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DIVISION OF ENVIRONMENTAL HEALTH, WORLD HEALTH ORGANIZATION
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HEALTH, SOLAR UV RADIATION AND ENVIRONMENTAL CHANGE



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Chapter 1

INTRODUCTION

1. BACKGROUND

The International Research Programme on Health, Solar UV Radiation and Environmental Change (INTERSUN) is a collaborative project of the International Agency for Research on Cancer (IARC), the Division of Environmental Health of the World Health Organization (WHO), and the United Nations Environment Programme (UNEP), coordinated by IARC.

INTERSUN has its origin in international concern over the potential health consequences of depletion of stratospheric ozone. Between 1978 and 1990, this depletion proceeded at an average rate of 0.26% per year between latitudes 65°S and 65°N (Stolarski et al, 1991) and decreases of a similar or greater degree can be expected during the 1990s (World Meteorological Organization, 1991). Because stratospheric ozone is the main atmospheric filter of short wavelength ultra violet radiation (UVR), depletion of this degree will almost certainly lead to increased UV irradiance at the Earth's surface (in the absence of compensating changes in cloud cover, tropospheric ozone, or other factors which also filter UVR), to be followed in turn by an increase in the adverse health effects of UVR. These effects include both non-melanocytic skin cancer and malignant melanoma (Chapters 3 and 5), cortical and posterior subcapsular cataracts of the eye, other ocular effects such as acute photokeratitis and pterygium (Chapter 9) and, possibly, suppression of cutaneous and systemic immunity (Chapter 8).

In the face of near certain increases in UV irradiance at the Earth's surface, it is important for reasons of public health and environmental management policy to:

- (i) make well-informed quantitative predictions of the population health impacts of these increases; and
- (ii) develop or improve and implement monitoring of both the exposure of human populations to solar UVR and the health consequences of this exposure.

Predictions of the health impact in the absence of behavioural adaptation to a change in ambient UVR are important to guide the primary, remedial policy responses directed at curtailing depletion of stratospheric ozone. For that objective, the essential relevant measure is the change in population disease incidence associated with a change in ambient UV irradiance. On the other hand, predictions of health impact on the assumption of behavioural adaptation are important to the development of short-term behaviour-based adaptive responses that will ameliorate the problem during the time it takes for environmental correction to be achieved. Development of these adaptive responses requires detailed knowledge of the relationship between sun-related behaviour and risk of disease at the individual level.

There are, at present, major deficiencies in the data necessary to predict the health impact of stratospheric ozone depletion and to monitor UV irradiance changes due to it and the behavioural adaptations and health consequences that may follow.

There is no global or even national network of centres able to measure in a standard manner and on an ongoing basis either spectrally specific or broad band UV irradiance in populated areas (Chapter 13). While ground level UV irradiance can be estimated for all

parts of the world by use of readings from the satellite-based Total Ozone Mapping Spectrometers (TOMS) and appropriate radiative transfer models (Frederick and Lubin, 1988; Madronich, 1992), these estimates have not yet been validated against actual ground measurements of UVR. Moreover, the limited steps towards adequate monitoring of UV irradiance at the Earth's surface have not taken the needs of public health monitoring into consideration.

Efforts have been made to predict the extent to which the incidence of non-melanocytic skin cancer and malignant melanoma will increase as a result of particular changes in UV irradiance (Chapter 2). These predictions, however, are of uncertain validity because of the lack of a well founded numerical relationship between UV irradiance at the Earth's surface and incidence of these skin cancers and are likely to be poor guides to public health and environmental policy (Armstrong, in press). Predictions of changes in the incidence or prevalence of ocular disorders (United Nations Environment Programme, 1989) are even less certain, and there exists, at present, no sound basis on which predictions of the immunological consequences of UV irradiance increases could be made.

There exist also, at present, no well established mechanisms for monitoring sun-related behaviour or health effects caused by solar UVR that would provide assurances, or otherwise, that public policy approaches to the health consequences of depletion of stratospheric ozone have been adequate. Among the health effects, only the incidence of malignant melanoma is measured both widely and potentially accurately (Muir et al, 1987). While the incidence of non-melanocytic skin cancers is measured by a number of cancer registries (Muir et al, 1987), the measurements of these cancers are not accurate (Chapter 6) and could not be relied on for public health monitoring purposes. There exists no programme of repeated standardised measurement of ocular or immunological effects of UVR in any population.

Recommendations have been made by a number of bodies for research that would remedy these deficiencies in essential public health information and monitoring systems (United Nations Environment Programme, 1989, 1991; World Health Organization, 1992; SCOPE, 1992).

The WHO Commission on Health and the Environment listed ultra violet radiation as a problem requiring research and recommended protection from the effects of excessive exposure to humans (World Health Organization, 1992):

"Methods should be developed to determine reliably and on a systematic basis the flux of ultraviolet light in the relevant wave bands and its trends at appropriate locations on the earth's surface".

"Excessive exposure of fair-skinned people to sunlight should be discouraged. Those who must work in the sun should routinely adopt protective measures".

