

## Supplementary material

This document contains additional detail in support of the paper by R. M. Lucas, S. Yazar, A. R. Young, M. Norval, F. R. de Gruijl, Y. Takizawa, L. E. Rhodes, C. A. Sinclair and R. E. Neale, Human health in relation to exposure to solar ultraviolet radiation under changing stratospheric ozone and climate, *Photochem. Photobiol. Sci.*, 2019, **18**, DOI: 10.1039/C8PP90060D.

### 1 Mechanisms underpinning changes in immune function following UV irradiation

#### 1.1 Stimulation of innate immunity in the skin

Foreign microorganisms, as well as microbes that are part of the skin microbiome that have been damaged by UV radiation,<sup>1</sup> express pathogen-associated molecular patterns (PAMPs) that are recognised by the Toll-like receptors (TLRs) present on the membranes of keratinocytes and other cells of the innate immune system. Binding of the TLR with its specific ligand activates transcription factors that drive the release of pro-inflammatory cytokines (signalling molecules regulating immunity), chemokines (molecules inducing directed chemotaxis), and anti-microbial peptides (AMPs; for a review of AMPs, see<sup>2</sup>). Notably, the active form of vitamin D (1,25(OH)<sub>2</sub>D) can be synthesised in the skin and induces synthesis of AMPs. These can be directly cytotoxic to pathogens and/or facilitate the cytotoxicity of natural killer cells and other cells of the innate immune system.<sup>1</sup>

In the skin there is considerable interplay between the innate and adaptive immune responses that may determine the nature of the immune response generated.<sup>3</sup> For example, AMPs can activate adaptive immune responses in the skin, and dendritic cells have properties of innate immune cells, but also present antigen to generate T-cell-mediated (adaptive) immune responses.<sup>3</sup>

#### 1.2 Suppression of adaptive immunity

Exposure of the skin and eyes to UV radiation modulates adaptive immune function through pathways that are both vitamin D-dependent and independent of vitamin D (reviewed in<sup>4</sup>, and shown in Fig. 1, main document, Lucas et al. 2019). UV photons are absorbed by chromophores in the skin, including DNA, RNA, trans-urocanic acid (UCA), and membrane lipids, including 7-dehydrocholesterol, the precursor of vitamin D. The resulting products, including a range of cytokines and chemokines,<sup>5</sup> stimulate migration of epidermal (Langerhans cells, LC) and dermal dendritic cells to local lymph nodes. Interactions between LC and immune cells in the germinal centres of the lymph nodes lead to an upregulation of regulatory T (T<sub>reg</sub>) and B (B<sub>reg</sub>) cells, and dampening of cell-mediated immune processes.<sup>4</sup> Mast cell numbers are increased following UV irradiation;<sup>6</sup> release of tryptase by mast cells catalyses the conversion of pro-opiomelanocortin into a range of neuropeptides, including  $\alpha$ -melanocyte stimulating hormone<sup>7</sup> that drives the tanning response.

Alterations in the skin microbiome following exposure to UV radiation<sup>1</sup> may also contribute to UV-induced immune suppression, and exposure to UV-B radiation alters the expression of immune-related genes,<sup>5, 8, 9</sup> possibly through epigenetic pathways. It is likely that there is considerable cross-communication between the different pathways that influence immune function.<sup>5</sup>

## 2 Cutaneous malignant melanoma

### 2.1 Pathogenesis of cutaneous malignant melanoma

The pathogenesis of cutaneous malignant melanoma (CMM), referred to as melanomagenesis, is a multi-step process, driven by mutations that alter cell growth, proliferation, differentiation, and cell death. CMM in younger people, and CMM occurring on the trunk, are more commonly associated with mutations in the *BRAF* gene (that encodes a key protein involved in control of cell growth).<sup>10</sup> In contrast, CMM in older people (associated with chronic sun exposure) more frequently demonstrate mutations in the *KIT* gene (which encodes the KIT protein, that influences cell proliferation, survival, and migration).<sup>11</sup>

Benign dermal naevi (moles) commonly contain a mutation in the *BRAF* gene, which may initiate melanomagenesis.<sup>12</sup> A recent meta-analysis estimated that 29% of CMM arose from a pre-existing nevus, with the remaining 71% arising *de novo*.<sup>13</sup>

