The impact of climatic and environmental factors on personal ultraviolet radiation exposure and human health

Executive Summary:

The aim of ICEPURE was to define factors that determine biomarkers of solar UVR-induced health outcomes. These included adverse acute factors that are associated with skin cancer and the beneficial effect of vitamin D synthesis. We also addressed behavioural factors. Field studies were done in adults and children in work and leisure situations in 4 EU countries in which personal UVR and ambient exposure was monitored.

- Skin cancer is a major health burden in the EU, and the incidence of malignant melanoma (the cause of the vast majority of skin cancer deaths) has increased in recent decades.
- Extensive epidemiological data show an association between UVR exposure and skin cancer, and this is supported by data on skin cancer mutations that are caused by UVR-induced damage to the skin's DNA.
- Different types of UVR-induced skin cancer are dependent on patterns of UVR exposure, e.g. acute holiday exposure or chronic occupational exposure, or sunburning exposure in childhood.
- Personal UVR exposure was measured in holiday and work situations and we studied the relationships between behaviour, biological outcomes and UVR dose.
- Laboratory studies were also done to help interpret the field data.
- More than 500 electronic personal dosimeters were individually calibrated against all day clear sky solar UVR.
- Danes, Poles and Spaniards received very high levels of erythemal UVR exposure over a large body surface area during a week in March in Tenerife, resulting in:
  - A very high frequency of sunburn.
  - High levels of DNA damage in skin and urine.
Complete suppression of the skin's immunity
A significant increase in vitamin D
- Personal behaviour has a critical role in exposure to UVR
- Polish children on a 2-week Baltic Sea summer camp obtained high UVR doses with a significant increase in vitamin D, but very high levels of DNA damage
  - Vitamin D increase in the sun is inversely proportional to baseline levels (as previously demonstrated in the laboratory)
  - Combined data from Danes, Austrians and Spaniards on ski and beach holidays showed that increased vitamin D and DNA damage are related to UVB dose (including body surface area) and that it is virtually impossible to increase vitamin D without considerable collateral DNA damage
- Farmers’ studies showed some regional differences in UVR exposure. In general the highest doses were received by the Spanish farmers, though the Danish farmers showed more “risk behaviour”
- Laboratory studies on human volunteers showed:
  - Irrespective of UVR spectrum, erythema is predictive of the suppression of the skin’s immunity (thus is a marker of immunosuppression) but not of vitamin D
  - DNA damage assessed in urine correlates with such damage in skin
- Animated body models were developed (and verified) to determine UVR exposure on any given surface area under any environmental/climatic situation
  - Modelling personal UVR exposure correlates well with that measured
  - It is possible to predict future personal UVR exposure using climate models
  - Surrogates of UVR exposures (e.g. latitude and ambient UVR) that are routinely used in studies of UVR health effects can result in a considerable exposure measurement error that in turn can lead to errors in estimating health effects
  - The error in estimating UVR health effects due to exposure measurement error accompanied by using surrogates of UVR exposure can be corrected by fortifying these aggregated estimates of UVR exposure by personal measures of UVR exposure obtained for a subset of study participants
- Based on Danish holidaymakers, people seek maximal UVR exposure and have ignored “safer sun” messages. There is possible scope to engage with the large EU sunscreen in the development of positive “safer sun” education
- Body models may be a good tool for public education on the health outcomes of UVR exposure
- Work is still required to determine UVR dose outcome and risk benefit relationships. This is much more difficult in the field than in the laboratory, but the field data are much more important
- The SunSaver used in the project has been shown to be a good research tool, but will require further development for routine use in epidemiological studies

Project Context and Objectives:
Solar ultraviolet radiation (UVR ~ 295-400nm) has important beneficial and adverse impacts on human health. The overall aim of the project was to define personal UVR exposure doses received, and their health consequences to the skin, during common leisure and working activities in Europe. This was done in field studies, also supported by some laboratory studies. Eight partners in 6 EU countries took part in the project.

