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LEADING ARTICLE

Stratospheric Ozone and Health

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Background. Stratospheric ozone is being depleted and ambient ultraviolet (UV) irradiance is probably increasing. While remedial steps have been taken through the Montreal protocols, at best it will take some 90 years for stratospheric ozone concentrations to return to the levels existing in the 1970s.

Methods. The evidence that these changes may have harmful effects on health has been reviewed.

Results. The direct harmful effects are skin cancer, ocular damage and, possibly, immune suppression with an increase in infectious disease. Indirect, harmful effects resulting from climate change, changes in atmospheric chemistry, and changes in food supply may also occur. Beneficial effects are also possible but have largely escaped attention. Quantification of these effects is either uncertain or impossible at present and the outcomes for health in 50 years time can only be guessed at.

Conclusions. To understand better the health consequence of stratospheric ozone depletion, we need to know the quantitative relationship between ambient UV radiation and skin cancer, whether or not UV radiation really causes cataract and other ocular effects and what the quantitative relationships are, whether effects of UV radiation on immune function produce detectable health consequences, whether there are important beneficial effects of increasing UV radiation and, ultimately, what the balance of all these effects might be on health on a global scale.

Effects of increasing ambient ultraviolet (UV) radiation on the incidence and severity of infection (Table 1) may turn out to be the most important direct harmful effects on health of stratospheric ozone depletion.

EFFECTS OF UV RADIATION ON IMMUNITY AND INFECTION

UV radiation can impair development of cell-mediated immunity in human beings.[1] Irradiation of skin with ultraviolet B (UVB), the sunburning part of the solar spectrum at the earth's surface, inhibits the development of contact sensitivity to dinitrochlorobenzene applied to the irradiated site (Figure 1). UVB may also inhibit sensitization to an allergen applied to non-irradiated skin; thus the effects of UVB on cell-mediated immunity may be systemic as well as local. The doses of UVB used in these studies varied from insufficient to cause sunburn through to sufficient to cause moderate sunburn. Significant to the potential importance of these effects is evidence that UVB can impair the development of contact sensitization in people with black skin as well as people with white skin.[2] Thus any clinical effects of UVB suppression of cell-mediated immunity may be applicable to a much larger proportion of the world's population than skin cancer, for example.

Apart from possibly affecting the development of immunity to natural infection, these effects of UVB could impair response to programmes of immunization with live, attenuated virus vaccines, such as measles vaccine, or response to BCG. UV radiation may also affect the activity of infectious agents. There is evidence that it can activate the replication of the human immunodeficiency virus in human T cells.[3] This effect is a consequence of damage to the proviral DNA integrated into the host cell genome. It is caused by the shortest wavelengths of UV radiation which, for practical purposes, means UVB.

What is the evidence that these or other effects of UV radiation can influence the incidence of clinically significant infection in humans? The only solid evidence is that exposure to UV radiation can reactivate latent infections with herpes simplex virus. In a controlled trial, subjects with a history of herpes labialis were exposed to four minimal erythemal doses of UVB, once after application of active sunscreen and once after placebo, double-blind and in random order. The results were very clear: 27 of 38 exposures (71%)

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NB This paper was presented as the Cruickshank Lecture to the Thirteenth Scientific Meeting of the International Epidemiological Association held in Sydney, 26–29 September, 1993. Robert Cruickshank was one of the founders and the first President of the International Epidemiological Association.

TABLE 1 *Summary of the main effects of solar ultraviolet radiation on the health of human beings*

Nature of effect	Direction of effect	Strength of evidence for effect
Effect on immunity and infection		
Suppression of cell mediated immunity	Harmful (?)	Sufficient
Increased susceptibility to infection	Harmful	Inadequate
Impairment of prophylactic immunization	Harmful	Inadequate
Activation of latent virus infections	Harmful	Inadequate
Effects on the eye		
Acute photokeratitis and photoconjunctivitis	Harmful	Sufficient
Climatic droplet keratopathy	Harmful	Limited
Pterygium	Harmful	Limited
Cancer of the conjunctiva	Harmful	Inadequate
Lens opacity (cataract)	Harmful	Limited
Uveal melanoma	Harmful	Limited
Acute solar retinopathy	Harmful	Sufficient (?)
Macular degeneration	Harmful	Inadequate
Effects on the skin		
Malignant melanoma	Harmful	Sufficient
Non-melanocytic skin cancer	Harmful	Sufficient
Sunburn	Harmful	Sufficient
Chronic sun damage	Harmful	Variable
Photodermatoses	Harmful	Sufficient
Other direct effects		
Vitamin D production	Beneficial	Sufficient
Other cancers	Beneficial	Inadequate
General well-being	Beneficial	Inadequate
Indirect effects		
Effects on climate, food supply, disease vectors, atmospheric chemistry, etc.	Probably harmful	Inadequate