In the Cancer Genome Atlas network, over 75% of CMM samples sequenced possessed a UV-signature in their mutation load (reviewed in<sup>14</sup>). In a recent study, CMM had the highest median number of mutations among 22 cancer types profiled,<sup>15</sup> with a high proportion of UV-signature mutations, and one of the highest rates of mutation per megabase, second only to squamous cell carcinoma (SCC) of the skin.<sup>16</sup> UV-induced mutations in genes encoding key proteins that protect the skin from UV-induced DNA damage, e.g., *TP53* (tumour suppressor factor p53 gene),<sup>15</sup> or the melanocyte response to UV radiation, e.g., *MITF* (microphthalmia-associated transcription factor gene), play an important role in melanomagenesis.<sup>17</sup>

Epigenetic alterations to DNA (e.g., methylation of a cytosine nucleotide) or chromatin (through histone modification), change gene expression without a change in the DNA base sequence.<sup>18</sup> A subset of CMM has been described that has elevated global DNA methylation and hypermethylation at specific cytosine guanine (CpG) dinucleotides in genes that are particularly involved in chromatin remodelling.<sup>19</sup> This subset was not clinically different from CMM without such changes.<sup>19</sup> Epidermal melanocytes are derived from neural crest progenitor (NCP) cells. In a zebrafish model, some NCP cells appeared to be epigenetically primed to become cancerous; i.e., the process of melanomagenesis may begin in melanocytes very early in life.<sup>18</sup>

There is growing interest in and research on the role of microRNAs (miRNA) in the development of CMM and disease progression. These are short (22-25 base pairs) non-coding RNAs that have actions in silencing and post-transcriptional regulation of gene expression. Table S-1 outlines some of the miRNAs implicated in CMM. Profiling of miRNA expression may have prognostic value for CMM, for example for metastasis to the brain.<sup>18</sup> To date, much of this work derives from studies in mice or CMM cell lines, but the research is providing new insights into pathogenic pathways, and thus therapeutic interventions.

**Table S-1.** Micro-RNAs implicated in cutaneous malignant melanoma (CMM).

<b>Micro-RNA</b>	<b>Evidence of association with CMM</b>
miRNA-21	Upregulated in CMM and more highly expressed in CMM and metastatic melanoma than in dysplastic nevi; overexpression of miRNA-21 may be oncogenic and play a key role in development of CMM. <sup>20</sup>
miRNA-26a	Suppresses the growth and invasiveness of CMM cells. <sup>21</sup>
miRNA-106b5p	Acts as a promoter of CMM progression. <sup>22</sup>
miRNA-125b	Appears to inhibit proliferation and invasion of CMM cells, thus playing an important role in progression and metastasis. <sup>20</sup>
miRNA-137	Inhibits growth and migration of CMM cells <sup>23</sup> ; downregulates expression of <i>MITF</i> (the master regulator of melanocyte development). Action is primarily as a tumour suppressor; lower expression is associated with poorer prognosis. <sup>20</sup>
miRNA-138	Promotes cell autophagy and apoptosis, and inhibition of cell proliferation. <sup>24</sup>
miRNA-203	Most highly expressed in human skin. Upregulation of miRNA-203 inhibits CMM cell migration; loss of expression is associated with greater tumour thickness and poorer prognosis. <sup>20</sup>
miRNA-211-5p	Induces activation of the survival pathway in CMM cells. <sup>25</sup>
miRNA-214	Also called ‘melano-miRNA’; may facilitate metastasis by promoting cell migration, invasion and extravasation. <sup>20</sup>
miRNA-625	Appears to have tumour suppressive actions that inhibit the development and progression of CMM. <sup>26</sup>

Long non-coding RNAs (lncRNA, > 200 bp) may also have a role in CMM; for example, the lncRNA, NKILA, suppresses growth of CMM via regulation of the NF-kappa- $\beta$  pathway.<sup>27</sup>

## **2.2 Diagnosis, treatment, and mortality in cutaneous malignant melanoma**

The considerable research on the pathogenesis of CMM has led to advances in diagnosis and treatment. For example, diagnosis has progressed from visual inspection of characteristics of a skin lesion, through dermoscopy, and more recently to the use of genetic markers<sup>28</sup> and artificial intelligence to diagnose and classify skin lesions using deep neural networks.<sup>29</sup>

The advent of immunotherapy and checkpoint blockade treatment for CMM has led to reduction of tumour size and improved survival.<sup>30</sup> CMM cells express co-inhibitory molecules that are able to hijack the body’s immune response to the tumour. Checkpoint blockade therapies prevent the interaction between these co-inhibitory molecules and their receptors, thus enabling the body’s natural immune responses against the tumour.