The main adverse effect of UVR exposure on human health is skin cancer, which includes basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma (MM). Photoageing of the skin is also caused by long-term exposure to solar UVR but we lack epidemiological data on this outcome. Furthermore, this is widely perceived as a cosmetic problem. BCC and SCC, though different in their pathogenesis, are often referred to as non-melanoma skin cancer (NMSC) and are much more prevalent than MM. Lethality is rare from NMSC and they are often poorly recorded in Europe, and in other parts of the world. Nonetheless, they place high financial burdens on European health services. The registration of MM is better but is very variable within Europe. The data on incidence of MM show large regional variations within Europe, but there is less variation with mortality. Options for the treatment of MM have improved recently, but MM remains a very serious diagnosis that is responsible for the vast majority of skin cancer deaths in Europe. The best options for MM are early diagnosis and prevention. Epidemiological data indicate that solar UVR is the most common cause of skin cancer in fair-skinned people who are at the greatest risk of skin cancer (for example most skin cancers appear on sun exposed sites). This means that, in theory, the majority of skin cancer could be prevented by behavioural modification. In practice, the incidence of MM has increased in many European countries, e.g. by approximately 7-fold between 1960-2010 in the Nordic countries (http://www-dep.iarc.fr/nordcan) and incidence of non-melanoma skin cancer in this region has increased about two fold between 1980-2010. In the UK, there has been a 10-fold increase in MM older males between 1975-1977 and 2008-2010 (http://www.cancerresearchuk.org). One possible explanation for this is the increase in travel for short holidays to sunny destinations which has become much more affordable because of budget airlines.
It is estimated that about 52% of the EU-27’s population took part in tourism in 2011, in other words made a trip of at least four nights during the year. In 2011, EU27 residents made 1.0 billion holiday trips, of which, about one quarter were outside the country of residence (outbound trips). Looking in more detail at these outbound holiday trips, Spain was the top foreign destination of EU27 residents in 2011 (13% of all outbound trips), followed by Italy and France (both 9%). It should be noted that these figures refer to trips made by EU residents. They do not include trips made by non-EU residents to the EU (data from Eurostat, the statistical office of the European Union). Many EU citizens also travel widely to non-EU destinations such as Florida and the Red Sea (before the “Arab Spring”).

Patterns of UVR exposure can determine skin cancer outcome. Chronic low dose UVR exposure is associated with SCC, whereas sunburning exposure is associated with MM and probably BCC. Sunburn in childhood has also been associated with MM later in life.

Skiing and beach sun holidays are popular in Europe and so were chosen as representative leisure activities. Holidays, especially sun-holidays enable sudden changes of climate where un-acclimatized skin cancer be exposed to high dose UVR. In the case of skin holidays, UVR intensity increases with altitude and snow reflects UVR. The destinations for weeklong breaks in March were Tenerife for the beach holidays and the Austrian Alps for skiing holidays. Tenerife is a very popular destination for tourists from Northern EU countries, and is approximately the same latitude as Florida and the Red Sea. In these studies, we compared adult populations from Austria, Denmark, Poland and Spain. In addition, we also studied Polish children during a two-week summer camp holiday on the Baltic Sea.

Farming was chosen as a representative working activity because it a ubiquitous and important outdoor economic activity in Europe, and represents a “chronic exposure” situation. Furthermore, it was possible to study families, including children, in which the spouse may not work on the farm or only work part-time. This enables comparisons of different occupations within families as well as comparisons between adults and children. Thus, we studied farmers in Austria, Denmark, Poland and Spain during 6-month periods.

The participants in all the studies wore personal UVR dosimeters (SunSavers) on their wrists. These electronic devices make frequent time stamped measurements of UVR exposure. The readout is in standard erythema doses (SED), which is a measure that is independent of personal sensitivity to erythema or the spectral quality of the UVR exposure. Participants of some studies also wore devices that measure solar UVB (~295-320nm) and UVA (320-400nm). Ambient UVR was also measured during the studies using a modified version of the SunSaver housed in ground stations. A major task in the project was the calibration of the SunSavers, which had to be done on an instrument-by-instrument basis against whole day clear sky conditions.

