCE

The erythemal-weighted irradiance should be determined by means of a calibrated spectroradiometer. This type of measurement, known as spectroradiometry, enables the intensity of UV radiation on a wavelength-by-wavelength step to be recorded over all the wavelengths present in the sunbed emission spectrum. A spectroradiometer is an expensive, complex piece of optical equipment, which is found mainly in laboratories with a special interest in photobiology. It is important that users of spectroradiometers have their own standard lamps (either deuterium or tungsten) regularly calibrated by a national standards laboratory so that these can be used to provide an absolute spectral sensitivity calibration of the spectroradiometer.

The technique is to place the input optics of the spectroradiometer on top of the plastic sheet of the sunbed or at the recommended tanning distance from a sun canopy. The spectral irradiance is measured in equal wavelength steps (e.g. 5nm) from 280 to 400nm resulting in a set of numbers like those shown in column 2 in the table below. The numbers in column 3 represent the erythema action spectrum. This is the relative effectiveness of UV radiation of different wavelengths to cause erythema (or redness) in human skin 8-24 hours after exposure. The numbers in each row of columns 2 and 3 are multiplied together in column 4. All the numbers in column 4 are summed to give (in this example this comes to 0.0355) and then multiplied by 5nm (the wavelength interval used in scanning the spectrum) to give the erythemal-weighted irradiance in W/m^2, which in this example is $0.0355 \times 5 = 0.18$ W/m^2. This number should not exceed 0.3 W/m^2.

nm	Spectral irradiance $W/m^2/nm$	erythema action spectrum	Erythemal weighted irradiance
280	0.00	1	0.0000
285	0.00	1	0.0000
290	0.00	1	0.0000
295	0.00	1	0.0000
300	0.00	0.64863	0.0000
305	0.01	0.21979	0.0015
310	0.03	0.0745	0.0020
315	0.11	0.0252	0.0029
320	0.32	0.00855	0.0027
325	0.76	0.0029	0.0022
330	1.51	0.00136	0.0020
335	2.44	0.00115	0.0028
340	3.35	0.00097	0.0032
345	4.08	0.00081	0.0033
350	4.71	0.00068	0.0032
355	4.83	0.00058	0.0028
360	4.48	0.00048	0.0022
365	5.57	0.00041	0.0023
370	3.09	0.00034	0.0010
375	2.27	0.00029	0.0007
380	1.52	0.00024	0.0004

nm	Spectral irradiance $W/m^2/nm$	erythema action spectrum	Erythemal weighted irradiance
385	0.98	0.0002	0.0002
390	0.70	0.00017	0.0001
395	0.44	0.00015	0.0001
400	0.28	0.00012	0.0000
		Sum	**0.0355**

Erratum in:
Int J Cancer. 2007 Jun 1;120(11):2526.

The association of use of sunbeds with cutaneous malignant melanoma and other skin cancers: A systematic review.

International Agency for Research on Cancer Working Group on artificial ultraviolet (UV) light and skin cancer.

Exposure to solar ultraviolet (UV) radiation is a known cause of skin cancer. Sunbed use represents an increasingly frequent source of artificial UV exposure in light-skinned populations. To assess the available evidence of the association between sunbed use and cutaneous malignant melanoma (melanoma) and other skin cancers, a systematic review of the literature till March 2006 on epidemiological and biological studies on sunbed use was performed in Pubmed, ISI Web of Science, Embase, Pascal, Cochrane library, Lilacs and Medcarib. Search for keywords in the title and in the abstract was done systematically and supplemented by manual searches. Only case-control, cohort or cross-sectional studies were selected. Data were abstracted by means of a standardized data-collection protocol. Based on 19 informative studies, ever-use of sunbeds was positively associated with melanoma (summary relative risk, 1.15; 95% CI, 1.00-1.31), although there was no consistent evidence of a dose-response relationship. First exposure to sunbeds before 35 years of age significantly increased the risk of melanoma, based on 7 informative studies (summary relative risk, 1.75; 95% CI, 1.35-2.26). The summary relative risk of 3 studies of squamous cell carcinoma showed an increased risk. For basal cell carcinoma, the studies did not support an association. The evidence does not support a protective effect of the use of sunbeds against damage to the skin from subsequent sun exposure. Young adults should be discouraged from using indoor tanning equipment and restricted access to sunbeds by minors should be strongly considered. Copyright 2006 Wiley-Liss, Inc.