## **3 Keratinocyte cancer**

### **3.1 Pathogenesis of keratinocyte cancer**

Most basal cell carcinomas (BCCs) arise as a consequence of mutations in genes in the hedgehog pathway that controls cell division and growth. This pathway is activated when sonic hedgehog protein binds to the Patched 1 protein (PTCH1), leading to loss of PTCH1

activity, and activation of the seven-transmembrane-span receptor protein (SMO).<sup>31</sup> This in turn results in upregulation of cell proliferation genes.

A small number of people inherit *PTCH1* mutations, leading to Gorlin's syndrome (also called basal cell naevus syndrome), which is characterised by early age of onset of BCC and a high incidence of multiple BCCs. In recent genetic profiling of 293 BCCs, up to 85% had alterations in components of the hedgehog pathway; 85% also had driver mutations in other tumour-related genes, including the *TP53* and *PTPN14* tumour suppressor genes, and the *MYCN* oncogene. Over 90% of single-nucleotide variants were of a UV-signature type (particularly C to T changes), underscoring the role of UV radiation in the pathogenesis of BCC.<sup>32</sup>

The most frequently identified gene mutations in sporadic SCC are inactivating mutations of the *TP53* tumour suppressor gene, with up to 50% of tumours affected. Other frequent mutations are in *CDKN2a* (which encodes two different tumour suppressor genes), *NOTCH1* (involved in regulating genes involved in differentiation, proliferation and apoptosis) and *TERT* (which encodes a component of the telomerase enzyme).<sup>33</sup>

### 3.2 Keratinocyte cancers and human papilloma virus

Meta-analyses have concluded that human papilloma virus (HPV) is significantly more likely to be found in SCC tumour tissue compared with normal skin, and that markers of HPV infection are associated with increased risk of SCC in immunocompetent people.<sup>34</sup> The significantly greater risk of SCC in organ transplant recipients compared with individuals without transplants, may be attributable to infection with HPV. A recent cohort study in organ transplant recipients found a modest increase in risk of SCC associated with the presence of 5 or more beta-HPV types in eyebrow hair follicles or a high viral load.<sup>35</sup>

Although these epidemiological findings suggest a role of HPV in SCC, it is not clear that this is causal. Many studies have been case-control in design, and it is possible that the presence of SCC in cases increased the risk of HPV infection or replication. In addition, many SCCs do not harbour detectable virus and the virus does not integrate into the host DNA, suggesting that, if HPV does influence the aetiology of SCC, it is via a different mechanism to infection with mucosal HPV types. Alternatively, UV-induced immunosuppression may have increased the risk of both SCC and HPV infection, despite there being no causal link between the two. However, in a recent cohort study, higher HPV load was associated with significantly higher (subsequent) incidence of SCC compared with low load or absence of HPV in eyebrow hair.<sup>35</sup>

Experimental models suggest a hit-and-run mechanism, in which viral oncogenes potentiate the accumulation of UV-induced DNA lesions (probably through inhibition of DNA repair and/or apoptosis) in crucial genes associated with SCC in humans. However, silencing of the viral oncogenes does not affect further tumour growth.<sup>36</sup> Most experimental studies have been conducted in transgenic or experimentally infected models, so their relevance to humans is not clear. To overcome this, a rodent model, has been developed (*Mastomys coucha*) in which infection with *Mastomys natalensis* papillomavirus (MnPV) occurs naturally. The animals spontaneously develop benign and malignant skin tumours (SCC) that are histologically similar to lesions found in humans. In this model, MnPV and UV radiation at doses achievable by humans act synergistically to cause SCC, and the viral DNA is lost as tumours became malignant.<sup>37</sup>

## 4 Uveal melanoma and exposure to UV radiation

There remains little direct evidence of an association between uveal melanoma (UM) and exposure to UV radiation. Incidence decreases from the north to the south in Europe (four-fold higher in Norway and Denmark than Spain and northern Italy<sup>38</sup>) and in the USA (nearly five-fold higher incidence at latitude 47-48°N compared to 20-22°N<sup>39</sup>). In a recent meta-analysis, there was no evidence of an association between surrogates of exposure to UV radiation (for example, outdoor leisure activity and occupational exposure to sunlight) and UM. However, there was a nearly three-fold increase in risk of developing UM in association with the presence of atypical cutaneous naevi, and a significant increase in risk associated with presence of iris naevi, cutaneous freckles, a greater number of common naevi, light eye colour (blue or grey), and a tendency to sunburn.<sup>40</sup> UV-signature mutations are less common in UM than conjunctival or cutaneous melanoma, and explain less than 5% of the UM population-specific risk.<sup>41</sup> It seems unlikely that exposure to UV radiation is a major risk factor for UM, with evidence more in keeping with an increased risk in relation to what are recognised as markers of a sun-sensitive phenotype.