The adverse health effects of solar UVR to the skin are both acute and long term, with skin cancer being the most serious long-term consequence. It is not possible to study the direct effects of solar UVR on skin cancer in a 4-year project, so DNA photodamage was chosen as an acute biomarker. The specific endpoint was the thymine dimer (T=T), which is a cyclobutane pyrimidine dimer (CPD). CPD are known to initiate the “UVR-signature” mutations (e.g. in p53) that are common in non-melanoma skin cancers such as BCC and SCC. They are also found in actinic keratoses (AK), which are a biomarker for SCC risk. There is good evidence that CPD may initiate sunburn, immunosuppression and photoageing. Immunosuppression is thought to play an important role in non-melanoma skin cancer and so was also chosen as an endpoint in field and laboratory studies. Acute clinical endpoints such as sunburn (as risk factor for melanoma) were also assessed as well as naevi (moles) that may also be a risk factor for skin cancer. It should be noted that not all endpoints were measured in all studies, some of which had biases to address specific aspects.

Vitamin D is the only established health benefit of solar UVR exposure. Its major role in bone health is well established, but there is increasing, though controversial, evidence that it is also important for a wide range of other health outcomes. Many studies have shown that people are insufficient or deficient and that status is seasonal with the highest values in summer. It is estimated that most people get most of their vitamin D by solar UVR-induced photosynthesis. In this context, we measured changes in vitamin D status during our studies. This was done by measuring serum 25(OH)D by mass spectrometry which is the most reliable way of assessing vitamin D status.

UVR-induced DNA damage (e.g. T=T) has been typically assessed in skin from punch biopsies, which is an invasive procedure that is not suitable for routine use. We have measured T=T in urine, which is a measure of the nucleotide excision repair (NER) of DNA damage. One of the goals of the project was to assess the relationship between DNA damage in the skin and its presence in urine. This was done in a laboratory study.

Exposure dose of UVR has been shown to be a major determinant of outcome, primarily in laboratory studies. However, irradiation
spectrum is also very important because the effects of UVR on health are very wavelength dependent. Solar UVR spectra (i.e. UVB:UVA ratio) vary considerably with the height of the sun. Sunburn (erythema) is the most widely used clinical method of assessing UVR exposure, and the SED index was used in all the field and laboratory studies. Laboratory studies were done to determine if erythema was predictive of immunosuppression and vitamin D synthesis, irrespective of irradiation spectrum. This is important because erythema is the most widely used measure of UVR exposure at an individual level and the SED is increasingly used in population studies.

Behaviour is known to be an important determinant of UVR exposure. One factor in behaviour is climate. Thus we aimed to improve measurement techniques and radiative transfer models to develop a better estimate of UVR in climate models and for prediction of future UVR levels that may occur with climate change.

There is a lot of epidemiological literature on the health effects of UVR, but most is based on surrogate measures of UVR exposure, such as latitude. The goals of the project included a review such literature and to determine UVR measurement error, and a means of correcting such error. The overall aim of this was to gain a better understanding of the relationship between UVR exposure and health outcomes.

Summary of Objectives

Measure personal UVR exposure in different work and leisure environments in Europe
- In relation to important leisure (skiing, beach) and working activities in Europe
- To validate existing UVR estimates in epidemiological studies
- To correlate personal UVR exposure with satellite and ground station data
  o UVR
  o Albedo
  o Aerosol
  o Cloud cover
- Use combined personal, satellite and ground station UVR data to develop new radiative transfer models that can be used in climate models to predict future UVR levels
- Determine the beneficial and harmful biological effects of UVR, and critical dose levels, in relation to personal UVR exposure including
  - Vitamin D synthesis
  - DNA damage
  - Immunosuppression
- Review the current health risks of UVR exposure and assess the impact of using personal UVR data on existing exposure relationships, and where possible, determine critical levels of exposure. The project was divided into 6 work packages (WP) and the results are presented under their respective WP.