An expert workshop on effects of increased UVR on biological systems convened by the Scientific Committee on Problems of the Environment (SCOPE) recommended, among other things, implementation of the following research priorities (SCOPE, 1992):

"Establish global UV monitoring networks for longterm trends in UV-B and its relation to other wavebands (UV-A and longer)."

"To assess accurately the overall impact(s) on the health of animals and humans, quantitative analyses are needed of UV-B radiation effects on sensitive mechanisms which

regulate the health of organisms. This new stage of quantitative questions will require full utilization of existing research capacity and a major expansion in this direction is essential."

Moreover, in a letter accompanying this report the President of SCOPE and the Chairman of the Scientific and Advisory Committee on UV-B Radiation stated (Stewart and De Fabo, 1992): "It appears, therefore, that there is a significant risk that ozone depletion will occur over heavily populated areas in the foreseeable future. Therefore, the need for assessing the accompanying increases in UV-B radiation and their impact on biological systems, including human systems, has now passed the theoretical stage. In fact, considering the long-term residence lifetime of chlorine in the atmosphere ..., a long-term commitment to research in UV-B radiation effects on the biosphere clearly needs to be started now as ozone depletion is expected to increase well into the next century."

Most recently, and most notably perhaps, is the recommendation of the United Nations Conference on Environment and Development, held in Rio de Janeiro in June, 1992, that "nationally determined action programmes, with international assistance, support and coordination, where necessary, should undertake, as a matter of urgency, research on the effects on human health of the increasing ultraviolet radiation reaching the earth's surface as a consequence of depletion of the stratospheric ozone layer." (United Nations Conference on Environment and Development, 1992). It is precisely to this need that INTERSUN is directed.

2. GENERAL OBJECTIVES

While the major initial emphasis in developing the INTERSUN programme was on skin cancer, it was recommended by the Peer Review Committee of the IARC's Scientific Council in November 1991 that if a network of centres were to be set up to monitor UV irradiance and skin cancer incidence it would be sensible and efficient to monitor, if possible, other health effects of solar UV radiation, such as its effects on the immune system and the eye. Collaboration with the Division of Environmental Health of the World Health Organization (WHO), and the United Nations Environment Programme (UNEP) is directed towards this wider aim and towards linking the relevance of the programme to wider environmental issues.

The general objectives of INTERSUN are:

To evaluate accurately the quantitative relationship between solar UVR at the surface of the earth and human health effects, develop reliable predictions of the health consequences of changes in UVR, provide baseline estimates of the incidence of health effects of UVR in representative populations around the world, and develop practical ways of monitoring change in these effects over time in relation to environmental and behavioural change.

The research programme will provide essential input into environmental and public health policy responses to depletion of stratospheric ozone and a means of monitoring the effects of these policies.

3. SPECIFIC OBJECTIVES

- 3.1 To describe accurately and quantitatively the relationship between ground level solar UV irradiance and incidence of skin cancer and the occurrence of health effects (particularly eye damage, and effects on the immune system) of UV radiation in human populations.

- 3.2 To estimate accurately the change in occurrence of health effects of UVR that would result from change in ground level solar UV irradiance due to environmental change.
- 3.3 To increase understanding of the relationship between personal risk of health effects of UVR and constitutional sensitivity to the sun and sun-related behaviour.
- 3.4 To develop and validate appropriate ways of monitoring human exposure to UV radiation and the occurrence of associated health effects.
- 3.5 To develop a network of centres monitoring trends in ground level solar UV irradiance, sun exposure of populations, and the occurrence of health effects of UVR.
- 3.6 To interpret these trends, as far as is possible, in relation to environmental change, changes in human behaviour, and the implementation of public policies aimed at ameliorating environmental change or human exposure to solar UVR.
- 3.7 To provide a basis for development and evaluation of interventions to reduce the occurrence of adverse health effects of solar UVR.

4. INITIAL PROGRAMME OF WORK

In outline, the following initial programme of work has been proposed for consideration:

- Identification of a set of collaborating centres at different latitudes in the one country and in different countries each with the following features:

- In an area with a population-based cancer registry;

- Have a population which is genetically sensitive to the full range of health effects of UVR (although there may be specific reasons for including populations with other genetic characteristics);

- Have a team of investigators with relevant expertise who are willing and able to undertake some or all of the following procedures.

- Setting up, in these centres, in collaboration with an established UV irradiance monitoring network, the capacity to measure accurately, on an ongoing basis, full spectrum solar UVB and UVA irradiances at the surface of the earth.

- Accurate measurement in these centres over a period of 3 to 5 years of: skin cancer prevalence and incidence; the prevalence of other cutaneous consequences of UV irradiation (e.g., prevalence of solar keratoses, prevalence of other indicators of sun damage to the skin, mutation of the p53 suppressor gene or other genes in skin biopsies); prevalence and/or incidence of immunological and ocular effects of solar UV irradiation; prevalence of constitutional characteristics that protect the body against the sun and against UV carcinogenesis (e.g., skin colour, eye colour, skin reaction to sunlight, capacity of cells to repair photoproducts in DNA); and prevalence of behaviours that promote or protect the skin and eyes from sun exposure.