## 5 Possible mechanisms of action of vitamin D in human disease

The active form of vitamin D, 1,25(OH)<sub>2</sub>D, has effects through both genomic and non-genomic pathways. Genomic actions are mediated by binding to a nuclear vitamin D receptor (VDR).<sup>42</sup> After activation by 1,25(OH)<sub>2</sub>D, the VDR binds to DNA sequences to modify transcriptional output. Rapid, non-genomic effects also involve binding to a membrane VDR or a membrane-associated rapid response steroid binding protein.<sup>42</sup> The effects of 1,25(OH)<sub>2</sub>D in maintaining calcium metabolism occur through upregulation of intestinal absorption, and reduction in renal loss, of calcium and phosphate, and possibly through direct effects on cartilage and bone.<sup>42</sup> A wide range of cell types possess nuclear VDRs, including adipocytes, pancreatic β cells, cardiac myocytes, and immune cells. Experimental studies show that 1,25(OH)<sub>2</sub>D promotes lipogenesis and insulin secretion, and is anti-proliferative, stimulates repair of DNA damage, and inhibits tumour angiogenesis and metastasis.<sup>42</sup> In the skin, topical 1,25(OH)<sub>2</sub>D, or therapeutic analogues, inhibit proliferation, stimulate differentiation, and suppress immune activity; they may thus be of value in disorders with an underlying basis in excessive proliferation and lack of differentiation, such as psoriasis and skin cancers.<sup>42</sup>

## 6 Phototherapy to treat human diseases

UV radiation is a potent modulator of human skin disease. Whereas it causes photosensitivity and photo-aggravation in many people, phototherapy with UV radiation is also beneficial in a range of skin conditions, including psoriasis, atopic dermatitis and vitiligo.<sup>43, 44</sup> Seemingly paradoxically, certain photosensitivity disorders, including polymorphic light eruption, can also benefit from phototherapy.<sup>45</sup>

Narrowband UV-B (peak 311-312 nm) is a popular form of phototherapy,<sup>43</sup> while broadband UV-B (280-320 nm) and psoralen-UV-A (PUVA)<sup>46</sup> are also used. UV-A1 (340-400 nm) phototherapy is effective in atopic dermatitis, localised scleroderma and systemic lupus erythematosus,<sup>47</sup> and is under exploration in conditions particularly involving the deeper (dermal) skin layer.

Psoriasis is a chronic autoimmune disease characterised by hyper-proliferation and inflammation of the skin. Phototherapy reduces the T-cell mediated inflammation in psoriasis, including downregulating Th-17 cell activity, while upregulating immunosuppressive cytokines including IL-10,<sup>48, 49</sup> and restoring the numbers of regulatory T

cells ( $T_{reg}$ ).<sup>50</sup> The latter may be responsible for the prolonged remissions that are frequently seen in psoriasis following phototherapy.<sup>44 51</sup>

In atopic dermatitis, there is impairment of the skin barrier and enhanced susceptibility to allergens, bacterial colonisation and infection, in addition to dysregulation of the skin immune system, thus providing many possible targets for phototherapy.<sup>44</sup> Narrowband UV-B phototherapy is reported to reduce the activity of the Th-2 and Th-22 axes, and to a lesser extent the Th-1 axis, in atopic dermatitis,<sup>52, 53</sup> with reduction in IL-22 correlating with improvement in clinical activity scores.<sup>52</sup> Narrowband UV-B treatment of atopic dermatitis may also operate through an antimicrobial effect, modulating AMP,<sup>54</sup> and reducing microbial carriage and exotoxin production.<sup>55</sup> Furthermore, UV irradiation assists the normalisation of the epidermal barrier.<sup>52, 56</sup> In contrast to psoriasis, remission with phototherapy is usually short in atopic dermatitis, which may be explained by residual genomic changes and sub-clinical inflammation.<sup>53</sup>

Rising temperatures and changes in humidity as a result of climate change have been hypothesised to alter the severity of atopic dermatitis and its associated itching.<sup>57</sup> Nevertheless, the challenges of separating out different climatic effects, and the reliance largely on ecological (correlation) effects, make any predictions highly speculative at this time.