Project Results:
- The personal dosimeters and ground stations performed as expected and gathered the UVR data as planned. However, the dosimeters required more manual intervention than expected to correct for background noise
- We compared some of our vitamin D analyses with an independent laboratory and found an excellent linear correlation (R^2 = 0.91) with an intercept close to zero
- Danes, Poles and Spaniards received very high levels of erythemal UVR exposure over a large body surface area during a week in March in Tenerife, resulting in:
  o A very high frequency of sunburn
  o High levels of DNA damage in skin and urine
  o Complete suppression of the skin's immunity
  o A significant increase in vitamin D
- We estimated that Danes had over 40% of their annual UVR exposure during a single week on a sun holiday in March. This is on un-acclimatized skin and such exposure may be major factor for melanoma risk
- Personal behaviour has a critical role in exposure to UVR. Danes essentially followed the sun
- Polish children on a 2-week Baltic Sea summer camp obtained high UVR doses with a significant increase in vitamin D, but very high levels of DNA damage
- Vitamin D increase in the sun is inversely proportional to baseline levels (as previously demonstrated in the laboratory)
- Combined data from Danes, Austrians and Spaniards on ski and beach holidays showed that increased vitamin D and DNA
damage are related to UVB dose (including body surface area) and that it is virtually impossible to increase vitamin D without considerable collateral DNA damage

- As might be expected, field data show much more variation than laboratory data where parameters can be tightly controlled
- Farmers’ studies showed some regional differences in UVR exposure. In general the highest doses were received by the Spanish farmers, though the Danish farmers showed more “risk behaviour”
- Summer exposure resulted in a significant increase in vitamin D in farmers, their spouses and children

Laboratory studies on human volunteers showed:
- Irrespective of UVR spectrum, erythema is predictive of the suppression of the skin’s immunity (thus is a marker of immunosuppression) but not of vitamin D
- DNA damage assessed in urine correlates with such damage in skin
- Animated body models were developed (and verified) to determine UVR exposure on any given surface area under any environmental/climatic situation
- Modelling personal UVR exposure correlates well with that measured
- It is possible to predict future personal UVR exposure using climate models
- Surrogates of UVR exposures (e.g. latitude and ambient UVR) that are routinely used in studies of UVR health effects can result in a considerable exposure measurement error that in turn can lead to errors in estimating health effects
- The error in estimating UVR health effects due to exposure measurement error accompanied by using surrogates of UVR exposure can be corrected by fortifying these aggregated estimates of UVR exposure by personal measures of UVR exposure obtained for a subset of study participants

Potential Impact:
The ICEPURE project has given us detailed quantitative and qualitative information of behaviour in the sun, as well as the short-term consequences of such behaviour. One of the most striking conclusions from our studies is that people, especially of Nordic origin, greatly over-expose themselves to holiday solar UVR and seem to misuse sunscreens as a licence to do this. In other words, they overestimate the level of UVR protection that they receive because they do not apply sunscreen at the thickness that is used for sun protection factor (SPF) testing. For example, people who use an SPF = 30 product will in practice get an SPF = 4, which is about 1/8th of the labelled protection. Our recent paper in the British Journal of Dermatology reported that Danes received >40% of their total annual UVR burden in a one week holiday with exposure to about 1/3 of ambient UVR. A Polish study group also received comparable levels of exposure. Such patterns of behaviour result in considerable sunburn that is an established risk factor for malignant melanoma and probably basal cell carcinoma. It seems that several decades of well intentioned advice to educated populations has been ignored. Our observations show that we have a long way to go in public health education and we need to devise much better strategies for this if we want to reduce the incidence of skin cancer in Europe.

An analyses of sun-behaviour within Danish farmer families showed that parents have little influence on the sun-behaviour of their children, with the exception of daughters being influenced by their mothers. This suggests that public health campaigns should be targeted directly at children. The most obvious approach is via the school system. This will require the education of teachers.

In general, government bodies and health organizations issue public health information. In the UK for example, by Cancer Research UK (CRUK) and the British Association of Dermatologists (BAD). Such messages are intermittent and generally have to be sought by individuals; they also tend to be negative. A more powerful approach might be for public health bodies to develop formal partnerships with the sunscreen industry that has large budgets for the promotion of sunscreens. Campaigns that successfully promoted the correct use (i.e. thickness) of sunscreens would reduce the level of molecular and clinical damage received by the skin. This would also be beneficial to the companies because they could sell more product and would have an impact on the European economy because many of the world's major global sunscreen companies (products and raw ingredients) are based in Europe, for example L'Oreal, Beiersdorf, Boots, BASF, DSM, Lancaster, Boots, Pierre Fabre.