- Modelling of the relationship, across the geographic areas, of the above measurements of incidence or prevalence of the major health effects of solar UV irradiation with measured solar UV irradiance at the surface of the earth, with

adjustment for differences between the populations in constitutional sensitivity to the sun and sun-related behaviour.

Validation of potentially simpler methods of measurement of the biological effects of UV exposure (e.g., non-malignant sun damage to the skin, mutation of the p53 suppressor gene in skin biopsies) as predictors of prevalence or incidence of major health effects of UV exposure (skin cancer incidence, prevalence of ocular damage, etc.) within the populations studied.

Conduct, within the populations being studied, of multi-centre collaborative case-control studies of the effects of constitutional characteristics, sun-related behaviour, and amount, time-relationships, and pattern of sun exposure on risk of skin cancer, ocular damage, and indicators of immunological effects, making use of prevalent and incident cases of abnormality identified in the prevalence and incidence surveys.

5. PURPOSE OF THIS DOCUMENT

This document was prepared as background to discussions held at a meeting of experts at IARC, 19-21 October, 1992. It does not represent a consensus view of those at the meeting, but has been edited following the meeting to take into account, as far as possible, relevant views expressed at the meeting and recommendations of the meeting.

The specific objective of the meeting was to provide expert guidance regarding the measurement of all variables relevant to the initial programme of work outlined above. The emphasis of the document, therefore, is on measurement of UV irradiance at the surface of the earth and its health consequences in human populations. In addition, however, it covers some additional relevant topics, including previous approaches to estimating the effects of solar UV irradiance change on incidence of skin cancer and melanoma (since their presumed inadequacy is a major part of the justification for the proposed IARC study), and statistical issues relevant to the proposed geographical correlation analysis (in particular control of confounding of UV irradiance with constitutional sensitivity to the sun and sun-related behaviour since this will be important to the validity of the predictive relationships produced by the initial programme of work).

The recommendations of the meeting of experts are listed in Chapter 15.

6. ACKNOWLEDGEMENTS

The important contributions made by those who attended the meeting of experts (see page 146) is gratefully acknowledged. Dr Jacques Estève undertook the basic statistical work necessary to estimation of the precision of estimates of the Biological Amplification Factor and prepared the applicable table (see Section 4.2, page 143). Mme Eva Démaret provided assistance in retrieving and organising the literature and in other ways and secretarial assistance was provided by Mrs Wira Fèvre-Hlaholuk and Ms Margot Geesink. We acknowledge also the substantial contributions made by those who provided unpublished data, particularly on the site distribution and thickness of melanoma, to facilitate this work.

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Chapter 2

HOW MUCH SKIN CANCER WILL A CHANGE IN SOLAR UV IRRADIANCE CAUSE?

1. PURPOSES

The purposes of this chapter are:

- 1.1 To outline general approaches to the measurement of the association between solar UV irradiance at the surface of the earth and incidence of skin cancer for the purposes of predicting the effects of changes in UV irradiance due to environmental change.
- 1.2 To summarise and discuss the assumptions underlying these approaches.
- 1.3 To summarise past estimates of the biological amplification factor for skin cancers.
- 1.4 To outline research that may lead to more accurate measurements of the associations between solar UV irradiance and skin cancer and other health effects of UV exposure for the prediction of the effects of environmental change.

2. INTRODUCTION

The complex of factors linking radiation from the sun with skin cancer in humans may be summarised as follows:

From Sun to Upper Atmosphere of the Earth

Radiation output from sun (as influenced by the solar cycle)

Distance of sun from the earth

From Upper Atmosphere of the Earth to Ground Level

Direct path length (as influenced by the solar zenith and solar angle)

Ozone (stratospheric and tropospheric)

Other atmospheric gases

Clouds

Other atmospheric aerosols

Altitude

Albedo (reflectance of ground and atmosphere)

From Ground Level Solar Radiation to Adverse Health Effects

Time spent outdoors in the sun

Outdoor protective behaviours (use of hat, prescription eyewear, sunglasses, clothing, chemical sunscreens)

Transmission of solar radiation through overlying tissues to target cells and other tissue components (as influenced by ethnic and other variables such as skin pigmentation, accumulation of pigment in the lens of the eye with age, pigmentation and thickening of the keratinised layer of the skin in response to sun exposure, etc.)

Susceptibility of target cells and other tissue components to damage by transmitted solar radiation as influenced by wavelength of radiation (described by the action

spectrum of the effect), age, amount and pattern of exposure, and other environmental and host factors.

Activity of post-damage protective processes (e.g., DNA repair, immunological surveillance against genetically altered cells) as influenced by both host and environmental factors.

The objectives of the INTERSUN project deal only with the third of these steps, and this chapter deals more specifically with techniques and results of measurement of the association between ground level solar radiation and one class of adverse health effects, skin cancer.

