Chapter 7

Summary and General Discussion

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It is well-known that UV exposure carries risks of sunburn and skin cancer. Even so, for the past several decades, people in Western cultures have sought exposure to the sun or to artificial sources of UV either to obtain a tan, or to gain some ill-defined health benefit. The FDA asserts that the risks of indoor UV tanning outweigh any potential benefits. However, the FDA also acknowledges that individuals continue to engage in this behavior and, therefore, the Agency desires to minimize the risks from this indoor UV exposure. The aim of this study was to develop new, improved guidance on exposure schedules for indoor tanning that will maximize benefits, while minimizing risks. We proposed to select the optimal schedule using two criteria: (1) that which produces the desirable effect (i.e. the tan) with the lowest cumulative UV dose and (2) that which produces the desirable effect with the smallest amount of DNA damage. The well-recognized benefit of increased Vitamin D and risk of photoaging from UV exposure will also be discussed.

1. Pilot Study - development of study exposure schedules

Current recommendations for UV tanning exposure schedules from the US FDA (FDA, 1986) are not well-adhered to (Kwon, 2002; Culley, 2001; Hornung, 2003), possibly because the low starting doses result in no visible pigmentation until 2 weeks into the tanning course (Caswell, 2000). For our exploration into new exposure schedules, we started with 3 exposure schedules that resulted in significantly different cumulative doses (14, 31 and 43 SEDs) and ended with schedules with cumulative doses of 19, 29 and 42 SEDs. All exposure schedules were constrained by the requirement for an initial dose of 1 SED and no single dose could exceed 6 SEDs to harmonize with the requirements in the international IEC 60335-2-27 standard for sunlamps/tanning appliances (IEC, 2012). Doses increased at each exposure session, by roughly 25%, 40% and 50%, respectively, for Schedules A, B and C. Based on the work of Bataille *et al.* (Bataille, 2000) and de Winter *et al.* (de Winter, 2001), we chose to limit exposure frequency (except for the 1st week) to a maximum of 2x/week to allow for DNA damage repair between exposures. We did not include the current FDA schedule in the study design because this would involve UV exposure that we believe is excessive and there is a published study (Caswell, 2000) that evaluated the FDA schedule with which to compare our results.

The exposure schedules were modified throughout the pilot study of 6 subjects (Chapter 2) to achieve the goals of the study, i.e. (1) development of at least one schedule that produced a tan comparable to that achieved in the Caswell study (Caswell, 2000) of the current FDA-recommended schedule, (2) more rapid development of the tan than in the current FDA schedule, (3) exploration of whether or not the cumulative dose could be reduced compared to current practice and (4) detection of possible saturation of pigmentation.

Regarding goal 1, the Caswell study produced skin color changes, measured as ΔE, ranging from 7.5 to 15 Chromametric Units (CU). The ΔE measured for subjects T5 and T6 in our pilot study had values ranging from 6.5 to 16 CU, similar to that of Caswell. Regarding goal 2, we found that administering exposures 3x/wk for the first week for subjects T5 and T6 resulted in the appearance of a light tan in approximately 1 wk. In addition, since the pigmentation appeared to saturate (in Schedules B and C) after the first 6 SED exposure in week 5, the second exposure of 6 SED was omitted and the schedules were modified accordingly and used in the main study of 40 subjects.

The pilot study (Chapter 2) of 3 different exposure schedules in 6 subjects resulted in the following conclusions:

- Sub-erythemal exposures given only 1x/wk were insufficient to produce more than minimal tanning (maximum visual grade of 'light brown tan' and mean ΔE of 2.7 CU).
- Sub-erythemal doses given 2x/wk required 10-17 days for a light tan to develop.
- Increasing exposure frequency to 3x/wk the first week accelerated time to appearance of light tan to approximately 1 week after first exposure, without producing erythema.
- A light-to-moderate tan could be achieved with a maximum per session dose of 3.8 SED and a cumulative dose of only 19 SED (i.e. Schedule A for T5 and T6).
- Moderate to dark brown tans were achieved with Schedules B and C which prescribed maximum doses of 6 SED and cumulative doses of 29 and 42 SED, respectively.
- Maximum pigmentation, as assessed visually and measured by L* was very similar for Schedules B and C in subjects T2, T5 and T6, despite the fact that the Schedule C site received a 40 -50% higher cumulative dose. This indicates that saturation of the pigmentation system has occurred.
- Visually, there was little to no significant erythema in most subjects during the tanning course.

