# Reply to the 'Comment on "The effects on human health from stratospheric ozone depletion and its interactions with climate change"' by W. B. Grant, J. Moan and J. Reichrath, *Photochem. Photobiol. Sci.*, 2007, 6, DOI: 10.1039/b705482c

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While the adverse health effects of solar UVB exposure are well recognised, the evidence available currently to link solar UVB with protection against various diseases through the production of vitamin D is less certain.

## Introduction

First we wish to acknowledge the considerable contributions made by the authors of the accompanying article[1] to research on the population-wide health impact of vitamin D status. Most importantly they have provided extensive evidence that correlates solar UVB exposure with reduced mortality from various types of internal cancers, and argue that this occurs through the production of vitamin D. Their conclusion, as summarised in the final paragraph of their article, is that the benefits of solar UVB exposure of human subjects greatly outweigh the adverse risks. This may be true, and the importance of solar UVB for good health has perhaps been underestimated until now because of earlier assertions that easily attainable small exposures of the head and hands to sunlight, or daily supplements of 200–400 IU of vitamin D, were presumed adequate for maintaining vitamin D status (*e.g.* see ref. 2). However a paradigm shift occurred with finding that the variable levels of 25-hydroxyvitamin $D_3$ (25(OH)D, calcidiol) in circulation are physiologically important for the extra-renal production of the active 'vitamin D hormone', 1,25-dihydroxyvitamin $D_3$ (calcitriol). Therefore, 25(OH)D levels in serum represent a more accurate measure of the vitamin D status of an individual than the more tightly regulated levels of the active hormone. This development revitalized the field of vitamin D research, and led to the conclusion that the minimally desired levels of calcidiol should rise from 30 to 75 nmol $L^{-1}$.[3] Interesting debates on UVB health effects and vitamin D supplementation have followed (*e.g.* see ref. 4) which we are well aware of. We have no intention of overestimating the adverse effects of solar UVB radiation, as Grant *et al*. seem to suggest.[1] However we admit to some reservations about the asserted simple and generalized causal relationship between the lifetime or annual UVB dose and a reduction in mortality of a broad range of cancers, and the postulated protective role of vitamin D in this process, even if we ignore the quantification of these effects (note, for instance, that time trends seem to be in conflict with geographical trends in cancer rates when related to UV exposures).[5] Moreover, it should be recognized that weighing the beneficial against the adverse effects of ambient UVB radiation is not simply a matter of addition and subtraction to arrive at an overall net positive or negative outcome.

The members of the United Nations Environment Panel (UNEP) on Ozone Depletion met in September 2006 to consider the consequences of increased terrestrial UVB exposure that would follow depletion of the stratospheric ozone layer. It is thought that the ozone layer formed once oxygen had increased to a certain level during the 'Great Oxidation', thus shielding the trophosphere from strongly cytotoxic UV radiation.[6] The consensus view regarding the health effects was published in *Photochemical & Photobiological Sciences* earlier this year.[7] It should be noted that we were required to evaluate information published since our last report in 2003[8] relating to the harmful outcomes of solar UVB radiation in the eye (pterygium and cataract), the skin (melanoma, basal and squamous cell carcinomas) and the immune system (immunosuppression regarding infectious diseases, vaccination and tumours), plus response strategies for dealing with the increased UVB exposure. Thus, beneficial health effects, *e.g.* mediated by vitamin D, represented only part of our remit but the importance attached to it can be gauged by the space devoted to the topic. This increased from one paragraph referring to 4 publications in our previous report in 2003[8] to a substantial section referring to more than 50 publications in the current report.[7] We believe that we provided a balanced view using the information available at the time the report was written, and incorporating the comments of the external reviewers. This view may, of course, change as more evidence gathers. However, while the many adverse health effects of solar UVB are experimentally or clinically proven and cannot be disputed, the evidence linking solar UVB exposure with protection against various diseases through the production of vitamin D is more indirect, in our opinion. The sections below provide some counter-arguments to the assertions made by Grant *et al.*[1]

## Melanoma

Grant *et al.*[1] conclude that ozone depletion may have only a minor effect on melanoma rates and that solar UVA irradiation,

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rather than UVB, is the crucial risk factor involved. While they summarise some of the evidence to support this view, several other findings do not. In particular the two transgenic mouse models, referred to in our current report, indicate conclusively that it was exposure of neonatal mice to the UVB waveband, and not to the UVA waveband, that led to the induction of the melanoma.[9,10] These experimental models may be criticised as not being 'natural', but they are the best available to date and are certainly more credible than the older *Xiphophorus* fish model where the action spectrum demonstrated that melanoma induction could be attributed to the UVA waveband.[11] It should also be noted that a recent review of all the published studies that analysed sequence variants in melanoma concluded that there was substantial evidence to support a role for direct UVB participation, especially at *TP53* and *CDKN2A*.[12]

With regard to sunscreens, while it is true that those in common use pre-1990 did not protect efficiently against UVA radiation, the ones produced after 1990 not only protected against both UVA and UVB, they also were more effective with significantly higher sun protection factors (SPFs). For example, by 2002 sunscreens with SPFs between 20–29 were sold most frequently in the UK and sales of even higher SPFs were increasing faster than any other SPF category.[13] Therefore it may not be valid to assume from the sunscreen studies that UVA exposure is a risk factor for melanoma. One consistent environmental risk factor remains episodes of sunburning and the action spectrum for erythema has maximum effectiveness at 300 nm, in the middle of the UVB waveband. Paradoxically, Autier *et al.*[14] showed recently that users of the sunscreens with the highest SPF had sunburns more frequently than those who did not use sunscreens. This finding may help to explain some of the conflicting results regarding the protective properties of sunscreens against skin cancers, including melanoma. It should also be noted that latitude or estimates of annual UVB dose cannot be considered as good surrogates for actual individual sunburn exposure relevant to melanoma risk. Moreover, a decision regarding the relative effectiveness of UVA or UVB cannot be made by comparing the steepness of the gradients in incidences against either UVB or UVA dose as information on dose dependence is also required. In brief, sunscreens and latitudinal dependence do not negate solar UVB as the dominant environmental risk factor for melanoma.