Most recent attempts at establishing a quantitative relationship between ground level solar radiation and skin cancer have been made to estimate how much the incidence of skin cancer would change, when a new steady state has been reached, in response to some specified change in solar irradiance. The variable used to summarise these predictions has been the biological amplification factor (BAF). The BAF may be defined as follows (de Gruijl and van der Leun, 1980):

$$\text{BAF} = (dI/I)/(dD/D)$$

where dI equals a small increment in the existing incidence of skin cancer, I , which results, in the steady state, from a small increment dD in the existing biologically effective exposure dose, D , of solar radiation (i.e. spectral dose weighted by the action spectrum for production of skin cancer). The value of BAF is commonly conceptualised as the percentage increase in skin cancer incidence that would result from a 1% increase in biologically effective solar UV irradiance at ground level. It may be made specific to type of measure of incidence (e.g. incidence density, cumulative incidence, prevalence, mortality), the type of skin cancer (BCC, SCC, or melanoma), the body site of skin cancer, and geographical area of residence, sex, and age of the population.

For completeness, two other amplification factors should be mentioned:

The optical or radiation amplification factor (RAF) which is the percentage increase in biologically effective solar UV irradiance at ground level that would result from a 1% depletion in stratospheric ozone;

The amplification factor (AF, as originally defined by JE McDonald) which is the percentage increase in skin cancer incidence that would result, in the steady state, from a 1% depletion in stratospheric ozone.

These three amplification factors are related simply:

$$\text{AF} = \text{RAF} \times \text{BAF}.$$

3. GENERAL APPROACHES TO ESTIMATION OF THE BIOLOGICAL AMPLIFICATION FACTOR

In theory, the best way to estimate BAF in humans would be to measure the lifetime exposure to the sun of each member of a population and relate this measurement to their probability of developing skin cancer either by way of a cohort or a case-control study. In practice this is very difficult. Difficulties in measurement of exposure aside, the cohort study is rendered practically impossible by the necessity to enroll a sufficiently large cohort of subjects at birth and to measure their exposure to the sun at reasonably frequent intervals throughout life thereafter. The case-control study is not able to obtain adequately quantitative measurements of sun exposure because of its dependence on recall over 40 years or more of details of sun exposure. Thus while these kinds of studies may be very useful, if conducted well, in supporting hypotheses about the role of sun exposure in causing skin cancer, documenting the effects on risk of skin cancer of pattern of sun exposure, particular

sun-related behaviours, and the interaction between sun exposure and constitutional characteristics and body site, etc., they cannot readily provide quantitative data that will allow the prediction of change in risk of skin cancer resulting from change in UV irradiance at ground level.

This leaves three general approaches to the problem:

- (a) Prediction of the relationship and estimation of BAF from dose-response relationships determined in animal (or other experimental) model systems;
- (b) Estimation of BAF from analysis of the association between age and incidence of skin cancer (on the assumption, among others, that age is a measure of cumulative exposure to solar radiation);
- (c) Estimation of BAF from the geographical association between solar UV irradiance and incidence of skin cancer in populations of humans resident at different latitudes.

Assumptions that must be made in all or some of the applications of these approaches are summarised below.

Approach (a) has not been attempted in its pure form, presumably because no one has been willing to make the necessary extrapolation from results in animals to relationships in humans. A parameter of the dose-response relationship between UV radiation and skin cancer in mice has been used, however, to eliminate the need for the assumption of reciprocity in approach (b) (de Gruijl and van der Leun, 1980). In addition, a dose-response model based on theoretical considerations and validated in animal experiments has been used with parameters derived from epidemiological studies in approach (c) to estimate the dose response relationship in humans (Slaper et al, 1986). These approaches give rise to a fourth general category of approach:

- (d) Mixed approaches using both the results of animal experiments and epidemiological studies.

In truth, all approaches which use epidemiological data could be classified as mixed approaches because of their dependence on action spectra that have been at least partly determined experimentally.

4. ASSUMPTIONS

The assumptions listed and discussed briefly below have been identified by one or more of a number of authors (notably Rundel and Nachtwey, 1978, de Gruijl and van der Leun, 1980, Beadle and Leach, 1982, and Slaper and van der Leun, 1987) or have been derived from first principles.

4.1 *Assumptions Common to All Approaches*

- 4.1.1 If UV irradiance is increased by a certain factor, the biologically effective dose of radiation is increased by the same factor for each body site at which skin cancer occurs.

This assumption would not be necessary if site specific estimates of BAFs were to be made. This has been done to a limited degree by some authors with some apparent, possibly chance, effect on BAFs (Scotto and Fears, 1987; Moan et al, 1989). The assumption is a plausible, however, since a change in stratospheric ozone should affect ground-level direct and diffused UV radiation, of a particular wavelength, in equal proportions.

- 4.1.2 The dose-response model is similar at different wavelengths and interactions do not occur between different wavelengths.

This assumption is implicit in the use of a single, spectrally weighted estimate of solar UV irradiance in estimating any dose-response relationship. It cannot be tested readily in humans. To the extent that there may be wave-length related changes in the skin that increase with chronic exposure and alter the skin's spectral transmission properties, this assumption may not be true. However, such changes appear not to occur in experimental animals for which a single action spectrum appears to be valid for carcinogenesis over a range of doses (de Gruijl, personal communication).