- The tan did not diminish appreciably for at least 3 weeks post-exposure. Therefore, after a tan is established, exposures given once every two to three weeks should be sufficient for tan maintenance, though this should be confirmed in a study designed specifically to evaluate the minimum exposure needed for tan maintenance.

2. Main Study

The exposure schedules (A, B, and C) that were administered to each of the 40 subjects in the main study and the spectra of the 2 different UV sources, or sunlamps, are shown in Chapter 3. We enrolled 40 subjects; 21 in the first group (Lamp 1) and 19 in the second (Lamp 2). These two lamps were thought to represent the range of spectral extremes most likely to be encountered in typical tanning beds in the US. The subjects were scheduled for 15 visits over a 7-week period for exposures and instrumental measurements. Each of the three 3 x 3 cm sites was exposed to a different exposure schedule (Chapter 3), with site X as the unexposed control. In addition, the left side of the back was used for determination of the individual minimal erythema dose (MED, which equals the lowest dose required to produce perceptible reddening with at least one border visible). At each visit, the UV-induced changes were photographed, evaluated by trained observers and measured non-invasively using various instruments. At the end of the study, modified shave biopsies were taken to quantify DNA damage and melanogenesis in the skin.

3. Conclusions

3.1 Pigmentation appears to saturate with exposure Schedule B

After the pilot study (Chapter 2), the 3 exposure schedules were fixed as shown in Chapter 3 for the main study which examined the dynamics of pigmentation induction with the 3 exposure schedules and 2 different UV tanning lamps. Schedule A, with a cumulative dose of 19 SEDs given over 4 weeks produced only light to moderate pigmentation, thus it was not deemed as an acceptable choice for most tanners. We found that dark brown pigmentation (by visual observation) could be produced by a cumulative UV dose of 42 SEDs given as 10 exposures over 5 weeks. However, comparable pigmentation could also be induced by a cumulative dose of 29 SEDs given as 8 exposures over 4 weeks. Thus Chapter 3 demonstrated that the pigmentation system reaches saturation, at least when assessed visually, which is the appropriate measure to use when evaluating the perceived aesthetic benefit of a tan. In addition, in Chapter 5 we found that the amount of melanin content measured in the biopsied sites exposed to Schedule B (29 SEDs) and C (42 SEDs) were not

significantly different from one another, while that in the site exposed to Schedule A (19 SEDs) was significantly lower. This suggests that the pigmentary system was close to its maximal stimulation under exposure Schedule B with appreciably lower total UV dose than Schedule C. Therefore, further exposure past this point does not contribute to the aesthetic benefit of the tan or the amount of melanin in the skin, but may contribute to other modalities of photoprotection, as is indicated by the results of Chapters 5 and 6, which showed the lowest amount of DNA damage in treatment site C, 24 h after the last exposure.

3.2 The UVA content of the source is important for efficient production of pigmentation

In Chapter 3, we learned that the 2%UVB/98% UVA lamp (Lamp 2) led to earlier and darker pigmentation than the 5% UVB/95%UVA lamp (Lamp 1), for equally erythemogenic doses. Interestingly, the differences in melanogenic effectiveness of the two UV sources used here would not be expected based on the melanogenesis action spectrum (Parrish, 1982), since the melanogenic-weighted dose per SED was higher for Lamp 1 than for Lamp 2 (161 vs 146 J/m^2) (Chapter 3). This indicates that the currently-accepted melanogenesis action spectrum that was developed using single, narrowband exposures may not be valid for repeated exposures to broadband UV (possibly hinting at interaction between effects from different wavelengths). Our results also suggest that by using a tanning lamp with proportionally more UVA radiation, an equivalent tan can be produced with less cumulative erythema-effective exposure. For example, using Schedule B, equivalent pigmentation, as measured by ΔE, was reached on day 19 (cumulative dose of 23 SEDs) with Lamp 2, whereas with Lamp 1, the same value for ΔE was not reached until day 24 (cumulative dose of 29 SEDs), a 26% higher cumulative dose.