Studies on children on a summer camp and holiday makers have shown that 1-2 weeks in the sun results in a very substantial increase in 25(OH)D which is the “gold standard” measure of vitamin D status. This clearly shows the benefit of solar exposure, albeit at very high UVR doses. However, as we show in figure 5.3.1 this is associated with very high levels of potentially carcinogenic DNA damage (CPD). This is not surprising given the similarity of the action spectra for the synthesis of pre-vitamin D and CPD (although the chromophores are different).

Previous studies by the coordinator have shown that the action spectra for erythema and CPD are the same, which suggests that
Erythema is initiated by DNA damage. This suggests that erythema is a surrogate for DNA damage (which can occur with sub-erythemal exposure). The laboratory work in the ICEPURE project also suggest that erythema is a surrogate for immunosuppression which we demonstrated in the field studies (see figure 5.4.3). In these studies we also showed that 3 SED (about 1 minimal erythema dose (MED)) UVA-1 (340-400nm: which is the major region of solar UVR from a physical point of view) suppresses skin immunity as well as 3 SED from solar type spectra. There are very few data that show a clinical outcome from environmentally relevant doses of UVA-1 and our results support the inclusion of UVA-1 filters in sunscreens, as has been required by the EC. In general, European companies have led the development of UVA-1 sunscreen filters.

Laboratory studies, including those done under ICEPURE, have shown vitamin D synthesis occurs with sub-erythemal UVR doses over small areas of skin. This project has also shown that sub-erythemal whole body exposure also results in considerable DNA damage. Further analyses/work will be required to determine the dose-response and spectral relationships between vitamin D synthesis and DNA damage for the development of public health advice.

Our accumulation of personal UVR exposure data, in the context of location and ambient UVR, is a valuable resource that can be used to validate behaviour/UVR exposure modelling studies of the type pioneered by Professor Brian Diffey (with whom we worked on one publication). Furthermore, we have developed animated human body models that can be used determine biologically weighted (e.g. erythema, vitamin D, DNA damage) exposure doses to any body site under any given climatic condition. We believe that these constructs may be developed as tools for public health information and well as studying the relationships between UVR exposure patterns and skin cancer. Our modelling of UVR exposure data matches actual UVR exposure (e.g. figure 6.3.3) and we are refining our model to predict UVR exposure into the future based on climate models. This will allow public health bodies to have advance warning and develop strategies to modify behaviour if UVR exposure levels are expected to be high.

Many studies have attempted to assess the relationship between UVR exposure and health outcomes by using surrogates of exposure such as latitude. These data have been used to suggest a relationship between UVR levels, vitamin D status and health outcomes. Our analyses however shows that this is a rather crude approach which may only work on large studies with a wide geographical distribution and is prone to ecological biases and measurement error. As part of this study, we demonstrated that the variation in personal exposure within the same city is about three times higher than the between-city variance in Europe. Behavioural factors such as time spent outdoors and summer holiday destination and behaviour are important determinants of personal UVR exposure, and determine to a great the variability in UVR exposure between people. We have developed statistical tools to integrate ambient UVR exposure and personal behavioural factor and quantity and calibrate exposure response relationships for this type of measurement error. We anticipate that our publication will influence future epidemiological studies to take personal UVR exposure and behaviour into account.

The SunSaver was the core of the ICEPURE project and has provided a vast amount of personal UVR exposure data. However, this device is very much a research tool that requires a considerable amount of work to obtain usable data. There is substantial variation in the sensitivity of the “erythema sensor” which meant that each SunSaver had to be individually calibrated under clear day conditions. Furthermore, there is variation in the background “noise” of each device which means that background has to be subtracted manually on a day by day basis which is very labour intensive. These problems would have to be resolved before the SunSaver could be advocated for "routine" epidemiology use.

The following improvements are intended to incorporate into the next generation of the UVR dosimeter, SunSaver. The result will be a combination of technical possibilities, battery lifetime, size of the housing and the cost.