- 4.1.3 The assumptions underlying any statistical model used are acceptable and the model has reasonable prospects of reflecting reality.

The two models used most commonly in epidemiologically based estimates of BAF have been the exponential model (log incidence varies as a direct function of dose) and the power model (log incidence varies as a direct function of log dose). In use of the power model (which has been preferred on the grounds of its use in the multistage model of carcinogenesis; Fears et al, 1977) there is the implicit assumption that all skin cancer is caused by exposure to solar UV, since when dose is zero, incidence is zero. This assumption may not be correct, at least in populations where sun exposure is low and exposure to other causes of skin cancer (e.g. polycyclic hydrocarbons and ionising radiation) occurs. Although, even in such populations, cancers not caused by solar UV probably constitute only a small proportion of the total. In addition, model predictions within the range of the data will not be very sensitive to the type of model chosen (provided that it fits the data well) and extrapolation much beyond the range of the data will not be necessary provided, in the case of a geographical approach, it is based on observations covering a wide range of UV irradiances.

4.2 *Approaches Using the Results of Carcinogenesis Studies in Experimental Animals*

- 4.2.1 UV-carcinogenesis is basically similar in animal (usually mouse) skin and human skin.

In commenting on this assumption, van der Leun (1984) stated: "There are undeniable differences between mouse skin and human skin; susceptibility to UV-induced skin cancer is different and probably also the adaptation of the skin to UV-exposure." The following points are also relevant:

- . The commonest skin cancer in humans, BCC, is rarely produced experimentally in animals;
- . The most commonly used animal model is now the albino hairless mouse. Use of this model would presumably exacerbate problems of difference in adaptation of the skin to UV-exposure by way of a pigment response.
- . There is evidence that the UV dose to skin cancer response relationship may be different between experimental animals and humans. The relationship in mice shows no evidence of either a threshold at low doses or a plateau in effect at high doses. Evidence of the latter has been found in two recent epidemiological studies of BCC (Vitasa et al, 1990; Kricker et al, 1991)

4.3 *Approaches Making Any Use of Measurements of the Incidence of Skin Cancer in Human Populations*

4.3.1 The skin cancer incidence rates have been measured accurately.

Most estimates of BAF for non-melanocytic skin cancer have depended on the two special surveys of skin cancer carried out by similar methods in the United States in 1971-72 (Scotto et al, 1974) and 1977-78 (Scotto et al, 1983). BAF for melanoma has usually been estimated from melanoma incidence obtained by way of routine cancer registration, or from melanoma mortality. It is doubtful whether any of these measurements of incidence have been accurate, and those for non-melanocytic skin cancer may have been underestimated by a factor of at least 2 (see Working Papers 4 and 6). That the BAFs for non-melanocytic skin cancer estimated by the same (power) model from incidence data collected by the same methods in partly overlapping populations in the two US surveys were some 30-40% different (Fears et al, 1977; Fears and Scotto, 1983) may have been due to different measurement errors in the two surveys. In addition, the BAFs from each were subject to quite wide random fluctuation because of small numbers of data points in the two surveys.

4.3.2 All members of the populations giving rise to the incidence rates have lived their whole lives in their present environment.

The presence, in the population, of migrants from areas of different UV irradiance will invalidate the use of the age-incidence relationship to estimate the UV dose-response relationship. In addition it will complicate and potentially invalidate comparisons between populations because of the potentially different lifetime exposure of the migrants to solar UV radiation. In principle, this problem can be dealt with by restricting analyses to the native-born population. This has not been done in any estimate of BAF.

4.3.3 The sun-related behaviour of all birth cohorts to which the incidence data relate has been more or less the same.

The existence of birth-cohort based trends in sun-related behaviour may distort the age-incidence relationship and invalidate its use to estimate the UV dose-response relationship. Similarly, different cohort-based trends between populations will complicate or invalidate modelling of dose-response by comparison between populations. Birth-cohort-based trends in incidence of melanoma, at least (there are no useful data for non-melanocytic skin cancer), appear to be common but may not differ greatly between populations (see Section 6). Pitcher and Longstreth (1991) partially addressed this issue by the use of cohort age-specific rates of melanoma rather than cross-sectional age-specific rates.

4.4 *Approaches Depending on Analysis of the Relationship of Skin Cancer Incidence with Age in Humans*

4.4.1 Incidence of skin cancer is sensitive only to cumulative dose of UV radiation and, therefore, dose of UV radiation can be represented equally well by average dose rate or duration of exposure - i.e. reciprocity.

This assumption is not supported by data in experimental animals (van der Leun, 1984). Nor is it consistent with most of the epidemiology of melanoma in which pattern as well as dose of exposure appears to be important (Armstrong, 1988). Recent data suggest also that there may be important pattern effects for non-melanocytic skin cancer, at least for BCC (Kricker et al, 1991).

- 4.4.2 The probability of skin cancer in an individual does not depend on whether or not he or she has had one before.

This assumption is not correct (Robinson, 1987; Karagas et al, 1993).