3.3 The exposure schedule does not need to be adjusted for different skin types

Current guidance (FDA, 1986) on exposure schedules recommends that they be adjusted for different skin types. Chapter 4 examined the tanning ability for Fitzpatrick (Fitzpatrick, 1993) skin types 2 and 3, using the 3 different exposure schedules and 2 different lamps. Indoor tanners will typically fall into skin types 2 to 4. Although we only studied skin types 2 and 3 in our study, we know that higher skin types can tan more efficiently than lower skin types. Based on our results and the results of other published studies that included skin type 4 subjects, we conclude that a single, universal exposure schedule can be used for all skin types

that are expected to engage in indoor tanning. The exposure schedule should be based on doses low enough to ensure that skin type 2 individuals do not burn. None of the 3 exposure schedules used in our study resulted in significant visible erythema in our subjects. Minimal perceptible erythema, detected by eye, has been shown to correlate with Oxy-Hb values of approximately 0.50. The average values in our study were well below this level. Thus, we conclude that exposure schedules for indoor tanning should be based on the minimum doses needed for tanning, not the maximum threshold dose for erythema (i.e. MED), as is done in current practice.

3.3 Dose frequency required for tan maintenance is significantly lower than for tan development

It is important to note that UV-induced pigmentation, once established, is relatively stable. The data presented in the pilot study (Chapter 2), though limited, show that light to moderate pigmentation was still visible in sites B and C even 3 months after exposures ceased. Chapter 3 showed that, on average, the pigmentation did not diminish appreciably for at least 3 weeks after the final exposure (Schedules A and B). In fact, in these 2 Schedules, the pigmentation diminished by less than 10% between days 23 (when exposures ceased) and day 37 (2 weeks later). Therefore, once a moderate to dark tan is produced, the exposures should not need to be repeated at intervals shorter than 2 weeks.

3.5 The optimal exposure schedule with respect to DNA damage/carcinogenic risk depends on the selected endpoint

Depending on the endpoint selected, the conclusions about the potential risks of the different exposure schedules may vary. It is well-known that cumulative UV dose is proportional to the risk of squamous cell carcinoma (SCC) (de Gruijl, 1983). A recent study by Tierney *et al.* (Tierney, 2015) showed that the risk of SCC could be determined from cumulative exposure to sunbeds, based on different exposure scenarios. Based on their model, an annual cumulative sunbed dose of 302 SEDs from 20 to 35 years of age would result in a relative risk of 2.8 for SCC at 55 years of age. This is comparable to what would be received by adherence to our Schedule C, since 42 SEDs over 8 weeks could lead to a maximum of 273 SEDs over a one-year (52 week) period, if the schedule were repeated every 8 weeks for the entire year. The Tierney model assumes a power-law relationship between cumulative dose and risk, therefore Schedules B and A would result in a proportionally lower risk. The tan

produced from Schedule A was not thought to be sufficiently dark to satisfy most tanners. Thus, based on SCC/cumulative dose as a risk metric, Schedule B would be the optimum choice since it resulted in a visually equivalent tan, with a 48% lower cumulative dose than Schedule C (Chapter 3). Since our studies indicate that tan maintenance could be achieved with exposures at intervals less than once every 2 wks, the cumulative annual dose could be lowered further (e.g. 161 – 188 SEDs/yr), which would be expected to result in a reduction in the risks of exposure.