Vitiligo occurs through autoimmune destruction of melanocytes, with involvement of cytotoxic T cells,<sup>58</sup> producing well-delineated white skin patches. It is the commonest depigmentation disorder, estimated to occur in 0.4-2% of the world's population.<sup>59</sup> It produces high psychological morbidity especially in those with darker skin types. Narrowband UV-B phototherapy is an effective treatment for vitiligo; the mechanisms of its action in this skin disease fall into 2 major areas.<sup>44</sup> Firstly, UV-B irradiation promotes the proliferation, differentiation and migration of melanoblasts and melanocytes, which move outwards from their immune-privileged site in the hair follicle bulge to the inter-follicular epidermis.<sup>60</sup> Secondly, several immunoregulatory properties of UV-B irradiation are anticipated to operate, including apoptosis of cytotoxic T cells. Reduction in IL-17 and IL-22 levels and increased  $T_{regs}$  are reported following narrowband UV-B phototherapy, with correlation of these changes to improved scores of vitiligo clinical activity.<sup>61</sup>

## **7 Health-related “side effects” of fears about stratospheric ozone depletion and the Montreal Protocol**

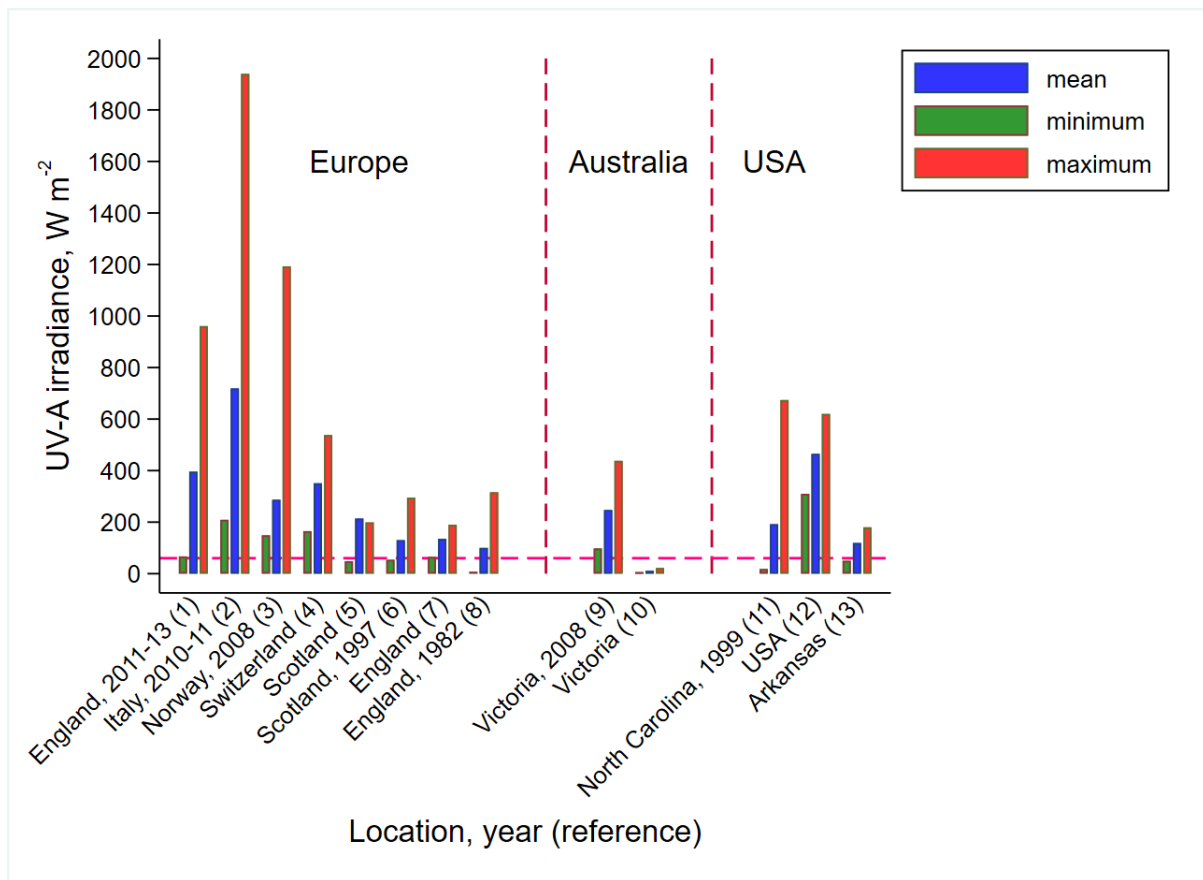
### **7.1 Sunbeds – history and demise**