4.5 *Approaches Based on the Geographical Correlation of Skin Cancer Incidence with Ground-Level UV Irradiance*

- 4.5.1 The correct action spectrum has been used to weight spectral UV irradiance when producing a single figure for ground level UV irradiance at each geographic location.

Because the spectral distribution of solar UV radiation at ground level varies by latitude, different action spectra will produce different distributions of irradiance by geographic area. The most commonly used action spectrum has been that implicit in the Robertson-Berger (R-B) metering system which, when compared with the action spectrum of human skin erythema, gives too much weight to longer wavelengths. Where different action spectra have been assumed, appreciable differences have been found in BAFs (see, for example, Moan et al, 1989, and Pitcher and Longstreth, 1991). The correct action spectrum to use remains, to some extent, an open question (de Gruijl and van der Leun, 1991). For non-melanocytic skin cancer, it would be reasonable to choose the recently described action spectrum for skin cancer in albino hairless mice (de Gruijl and van der Leun, 1991) which appears similar to that for production of thymidine dimers in human skin (Freeman et al, 1989). The correct action spectrum for melanoma is less certain; indeed, recent data from the hybrid fish model for melanoma of Setlow (unpublished) suggest that there may be quite important effects in the UVA.

- 4.5.2 The correct measure of ground level UV irradiance has been chosen.

Different measures of ground level irradiance (e.g. average annual total irradiance, average annual peak irradiance, average annual irradiance between the hours of 8:00 am and 8:00 pm, etc.; Moan et al, 1989; Pitcher and Longstreth, 1991) have produced appreciably different BAFs. Presumably, the correct choice would be that measure which correlated best with average exposure of the skin to biologically effective UV radiation. The choice could vary with body site, and would probably be influenced by the relationship of pattern of exposure to the risk of the skin cancer in question.

- 4.5.3 Possible confounding of the relationship of ground level UV irradiance with constitutional sensitivity to the sun and sun-related behaviour is either unimportant or has been taken adequately into account.

Neither is likely to be unimportant. Constitutional sensitivity to the sun has a strong north-south gradient in Europe, and some self-selection of sensitive phenotypes for residence in less sunny areas may have occurred in the new world. Similarly, sun-related behaviour is strongly influenced by climate with greater exposure occurring in areas of greater solar irradiance. Thus confounding by these variables must be taken into account. It has been attempted in only a minority of estimates of BAF (and only for melanoma) which it has reduced by 20% to 40% (Scotto et al, 1987; Pitcher and Longstreth, 1991). In addition, the way in which these potentially confounding variables should be measured and controlled statistically is problematic (see Chapter 14) and the approach so far used (linear regression modelling of population aggregate estimates of confounding variables) is probably not correct.

5. REVIEW OF PAST ESTIMATES OF THE BIOLOGICAL AMPLIFICATION FACTOR

Table 1 summarises past estimates of BAF that could be found and their derivation reviewed in the original literature. In preparing this review, the issue of random variability in the estimates has been largely ignored, both for simplicity and because it has not been consistently or adequately documented by those who have made the estimates. It is not an unimportant issue. For example, the estimates of BAFs for incidence of non-melanocytic skin cancer made by Scotto et al (1983), based on eight data points, have 95% confidence intervals that extend from about -50% to +50% of the point estimates; at the other extreme, the unadjusted estimates made for melanoma mortality by Pitcher and Longstreth (1991) from 215 data points have much narrower 95% confidence intervals (about -11% to +11% of the point estimates).

Briefly, a number of matters arise from this table.

- 5.1 Most of the estimates of BAFs depend either wholly or partly on data from either the US skin cancer survey carried out in 1971-72 in association with the Third National Cancer Survey (estimates of Scotto 1975, Fears 1976, Green 1976 (second USA estimate only), Fears 1977, Rundel 1978, and de Gruijl 1980 (partly)) or the subsequent survey carried at in 1977-78 (Scotto 1983, Fears 1983, Rundel 1983, Slaper 1986, de Gruijl 1991). In the main, the US data have been correlated with estimates of solar UV irradiance obtained from a network of geographically co-located R-B meters. In other geographical correlation studies, model estimates of UV irradiance have been used. The different estimates based on the US surveys differ in the models applied to the data, the action spectra assumed, and in whether or not R-B meter or model estimates of UV irradiance were used.
- 5.2 The statements has been commonly made that BAFs for non-melanocytic skin cancer are higher for SCC than BCC. This statement is based on the 1977-78 US survey. The only other independent study to give the necessary amount of detail (Moan, 1989, in Norway) showed a difference in the opposite direction.
- 5.3 Apart, perhaps, from the BAFs based on the 1971-72 US survey, the results obtained by Green et al (1976) should probably be ignored because none of them are based on skin cancer incidence data of any credibility.
- 5.4 It is of interest to note that the BAFs estimated by de Gruijl and van der Leun (1980) using the dose-response relationship in mice and the age-incidence relationship from the 1971-72 US survey are quite close to other estimates made only from the 1971-72 survey. How this similarity should be interpreted is problematic, however, given the likely substantial inaccuracy of the 1971-72 US incidence data.
- 5.5 The appreciably different BAFs obtained for non-melanocytic skin cancer by Fears et al (1977) from the 1971-72 survey (3.0 males and 2.4 females) and Fears and Scotto (1983) from the 1977-78 survey (1.8 males and 1.4 females) give some indication of the possible effects of error in measurement of skin cancer incidence in these surveys. Random variation could also account for part or all of this difference.
- 5.6 The possible effects of confounding of ambient solar UV irradiance with constitutional characteristics and sun-related behaviour are shown by the results of Scotto and Fears (1987) and Pitcher and Longstreth (1991) with respect to melanoma (note, however, that the method of adjustment is probably incorrect). In the first, adjustment reduced the BAFs from an average of 0.7 to 0.4 in males and 0.8 to 0.5 in