Chapter 5 found that facultative pigmentation protects against subsequent UV-induced DNA damage, but not as effectively as constitutive pigmentation, which indicates that natural skin color and race/ethnicity play an important role in UV protection. An earlier study from our group (Yamaguchi, 2006) showed that the decreased photocarcinogenesis seen in dark skin types, e.g. skin type 6, may be a result of both decreased DNA damage due through more effective filtration by melanin and more efficient removal of UV-damaged cells through apoptosis. Thus, facultative pigmentation induced by repeated UV exposures, while protective, is not as efficient as constitutive pigmentation. Repeated exposures to UV can also lead to increased thickening of the stratum corneum and epidermis which results in decreased transmission of UV (de Gruijl, 1982). De Winter, (2001) found a 42% increase in the thickness of the whole epidermis after 3 wks of 3 exp/wk, with doses increasing by 20% each exposure. They found markedly reduced CPDs in skin that had been exposed to 3 wks of repeated exposures and, significantly, the amount of DNA damage in the basal layer was not signficantly different than that in the unexposed control site which is important since damage to basal cells is more likely to be carcinogenic. The cumulative doses applied in the de Winter study were 31.1 and 57.2 SEDs in the two groups (light and dark skin type) of subjects, similar to our cumulative doses.

In Chapters 5 and 6, we found that there was no significant difference between levels of CPDs (whether measured as overall intensity per area of the skin or as the number of CPD-positive cells per mm of skin) in sites exposed to Schedules A and B after the last exposure, but CPD levels in sites A and B were significantly higher than in site C ($p < 0.01$). Since the melanin content and visual tan were similar for Schedules B and C, there must be other photoadaptation factors at play here. Biopsies of sites A and B were taken on day 24, one day after their final UV exposure, while the biopsies of site C and X were taken one week later on day 31, one day after the final UV exposure for site C. This allowed more time for DNA repair in site C from previous exposures, even though site C was exposed to two additional 6

SED exposures after day 24. It is interesting that even though site B was exposed to 10 more SEDs than was site A, the level of CPDs in the 2 sites was similar 24 hr after the final UV exposure. However, the melanin content in site B was significantly higher than in site A, which could account for the increased photoprotection of site B.

The site exposed to Schedule B had the highest values for oxyhemoglobin (Oxy-Hb) levels, assessed through diffuse reflectance (DR) measurements (Chapter 6), and sites A and C were not statistically significantly different from one another. Oxy-Hb levels by DR are related to the amount of inflammation or erythema in the skin and not as subject to masking by pigmentation as are other instrumental measures of erythema, e.g. the Diastron Erythema Index. Melanoma has been associated with severe sunburn in epidemiological studies and some studies have reported that chronic exposure to UV (as in outdoor workers) does not increase the risk for melanoma (Elwood, 1992). This 1992 review found that the risk for melanoma increased for individuals with greater than 20 'whole body equivalent hours' (WBEH) of UV exposure, but then fell as exposure increased further. This amount of exposure is approximately equivalent to 100 SEDs based on the author's description of this dose metric. Interestingly, the author found that for exposures between 100 and 200 WBEHs, the risk of melanoma started to fall and went below 1.0 for exposures greater than 200 WBEHs. This indicates that chronic solar exposure could be protective for melanoma, possibly due to decreasing the risk of sunburn through photoadaptation. Our results indicate that Schedule C – with lower relative erythema and DNA damage than the other 2 schedules – could be the optimal choice if melanoma is the endpoint of concern. The use of this schedule year-round could result in a cumulative exposure of 273 SEDs per year. However, sunbed exposure is not equivalent to exposure received by outdoor workers in terms of dose rate and percentage of the body exposed, so the results of Elwood should not be construed as an endorsement of year-round use of sunbeds. In addition, there has been a more recent case-control study (Lea, 2007) that found that chronic UVB exposure also plays a role in melanoma etiology. Thus, a long-term study in a suitable animal model would be required to fully explore the relationship between different exposure schedules and the risk of melanoma.