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World Health Organization

Fact sheet N°287
March 2005

Sunbeds, tanning and UV exposure

The desire to acquire a tan for fashion or cosmetic purposes has led to a large increase in the use of artificial tanning sunbeds in, mostly, developed countries. Use of sunbeds for tanning continues to increase in popularity, especially among young women.

Sunbeds used in solariums, and sun tanning lamps, are artificial tanning devices that claim to offer an effective, quick and harmless alternative to natural sunlight. However, there is growing evidence that the ultraviolet (UV) radiation emitted by the lamps used in solariums may damage the skin and increase the risk of developing skin cancer.

Some 132 000 cases of malignant melanoma (the most fatal kind of skin cancer) and over two million cases of other skin cancers occur worldwide each year. One in every three cancers diagnosed worldwide is a skin cancer. Most skin cancers are attributable to over-exposure to natural UV radiation. A fact sheet indicating the adverse health consequences from natural (i.e., sun) UV exposure issued by the World Health Organization (WHO) can be found at the link to the right.

This fact sheet is the complement of the above, providing information on artificial sources of UV. Primary among these artificial sources is sunbeds, and this fact sheet looks at the health consequences of sunbed usage and how they can be managed. Information for this fact sheet comes from WHO sponsored meetings and workshops, recent scientific literature, reviews by WHO Member States and the recommendations of international NGOs.

Health consequences

Skin cancers

Exposure to UV, either naturally from the sun or from artificial sources such as sunlamps, is a known risk factor for skin cancer. Short-wavelength UVB (280-315 nm) has been recognized for some time as carcinogenic in experimental animals, and there is increasing evidence that longer-wavelength UVA (315-400 nm) used in sunbeds, which penetrates more deeply into the skin, also contributes to the induction of cancer. A study conducted in Norway and Sweden showed a significant increase in the risk of malignant melanoma among women who had regularly used sunbeds.

Additional exposure to UV from sunbeds is likely to enhance the well-known detrimental consequences of excessive solar UV exposure. There is no evidence to suggest that UV exposure from any type of sunbed is less harmful than UV exposure from the sun. Pre-cancerous actinic keratoses and Bowen's disease have also been found in sunlight-protected but sunbed exposed skin in fair-skinned users after just two to three years of regular sunbed use.

Skin ageing, eye damage and other adverse health effects

Any excessive exposure to UV, not just from sunbeds, can result in structural damage to human skin. In the short term this damage can be due to burning, fragility and scarring and in the longer-term as photoageing. Photoageing, caused by the breakdown of collagen in the skin by UV, manifests itself as wrinkling and loss of elasticity.

The effects of UV on the eye include cataracts, pterygium (a white coloured growth over the cornea) and inflammation of the eye such as photokeratitis and photoconjunctivitis. Furthermore, excessive UV exposure can suppress the immune system, possibly leading to a greater risk of infectious diseases.

Some skin types are unsuitable for tanning

Based on their susceptibility to sunburn, skin types are classified into six different classes (I – VI). People with skin type I have the lightest skin and may not have even a light tan after repeated exposure to a sunbed. Instead, their skin generally suffers sunburn reactions. People with skin type I are more likely to use sunbeds than people with darker skin.

The ability of the consumer to recognize their skin type as not suitable for sunbed use is based on either self-diagnosis, or worst, a bad experience of sunburn. For this reason sunbed operator training is needed to ensure correct skin type diagnosis. While skin type II and higher can tan, skin damage can still occur following excessive exposure to UV.