females, and in the latter the corresponding reductions were 1.0 to 0.8 and 0.8 to 0.5. No similarly adjusted estimates have been made for non-melanocytic skin cancer. The necessary data were collected in the 1977-78 US survey (Scotto and Fears, 1978) but, apparently, were never used for this purpose.

- 5.7 The unadjusted BAFs for melanoma show substantial variability from one set of data to another. The lowest are those based on incidence and mortality in the USA (0.7 to 1.0 in males and about 0.8 in females) and the highest those based on incidence in Scandinavia (1.3 to 1.9 in males and 2.2 to 3.2 in females). Australia falls in the middle. Problems in measurement of the incidence of melanoma in some countries (see Sections 6 and 7) and the presence of strong cohort-based trends in some of the rates may have contributed to these differences.

Table 1. Summary of values estimated by various investigators for the biological amplification factor (BAF) for non-melanocytic skin cancers and cutaneous malignant melanoma

Author ¹ & Year	Approach ²	Population	Sex	NMSC ³ Inc.	BCC Inc.	SCC Inc.	Melanoma Inc.	Melanoma Mortality.
Elwood 1974 ⁴	(c) ⁴	USA & Canada	MF					0.4-1.0
Scotto 1975 ⁵	(c) ⁴	US north	MF	1.5			1.5	
		US central	MF	2.1			2.0	
		US south	MF	2.6			2.5	
Fears 1976	(c) ⁴	US north	M	1.8			1.5	0.8
			F	1.6			1.3	0.3
		US central	M	2.4			2.0	1.0
			F	2.1			1.8	0.9
		US south	M	3.1			2.5	1.3
			F	3.0			2.2	1.1
Green 1976	(c) ⁴	Texas	MF	2.7				
		Australia	MF	2.6				
		USA ⁶	MF	2.0				
		USA ⁶	MF	1.7				
		Canada	MF	1.2				
		England	MF	1.1				
		Scotland	MF	0.9				
Fears 1977 ⁷	(c) ⁷	USA ⁷	M	3.0			2.4	
			F	2.4			2.2	
Rundel 1978	(b)	USA	M	3.7-4.3				
			F	3.4-4.4				
	(d) ⁸	USA	M	2.7-3.1				
			F	2.5-3.1				
Beadle 1978	(b)	E&W	MF	3.5-4.3				
	(d) ⁸	E&W	MF	2.9				
De Gruijl 1980	(d) ⁹	USA	M	2.6				
			F	2.3				

Table 1 continued

Author ¹ & Year	Approach ²	Population	Sex	NMSC ³ Inc.	BCC Inc.	SCC Inc.	Melanoma Inc.	Melanoma Mortality.
Scotto 1983	(c) ⁴	USA 8 centres	M		1.3- 2.6	2.1- 4.1		
			F		1.1- 2.1	2.2- 4.3		
Fears 1983	(c) ⁷		M	1.8				
			F	1.4				
Rundel 1983 ¹⁰	(c)	USA north central & south	M		1.8- 2.2	2.4- 2.8		
			F		1.1- 1.5	1.6- 2.1		
Slaper 1986 ¹⁰	(c) ⁷	USA 8 centres	MF		1.7	2.9		
Scotto 1987	(c) ⁷	USA 7 areas	M ¹¹				0.6	
			M ¹¹				0.8	
			M ¹¹				0.3	
			M ¹¹				0.5	
			F ¹¹				0.5	
			F ¹¹				1.0	
			F ¹¹				0.4	
Giles 1989	(c) ⁴	Australia 3 states	MF				1.1- 1.7	
Marks 1989	(c) ⁴	Australia 3 states	MF	1.4- 2.4				
Moan 1989	(c) ⁷	Norway 6 areas	M		1.5- 2.0 ¹²	1.2- 1.5 ¹²		
			F		1.6- 2.1 ¹²	1.6- 1.8 ¹²		
de Gruijl 1991	(c) ¹³	USA	MF		1.4 ¹³	2.5 ¹³		
Pitcher 1991	(c) ^{4,7}	USA 215 SMAs	M ¹⁴					1.0
			M ¹⁴				0.8	
			M ¹⁴				0.4	
			F ¹⁴				0.8	
			F ¹⁴				0.5	
Moan 1992	(c) ⁷	Norway	M				1.9	
			F				3.2	
		Finland	M				1.3	
			F				2.2	
		Sweden	M				1.9	
F					2.3			

Footnotes to table 1.