3.6 The instrumental assessment of erythema may be able to be used as a surrogate for DNA damage in skin after repeated UV exposures

Young *et al.* (Young, 1998) found that the measure of erythema using an Erythema Index meter could serve as a non-invasive surrogate for DNA damage after a single exposure of

UV. Our study (Chapter 6) showed this not to be the case for individuals after repeated exposures to UV. However, the measurement of Oxy-Hb levels in the skin using diffuse reflectance spectrometry, does show promise for this approach. We found that on average the Oxy-Hb levels in sites A and C were similar, despite site C receiving 2.2 times as much cumulative dose as site A. Site B had the highest average Oxy-Hb levels and site C had the lowest. Similarly, site C had on average the lowest amount of DNA damage. In addition, in the group of subjects exposed to Lamp 2, the mean Oxy-Hb values followed the same pattern over the different treatments as did mean CPD density levels ($R^2 = 0.94$, $p = 0.03$). However the pooled individual results showed no appreciable correlation between Oxy-Hb and DNA damage. Apparently, the variation in individual (adaptive) responses, most crucially the ultimate DNA damage repair, deteriorates the correlation. Nevertheless, the overall reasonable correlation between averages over the different treatments leads us to infer that perhaps improved methods of measuring both erythema and DNA damage could better uncover a relationship between these two metrics. In addition, since we know from our previous studies (Tadokoro, 2003) that DNA damage peaks immediately after UV exposure and drops significantly by 24 h, increased sensitivity in the measure of DNA damage could be attained by taking biopsies immediately after the final UV exposure (eliminating final repair), while measuring the ensuing inflammation/ erythema 24 h later.

3.7 Studies of repeated UV exposure lasting longer than 8 weeks would be needed to assess the effect of different exposure schedules on photoaging

Previous studies (Leveque, 1988; Adhoute, 1992) have shown that chronic exposure to natural and simulated sunlight causes measurable changes in the elastic properties of the epidermal layers of human skin. In this study, we investigated the utility of the Diastron Ballistometer (Diastron, Andover, U.K.), a dynamic indentation instrument, to evaluate mechanical changes in the skin after repeated exposures to UV, using 3 different exposure schedules. The Ballistometer measures the resulting displacement of the skin surface as a function of time, which is a measure of skin elasticity. Skin elasticity, measured by the Diastron Ballistometer, has been shown to be an indicator of photoaging (Woo, 2014). We took measurements for 9 out of the first 11 subjects. Analysis of the indentation depth (a measure of skin stiffness) and the coefficient of restitution (CoR) for these subjects showed that no differences between the 3 exposure schedules (or even the unexposed control) in a given subject could be detected. In addition, we often had difficulties getting the instrument to ’trigger’ over the soft skin of the lower-mid back. Thus we conclude that changes in skin

elasticity (a surrogate for photoaging) could not be detected with the Ballistometer for the 8 to 10 UV exposures administered over 4 to 5 weeks in our study. Most likely, a longer-term study would be needed to show a significant difference between exposed and unexposed skin, and between the different schedules.

3.8 A benefit from UV exposure – increased Vitamin D status – would likely result from exposure to Schedules B and C

It is well known that UVB exposure is effective in producing increased levels of Vitamin D in the skin. Although we did not assess the Vitamin D status of the subjects in our study, it is useful to compare the 3 exposure schedules used here with a schedule that has been shown to significantly increase the Vitamin D status of human subjects exposed to a sunbed (de Gruijl, 2012). In the de Gruijl study, 35 subjects were exposed to a commercial sunbed 3 times per week for 8 weeks. The total cumulative doses received by the subjects ranged from 26 to 39 SEDs. Thus, the exposure schedule used by de Gruijl and colleagues was comparable to exposure Schedules B and C used in this study (cumulative doses of 29 and 43 SEDs over 4 to 5 weeks). The de Gruijl study found that this pattern of exposure was sufficient to cause a significant increase in serum levels of 25 hydroxyvitamin D (25 (OH)D); from 62 to 109 nmol/l ($p < 0.001$). Thus it is highly probable that similar increases in Vitamin D would be observed in subjects subjected to full-body exposures to the two schedules B and C used in our study, potentially conveying associated health benefits. Another study (Bogh, 2012) looked at the minimum UV exposure required for maintenance of summer 25(OH)D levels during winter and found that an exposure to one SED of UVB every second week to ca. 88% of the whole body was sufficient for skin types I - IV. This indicates that after our exposure Schedules B or C, Vitamin D levels could be increased and thereafter maintained with as little as one SED exposure, every other week, to both sides of the body in a sunbed.