## Cancer

Here the consequences of excessive solar UVB exposure on the risks of developing non-melanoma skin cancer (NMSC) are clear but any net benefit on overall cancer incidence or mortality is difficult to estimate as yet. Boscoe and Schymura[15] indeed found the incidence of, and mortality from, 12 types of organ cancer to be strongly negatively correlated with ambient UVB and another 9 weakly negatively correlated. However there were also 9 types that showed no correlation and 5 with a positive correlation, and a straightforward explanation for the disparity between the different tumours is hard to find. It is important to establish whether the UVB–vitamin D link is solely responsible for the observed latitude gradient in the incidence of several cancers, as reported by Grant *et al.*[1] While a positive effect of sunlight exposure on several diseases cannot be denied, the exact contribution of vitamin D to this process is not clear and there may be an alternative explanation, as indicated in our report, such as the UV-induced release of the neuropeptides, α-melanocytes stimulating hormone and calcitonin-gene related peptide, or suppression of melatonin levels. In addition there are long-term trends in increasing skin cancer incidence amongst people with fair skins which would imply an increasing exposure to solar UVB, rather than a reduction. Indeed, although incidence rates are lower in countries further from the equator, in every country where records are kept, NMSC is rising and is predicted to have a large impact on healthcare costs.[16] There is also published information from the Women's Health Initiative Observational Study involving more than 93000 individuals indicating that women, in whom NMSC has occurred, have a 2.3 times increased chance of reporting a second cancer (other than NMSC).[17] These malignancies included breast, endometrium, colon and Hodgkin disease. As past sun exposure is an undisputed risk factor for NMSC, this finding argues strongly against a protective role for solar UVB in a wide range of tumours in women.

One huge difficulty in this area is the assessment of a person's past sun exposure. Attempts are being made now by the use of questionnaires/interviews asking about recalled number of sunburns, lifetime hours of sun exposure, holidays in a sunny climate or leisure time spent outdoors. Histopathological examination of skin biopsies from sun exposed and unexposed sites can also give information on this point. However levels of circulating 25(OH)D have not generally been measured in individuals in these reports, and prospective studies that monitor personal sun exposure, 25(OH)D levels and protection against a particular disease are urgently required. Several publications relating vitamin D status or intake with cancer risk are beginning to be available but do not present a coherent picture as yet: for example, an increased risk of pancreatic cancer has been reported for increased levels of 25(OH)D,[18] whereas the opposite was found for high vitamin D intake.[19] It is recognised that solar UVB exposure, as determined by latitude or region, is only one determinant of vitamin D status and may even be a minor determinant.[20] Other factors include vitamin D intake, skin pigmentation, obesity, sunshine holidays and activity outdoors.

## Viral infections

Certain respiratory viral infection, such as influenza A and B and respiratory syncytial virus (RSV) occur predominantly during the winter months; as mentioned by Grant *et al.*[1] and in our report,[8] it has been suggested that the lower circulating levels of 25(OH)D at that time of the year might lead to lowered innate immune response to the viruses, and hence account for the seasonality in incidence. While this hypothesis is intriguing and is certainly worthy of further experimentation, more complex explanations need to be considered, particularly the transmission properties of the microorganisms themselves, in addition to seasonal changes in human behaviour. For example, a recent study has examined the relationship of metereological conditions to community outbreaks of RSV in cities world-wide that vary markedly in latitude and climate.[21] Two of the major factors determining RSV activity were temperature (peaks about 24 °C and below 5 °C) and humidity (greatest at 40%). It was demonstrated that, in places with persistently warm temperatures and high humidity, such as Miami, or with cold temperatures throughout the year, such as Winnipeg,

RSV activity was continuous throughout the year. It was only in temperate climates that the activity was maximal in the winter months. There was an inverse correlation of solar UVR radiance with RSV activity at 3 out of the 4 sites where data were available but this association was less strong than that of temperature or humidity. It was suggested that weather conditions that enable RSV to maintain viability in large-particle aerosols lead to year-round transmission. In addition lower temperatures enhance the stability of the virus, thus prolonging survival outside the body. The solar UVB could play a role in inactivating the virus during transmission or could enhance innate immunity, as mentioned above. The largely unknown relationships that determine the seasonality of viral respiratory infections is further illustrated in a report where different coronaviruses were isolated from patients in Hong Kong with acute respiratory tract infections.[22] Some types caused peaks in the winter while others were absent in the winter. The reason for the variation in seasonality of these closely related viruses is not apparent. A similar picture has emerged for parainfluenza virus infection in the United States where a recent paper has shown, over a 14 year period, that the peak seasonality for serotype 1 was late September–December, while it was April–June for serotype 3.[23]

We hope that this exchange of views may stimulate further research into this fast-moving, fascinating and significant area. From the viewpoint of the UNEP on Ozone Depletion, it is most important to attempt to predict the consequences of an increase in solar UVB on human health. From the viewpoint of the general public, it is most important to provide the best guidance possible regarding 'sun behaviour', and scientific debate is certainly part of this process that we welcome.

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