The first sunbed – the incandescent light bath – was developed in 1891 by John Harvey Kellogg (the inventor of Corn Flakes) as an “*aid to good health*”.<sup>62</sup> In 1903, Finsen was awarded the Nobel Prize for medicine for his work on phototherapy, and during the early 20<sup>th</sup> century sun baths and sunlamps were used for their purported health benefits, for example, for skin conditions. In 1975, a German scientist developed and patented the tanning bed, emitting 95% UV-A and 5% UV-B, at a time when a tan was becoming fashionable.<sup>62</sup>

There are no analyses of possible links between recognition of stratospheric ozone depletion and the growth in interest in indoor tanning. However, it is conceivable that the recognised threat of large increases in ground level UV-B radiation as a result of ozone depletion and ensuing concerns about the high risk of skin cancer,<sup>63</sup> alongside the social desirability of a tan, may have led to what was perceived as a safer form of tanning – sunbeds. Whatever the underlying reasons (and no doubt driven by commercial interests), the number of sunbeds and the number using them rapidly increased over the latter years of the 20<sup>th</sup> century.<sup>64</sup>

By the early years of the 21<sup>st</sup> century, across Australia, Europe, and the USA, 14% of the general population of adults, 43% of university students, and 18% of adolescents had tanned indoors in the previous year.<sup>65</sup> In the USA in 2010 there were ~30 million indoor tanners<sup>66</sup> using ~25,000 indoor tanning facilities. In the UK there were 5350 tanning salons in operation in 2009, including 484 in Scotland.<sup>67</sup> In many countries, statistics on the number of tanning beds are not available, as no registration is required.

In 2009, the International Agency for Research on Cancer (IARC) classified tanning devices as carcinogenic to humans.<sup>68</sup> A systematic review of measurements of UV radiation in indoor tanning devices showed that typical values were higher than those from natural solar radiation and that there was wide variation between devices. The erythema-weighted UV irradiances were highest in the most recent studies (see Fig. S-1).<sup>69</sup> In particular, UV-A irradiances were very high in some devices, far exceeding solar levels.



**Fig. S-1** UV-A irradiance in tanning beds around the world. Data from.<sup>69</sup> Pink horizontal dotted line represents natural solar UV-A irradiance at midday in the tropics. References: 1<sup>70</sup>; 2<sup>71</sup>; 3<sup>72</sup>; 4<sup>73</sup>; 5<sup>74</sup>; 6<sup>75</sup>; 7<sup>76</sup>; 8<sup>77</sup>; 9<sup>78</sup>; 10<sup>79</sup>; 11<sup>80</sup>; 12<sup>81</sup>; 13<sup>82</sup>

Sunbed use has been linked to an increased risk of CMM, with the strongest risk for first exposure to indoor tanning before age 30 years.<sup>83</sup> A recent systematic review has challenged this view, on the basis that studies are generally of low quality and with high risk of bias.<sup>84</sup> Of note, a recent study showed that people who frequently used sunbeds also reported never or seldom using sun protection when outdoors.<sup>85</sup> This highlights the difficulty of separating indoor from outdoor tanning, and thus providing high quality evidence that indoor tanning

causes CMM. Nevertheless, the precautionary principle suggests control is required for this extraneous source of high dose UV radiation used for purely cosmetic purposes.

Additionally, there is risk of harm to the eye during sunbed use through insufficient provision and/or use of protective eyewear – this is of particular concern in young people owing to the immaturity of the lens and hence its greater transmission of solar radiation in UV wavelengths.<sup>86</sup>

Control of sunbeds began in 1997, when France banned indoor tanning for minors. The World Health Organization maintains a database of national regulations on access and control of sunbeds;<sup>87</sup> examples of control legislation are provided in Table S-2.