4. Summary

In summary, none of the 3 schedules studied here proved to be 'optimum' on the basis of having the lowest cumulative dose AND the lowest amount of DNA damage, while producing desired benefits (i.e. a tan and increased Vitamin D status). Schedule A was clearly the least 'optimum', producing relatively high levels of DNA damage (at the end of the tanning course) and a less than satisfactory tan. Schedule B was able to produce the same amount of pigmentation as Schedule C, using a 45% lower dose. On the basis of preventing adverse effects of chronic UV exposure, e.g. SCC and photoaging, Schedule B would be

preferable to Schedule C. As others have shown, we found that repeated exposures above a certain level seem to confer less DNA damage due to photoadaptive processes (including pigmentation and epidermal hyperplasia) triggered by the insult of UV exposure over time. The fact that outdoor workers with chronic UV exposure have lower risk for melanoma than indoor workers (Elwood, 1992) indicates that chronic UV exposure may be protective for this disease. However, until more is known about the exact etiology of melanoma, the most deadly of all skin cancers, we cannot recommend that more UV exposure is preferable to the minimum that is required to achieve the desired endpoint, i.e. the tan. We also showed that exposure schedules do not need to be adjusted for different skin types, as is current practice. Our studies showed that repeated UV doses that are able to produce a moderate tan (without sunburn) in skin type 2 subjects, can also produce a similar, or darker, tan in skin type 3 subjects. Since skin type 4 subjects can tan even more easily, the same exposure schedule can be used for them, as well. Using a single exposure schedule for all skin types provides similar benefits to skin types 3 and 4, while minimizing the UV burden and associated risks. Lastly, we showed that a UV source with a high proportion (98%) of UVA compared to UVB (2%) produces similar tans more rapidly and with lower cumulative doses than a UV source with a 95%/5% UVA/UVB ratio. Thus, our Schedule B, with a 98%/2% UVA/UVB ratio source was found to be the most efficient exposure schedule in terms of maximizing the benefits (i.e. a tan and increased Vitamin D status) and minimizing the risks (SCC and photoaging) of repeated exposures and this schedule can be used in all skin types that are expected to tan indoors. These results formed an important basis for FDA's 'Proposed Rule' of December 18, 2015, to amend and improve the outdated 1985 Performance Standard for Sunlamp Products, particularly by declaring that the tanning action spectrum should no longer be used for broadband sunlamps, and in limiting a) the number of exposures per week (max 2), b) the cumulative dose (max 30 SED) and c) the recommended exposure schedule to one indiscriminately of skin type.

Overall Conclusions

Schedule A was only able to produce a light to moderate pigmentation.

Schedule B and Schedule C produced similar, moderate to dark pigmentation.

The 98%UVA/2%UVB lamp produced pigmentation – measured by ΔE - equivalent to that produced with the 95%UVA/5%UVB lamp more rapidly and with lower cumulative erythemal doses.

The greater efficiency in producing pigmentation of the 98%UVA/2%UVB lamp was not predicted by the Parrish (1982) melanogenesis action spectrum.

Exposure schedules need not be adjusted for skin type since higher skin types tan more efficiently than lower skin types.

Schedule B is preferable on the basis of producing a moderate to dark tan with lower cumulative dose.

Schedule C is preferable for better skin acclimation (assessed by Oxy-Hb and DNA damage 24 hrs > final exposure).

Recommendations

Intentional tanning is not recommended since any UV exposure causes skin damage!

If you must tan:

- Use no more than 2 exposures per week and doses per session ≤ those in Schedule B for skin types II – IV to achieve a moderate to dark tan with the lowest cumulative dose and produce a significant increase in Vitamin D status.
- After the desired level of tan is achieved, it should be able to be maintained with one exposure ≈ 6 SED every two weeks.
- Use a lamp with ≥ 98% UVA for most efficient cosmetic tan.

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