1. Automatic baseline adjustment (very labor demanding to do manually) (has been confirmed that it is possible)
2. Smaller in size, possible designed as a jewelry (we cannot get a smaller sensor at this time)
3. Rechargeable battery, possibly wireless by induction
4. Movement sensor (confirmed possible)
5. Wireless transfer of data (confirmed possible, but may increase size and lower battery lifetime)
6. Each averaged UV and movement measurement is followed by the Standard deviation to show the variations during the measurement period.
7. Waterproof
8. High speed sample rate mode (more than 1 measurement per second)
9. Larger memory (confirmed possible)
10. Add on: GSM modem (or a smartphone) that can transfer data using the mobile network (confirmed possible, useful in ground stations)

ICEPURE has initiated two successful current grant applications that have been based on the experience gained from the project and the use of some of the material from the participants. One is to Professor Young and is supported by the UK Department of Health; a two-year project (£310,426) entitled “Vitamin D photosynthesis: interactions with melanin and UVR spectrum. The other, awarded to Professor Mark Nieuwenhuijsen, is “Solar ultraviolet radiation exposure: genetic background and molecular mechanisms” which is a 3 year project (€194,000) supported by the Spanish Government.

Professor Mark Nieuwenhuijsen is conducting an EC funded project (HELIX) in 6 birth cohorts in Europe that will assess as many environmental exposures as possible (exposome). This will include UVR exposure in the form of modelling and measurement using the SunSaver in collaboration with Professor Hans Christian Wulf.

Finally, ICEPURE was a truly multi-disciplinary European study that enabled dialogue and interaction between a very diverse group of clinicians, biological and physical scientists and epidemiologists. All have benefited from this experience that is likely to result future collaborations and enhanced research programmes.

Main Dissemination Activities
The project has resulted in several publications in peer-reviewed journals, a list of which is given in Table A1. Several other manuscripts are in various stages of submission.

The ICEPURE coordinator arranged and chaired two ICEPURE themed symposia at major international photobiology congresses, one at the 14th Congress of the European Society for Photobiology (ESP), Geneva, 1-6 September 2011 and the other at the 36th Congress of the American Society for Photobiology (ASP), Montreal, 23-27th June 2012. The ESP and the ASP are the world's the main photobiology societies. Both symposia were very well attended and were an excellent opportunity to publicize and disseminate the ICEPURE programme. Thus, there can be few interested parties in all parts of the world who are not aware of the ICEPURE project.

ICEPURE was also highlighted at a lecture given by Professor HC Wulf during at conference on Human Health and the Impact of Environmental and Climatic factors held in Copenhagen on 25th April 2012. We were also invited to present a poster at this meeting to summarize the ICEPURE project. This meeting was well attended by scientists, journalists and policy makers including Per Okkels, Permanent Secretary of State at the Danish Ministry of Health and Christel Schaldemose, who is a member of the European Parliament and is a member of the European Parliament Against Skin Cancer (MAC); an all-party informal group committed to promoting action on cancer as an EU priority and harnessing European health policy support to that end. Representatives of EUROSKIN, the European Skin Cancer Foundation, Euromelanoma and the International Task Force on Skin Cancer Screening also attended the meeting. These organizations have an interest in the prevention of skin cancer. Thus, this meeting was an excellent opportunity to promote the ICEPURE project. In parallel with this meeting was a well attended poster exhibition open to the public and the press. HRH Princess Marie of Denmark opened this event.

Professor Young has given ICEPURE-based presentations to the UK Department of Health and its Scientific Advisory Committee on Nutrition (SACN), which is preparing a report on vitamin D. He has also been asked to join the Advisory Group on Non-ionizing Radiation (AGNIR) to co-prepare a report on vitamin D. AGNIR provides advice which may be used for public health purposes via Public Health England.

Professor Young was also a member of the FP6 EU GenoMEL (Melanoma Genetics Consortium) project. He also informed this group of the ICEPURE project and presented an overview of some of the data at its meetings, including its meeting in Tel Aviv, 3-5th May 2011. Professor Young and the group from BBH made informal connections with the US-based Gene, Environment, Melanoma (GEM) international group and were invited to give presentations on the ICEPURE project at their meeting in Toronto, 27-29th July 2009.

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