Dangers associated with childhood UV exposure

Childhood exposure to UV and the number of times a child is burnt by UV, either from the sun or from sunbeds, are known to increase the risk of developing melanoma later in life. For this reason, particular attention is required to ensure children and adolescents do not use sunbeds. The United States Department of Health and Human Services has classified exposure to sunlamps or sunbeds as "known

to be carcinogenic to humans" and states that the longer the exposure, the greater the risk, especially to people exposed before the age of 30 years.

About sunbeds

Sunbeds emit predominantly UVA and some UVB, both of which can damage the DNA in cells of the skin. However, in recent years, lamps of sunbeds have been manufactured that produce higher levels of UVB to mimic the solar spectrum and speed the tanning process. While UVB has well known carcinogenic properties and whose excessive exposure is known to lead to the development of skin cancers, recent scientific studies suggest that high exposures to the longer wavelength UVA could also have an impact on skin cancer occurrence.

As with sun exposure, recent studies indicate a relationship between the use of sunbeds and malignant melanoma as well as non-melanoma skin cancers such as squamous and basal cell carcinomas. Thus, the consequences of regular sunbed use may include disfigurement from removal of skin cancers, early death if the cancer is a malignant melanoma, as well as substantial costs to national health systems for screening, treating and monitoring skin cancer patients.

Health benefits

Aside from tanning, many people claim that use of sunbeds helps them to be more relaxed and have a feeling of wellbeing. It is difficult to quantify such claims.

While sunbed use may increase vitamin D synthesis, predominantly from the UVB component, for the majority of the population, incidental exposure to the sun, combined with normal dietary intake of vitamin D, provides adequate vitamin D for a healthy body throughout the year. If people require more vitamin D than the sun can provide (for example, because of living in polar regions) this should be supplemented through diet rather than sunbed use.

Only in very rare and specific cases should the medically-supervised use of sunbeds be considered. Medical UV devices successfully treat certain skin conditions such as dermatitis and psoriasis. These treatments should only be conducted under qualified medical supervision in an approved medical clinic and not unsupervised either in commercial tanning premises or at home using a domestic sunbed.

There is a widespread false belief that a tan acquired using a sunbed will offer good skin protection against sunburn for a holiday in a sunny location. In reality, a tan acquired using a sunbed offers only limited protection against sunburn from solar UV. It has been estimated that a sunbed tan offers the same protective effect as using a sunscreen with a sun protection factor (SPF) of only 2-3.

Strong case for effective regulations governing sunbed use

As long as sunbeds are available to the public, there is a need for guidelines or legislation to reduce the risks associated with their use. WHO encourages governments to formulate and enforce effective laws governing the use of sunbeds. In countries where voluntary industry codes of practice exist, the sunbed owners have generally not shown significant capacity to self regulate effectively.

Of highest regulatory priority should be the restriction of use by persons under 18 years as well as banning unsupervised trained personel. WHO recommendations are consistent with those of the International Commission on Non-Ionizing Radiation Protection (ICNIRP) and the European Society for Skin Cancer Prevention (EUROSKIN).

The key reasons why regulations are necessary

- Increase in the number of unsupervised commercial sunbeds - Without trained staff and adequate health care advice, the potential for harm to the uninformed consumer is much greater. This, combined with competitive pricing strategies such as unlimited sessions within a specific time frame, increases the likelihood of skin damage.
- High intensity of UV output - Some machines have the capacity to emit very high levels of UV, many times stronger than the midday summer sun in most countries. In a largely unregulated industry where training of staff is not mandatory, this increases the health risks considerably.
- Exposure time and intervals between tanning sessions - Reasonable sunbed use includes keeping to recommended exposure times (which depends on the type of machine used) and having sufficiently long breaks between tanning sessions. Normally at least 48 hours are needed between tanning sessions for repair of UV-induced DNA damage in skin cells
- Eyewear - UV protective eyewear (such as goggles) must be worn during tanning sessions to protect the eyes.
- Effect of certain drugs and cosmetics - Some drugs, for example anti-depressants, antibiotics, psoralens, antifungals, and antidiabetics as well as some cosmetics make the skin more photosensitive and therefore decrease the time it takes for the skin to burn.
- The size of the skin area exposed - Modern 'clam-type' sunbeds and canopies can expose more skin area to UV than outdoor situations, therefore increasing the health risk. Here young people, , are more sensitive to UV-induced damage from this "all-over" tanning.