An Australian study monitoring advertisements on Gumtree and e-Bay to sell sunbeds or seeking access to a sunbed, found a reduction in units for sale following the ban on sunbeds and an increase in the price sought, but an increase in the ‘access wanted’ advertisements.<sup>88</sup> Ongoing monitoring of possible illegal or ‘underground’ use of sunbeds is recommended to ensure the health benefits of banning sunbed use.

**Table S-2.** Regulation of sunbed use in selected countries, including by age where relevant.

<b>Country</b>	<b>Control status</b>
Brazil	Banned for < 18 years in 2002; complete ban, 2009
Australia	Complete ban all states and territories, 2016
New Zealand	Ban for < 18 years, Jan 2017
Scotland	Ban for < 18 years, 2009
Belgium	Banned for < 18 years, 2009; from 2019 every user will need a unique electronic pass to log on to control use by minors and a first-time user must have a skin type certificate from a medical doctor
Norway	Banned for < 18 years, July 2012; from Jan 2017 all tanning studios must have an age control system
Denmark	No age limit
Sweden	Banned for < 18 years, Sept 2018
Canada	Banned for < 18 years in British Columbia (Oct 2012), Alberta (Jan 2018), Manitoba (Jan 2016), Saskatchewan (Nov, 2015), Ontario (Oct 2013), Quebec (Feb 2011), Prince Edward Island (Sep 2013); for < 19 years in New Brunswick (Jun 2013), Nova Scotia (May 2011), Newfoundland and Labrador (Jun 2012), and the Northwest Territories (Mar 2013)
USA	Banned for < 18 years in California, Delaware, District of Columbia, Hawaii, Illinois, Kansas, Louisiana, Massachusetts, Minnesota, Nevada, New Hampshire, North Carolina, Oregon, Texas, Vermont, Washington, Jan 2017.



## 7.2 Growth of research

An upsurge in research that followed the Montreal Protocol, has been important in discovering the mechanisms underlying UV-induced skin cancer, and has thus led to the development of new therapeutic agents and diagnostic tools. The development of new apps for monitoring personal sun exposure, and monitoring devices for use in research are discussed above, and in ref.<sup>89</sup> In addition to these electronic tools, novel biomarkers of acute or chronic sun exposure are being developed for use in research studies (see also ref.<sup>90</sup>). These advances are discussed below.

## 7.3 Biomarkers of sun exposure

Conjunctival UV autofluorescence (CUVAF) photography was developed to detect and quantify UV-induced damage on the surface of the eye.<sup>91</sup> Eyes with pterygia have larger areas of CUVAF,<sup>92,93</sup> while myopic eyes have less.<sup>94,95</sup> Greater CUVAF area is associated with older age, greater proportion of the day spent outdoors while working,<sup>96</sup> and less frequent use of sunglasses, in adults.<sup>97</sup> Larger CUVAF areas were measured in Caucasian children with lighter skin pigmentation, eye and hair colour, increased number of lifetime sunburns, freckling by the end of previous summer, and less use of sunhats.<sup>98</sup>

Iris freckles are dark spots on the coloured part of the eye (iris), formed by the accumulation of cells containing melanin. They do not have malignant potential, but seem likely to indicate a high cumulative dose of UV radiation, as well as constitutive sensitivity to the sun.<sup>99</sup> Iris freckles are more common with increasing age, lighter eye colour, greater lifetime number of sunburns and severe sunburns, and not using sun protection. Thus, they may have use as markers of the biological dose of UV radiation to the eye.

Skin surface topography, using silicone impressions of the back of the hand, has been used for some years to measure cumulative exposure to UV radiation and photoageing.<sup>100</sup> Recent techniques in digital analysis of the silicone impressions may provide much finer-grained scoring allowing more precise tracking of changes over time.<sup>101</sup>

The assessment of DNA photodamage in the skin requires the taking of a biopsy, which is not suitable for large-scale screening. Most DNA lesions are repaired by nucleotide or base excision repair and some of the excision fragments can be detected in urine; this offers the potential for assessment of DNA damage in research studies.<sup>102</sup> However, at present there are no techniques that are economically suitable for large-scale use. An alternative possibility is the use of a suture-free and minimally-invasive microbiopsy.<sup>103</sup>

A positive correlation between self-reported personal sun exposure and the frequency of micronuclei and demethylation in long interspersed nucleotide elements (LINE-1) in peripheral blood lymphocytes suggests that these changes may allow an objective assessment of exposure to UV radiation.<sup>104</sup> These changes may represent useful markers in exploring pathogenetic pathways, but expense currently precludes their common use.

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