- 1 Only first author of multiply-authored papers has been listed.
- 2 (b) = analysis of age-incidence relationship; (c) = analysis of geographical correlation; (d) = combination of experimental dose-response and epidemiological data.

- 3 NMSC = non-melanocytic skin cancer (i.e. basal cell carcinoma (BCC) + squamous cell carcinoma (SCC)).
- 4 Exponential model of age-standardised incidence/mortality by UV irradiance. Results for Elwood et al (1974) given in Elwood (1989).
- 5 Amplification factors calculated by Green (1977). Fears et al (1976) and Scotto et al (1975) used the same skin cancer incidence data (special survey associated with the Third National Cancer Survey) but, respectively, model estimates and Robertson-Berger Meter measurements of UV irradiance.
- 6 First is Second National Cancer Survey and second is Third National Cancer Survey.
- 7 Power model of age-standardised incidence/mortality by UV irradiance. Fears et al (1977) used same data as Fears et al (1976) but a power model instead of an exponential model.
- 8 Values of the biological amplification factor corrected by de Gruijl and van den Leun (1980) with animal dose-response model to eliminate need for assumption of reciprocity.
- 9 Used the exponent of dose in the experimental dose-response relationship in mice and the exponent of age in the power model of Fears et al (1977) based on the Third National Cancer Survey.
- 10 Same data as Scotto et al (1983). Rundel (1983) used a different approach to modelling. A log normal distribution was fitted to the age-incidence relationship in each geographic area and the mean onset time for each skin cancer estimated. The reciprocal mean onset times were then modelled as a linear function of UV irradiance across the geographic areas.
- 11 For each sex, the first two amplification factors are those for trunk and lower extremities and face, head, neck and upper extremities respectively. The second two are for these two site groups but adjusted for possible confounding of ambient solar UV irradiance by ethnic origin, pigmentary characteristics, use of sunscreens, and hours per week of outdoor exposure.
- 12 Results shown are for all sites and the CIE action spectrum. BAFs varied according to whether annual average UV irradiances were estimated for the whole day (highest BAFs), 8 am to 8 pm, or 10 am to 2 pm (lowest BAFs). BAFs varied by about the same amounts if calculated separately for head and extremities, or if calculated assuming an action spectrum for mutation of human cells instead of the CIE erythral action spectrum.
- 13 These estimates are quoted by Longstreth et al (1991). It has been assumed that they were made in the same way as those of Slaper et al (1986) but with reference to a new action spectrum.
- 14 For each sex, the first BAF is from an exponential model with DNA damage weighted annual average peak UV irradiance, the second is the same but adjusted for ethnic origin, household income, outdoor occupation, and education, and the third is with DNA damage weighted annual average total UV irradiance adjusted as for the second. Use of the power instead of the exponential model or erythema instead of DNA damage weighting had much smaller effects on the BAFs.

6. PROPOSED APPROACH

It seems reasonable to conclude from this brief review that the only approaches to estimation of the BAFs for skin cancer (and, therefore, to estimation of the likely consequences of ozone depletion for skin cancer) likely to be viable are approaches (c) (geographical correlation) and (d) (combined approach by use of experimental and

epidemiological data). In (d) the major role of experimental results would most likely be in providing the action spectra and guiding the construction of biologically plausible models for the analysis of the epidemiological data.

Past implementations of these approaches have been wanting in a number of respects. First, they have been based on skin cancer incidence data of very doubtful accuracy; second, they have failed, in the main, to take account adequately (or not at all, in the case of non-melanocytic skin cancer) of possible confounding of ambient solar UV irradiance with constitutional and behavioural variables; third the analyses have generally not taken account of the potential complexities introduced by migrant populations and birth-cohort-based trends in incidence.

The INTERSUN project proposes to deal with the first two of these deficiencies by obtaining uniform and comprehensive estimates of skin cancer incidence and relevant constitutional and behavioural characteristics in a number of carefully selected populations around the world. The ways in which this may be done are discussed in detail in Chapters 4, 6, 10 and 11. To control confounding and deal with the issue of cohort-based trends will require very careful consideration of the way the data collected should be analysed by an appropriately expert group of photobiologists, epidemiologists, and biostatisticians/mathematicians - some consideration of the statistical aspects of these matters is given in Chapter 14. Ideally, this consideration would be made before the protocol is finalised to ensure that data collection is adequately informed by the needs of modelling and analysis.

While other health consequences of an increase in solar UV irradiation at ground level have generally not received the same attention that the skin cancers have, and few attempts have been made to estimate biological amplification factors, it may be assumed that the same basic principles would apply. Thus it is logical and sensible to include these other health effects in any future major study aimed at estimating BAFs (or some similar parameter) for skin cancers.

The other work that has been proposed for the INTERSUN project (see Chapter 1) will contribute to this general direction by strengthening the empirical basis for designing particular dose-response models and controlling confounding.

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