ICNIRP recommendations

In its 2003 publication ICNIRP recommends against the use of UV-emitting appliances for tanning or other non-medical purposes. ICNIRP states that the following groups are at particularly high risk of incurring adverse health effects from UV, and therefore should be particularly counseled against the use of tanning appliances:

- People who have skin phototypes I or II;
- Children (i.e., less than 18 years of age);
- People who have large numbers of nevi (moles);
- Persons who tend to freckle;
- Individuals who have a history of frequent childhood sunburn;
- People who have pre-malignant or malignant skin lesions;
- People who have sun-damaged skin;
- Those who are wearing cosmetics. These may enhance their sensitivity to UV exposure; and
- Persons taking medications. In this case they should seek advice from their physician to determine if the medication will make them UV-sensitive.

Action of the World Health Organization

INTERSUN, the Global UV project, is a collaborative project between WHO, the United Nations Environment Programme, the World Meteorological Organization, the International Agency on Cancer Research and ICNIRP that aims to reduce the burden of disease resulting from exposure to UV radiation. The project assesses and quantifies health risks, and develops an appropriate response through guidelines, recommendations and information dissemination. Beyond its scientific objectives, INTERSUN provides guidance to national authorities and other agencies about effective sun awareness programmes. These address different audiences such as occupationally exposed people, tourists, school children and the general public.

In 2003 WHO published a brochure entitled "Artificial tanning beds: risks and guidance" providing advice to the public, operators of sunbed facilities and member states on how sunbeds could be managed to protect public health.

Further information

Agar NS, Halliday GM, Barnetson RS, et al. (2004) The basal layer in human squamous tumors harbors more UVA than UVB fingerprint mutations: a role for UVA in human skin carcinogenesis, Proc Natl Acad Sci 101(14):4954-9.

AGNIR (2002) Advisory Group on Non-ionising Radiation Health. Effects from Ultraviolet Radiation. Documents of the NRPB 13 (1).

ICNIRP (2003) International Commission on Non-Ionizing Radiation Protection. Health Issues of Ultraviolet Tanning Appliances Used for Cosmetic Purposes. Health Physics 84: 119-127.

IEC (1995) International Electrotechnical Commission. Safety of household and similar electrical appliances. Part 2: Particular requirements for appliances for skin exposure to ultraviolet and infrared radiation. Geneva:IEC 335-2-27.

McKinlay A and Repacholi MH (2000) Ultraviolet Radiation Exposure, Measurement and Protection. Radiation Protection Dosimetry 91(vols 1-3).

United States Department of Health and Human Services (2004) 11th Report of Carcinogens. National Institute of Environmental Health Sciences, Research Triangle Park, NC. p III-266-267.

Veierød MB, Weiderpass E, Thörn M, et al. (2003) A prospective study of pigmentation, sun exposure, and risk of cutaneous malignant Melanoma in women. J Nat Cancer Inst 95:1530–1538.

WHO (1994) World Health Organization. Environmental Health Criteria 160. Ultraviolet Radiation Geneva.

WHO (2003) World Health Organization. Artificial tanning sunbeds - risks and guidance. Geneva

Young et al. (2003) UV-induced pigmentation in human skin. In: P.U. Giacomoni, ed. Sun Protection in Man. Amsterdam: Elsevier; pp. 357-375

Young A (2004) Tanning devices - Fast track to skin cancer?, Pigment Cell Res, 17: 2-9.

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