after placebo produced clinical signs of herpes and in 25 of these exposures (66%) virus was isolated from the lesion; no signs of herpes were observed in 35 exposures after sunscreen although virus was isolated from the usual site of herpes in one subject (3%).[4] The exact mechanism whereby UV radiation reactivates herpes simplex virus infections is not known. Specifically, we do not know whether it suppresses local immunity to the virus, activates the virus, or acts in some other way.

These limited data suggest that we should be concerned about the effects that an increase in ambient solar irradiance might have on the incidence of infectious disease.

If Robert Cruickshank were alive today, he would be concerned. Primarily a bacteriologist and clinical microbiologist, Cruickshank had a wide interest in clinical infectious disease and its epidemiology and prevention as the titles of some of his papers show: the bacterial infection of burns;[5] an outbreak of Sonne dysentery;[6] the epidemiology of some skin infections;[7] influenza and measles vaccines;[8] the influence of age and nutrition on the incidence and control of enteric infections.[9]

Cruickshank's Malcolm Morris Memorial Lecture at St Mary's Hospital, London, in 1951 was on the epidemiology of some skin infections.[7] In it he made the observation that staphylococcal impetigo 'has its greatest incidence in the summer months ... occurs commonly in areas with hot dry summers, as in Central Europe and the Middle West of America ... [and] ... its

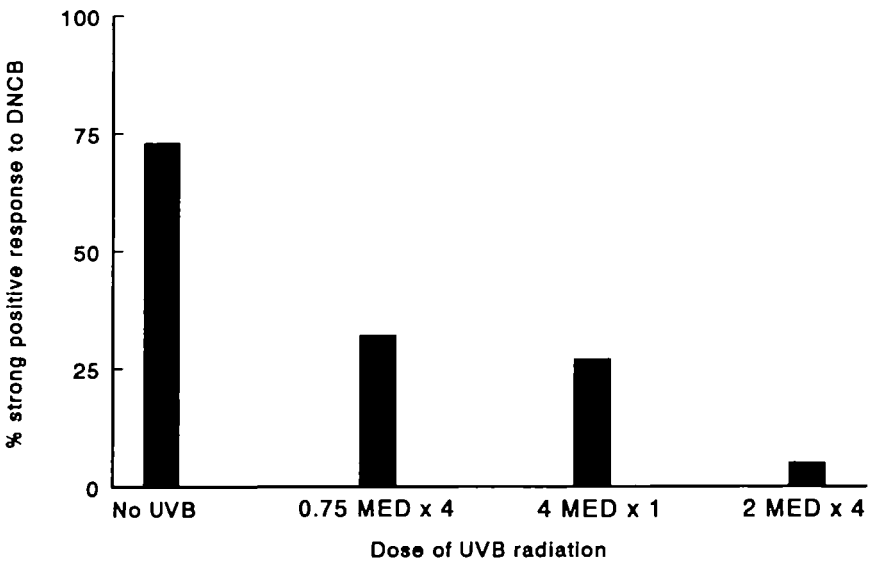

FIGURE 1 *Effects of several different doses of UV radiation to the site of subsequent sensitization with dinitrochlorobenzene (DNCB), in groups of 20–22 subjects, on the later response to challenge with DNCB at a distant site—a measure of delayed type hypersensitivity to DNCB (prepared from Cooper et al.[1])*

prevalence among unseasoned male Service personnel in the summer months indicates that unusual exposure to the sun plus shaving helped to initiate the infection'. This observation adds to the plausibility of significant effects of ambient UV radiation on the epidemiology of infectious disease.

Cruickshank was one of the founders, in 1954, of the International Corresponding Club which later became the International Epidemiological Association. Had its founders been confronted with the possibility that increasing UV irradiance would affect the incidence of infectious disease, they would have asked, as we should, three questions: Is there a problem? How big will it be? and, armed with that information, What should be done about it?

For the effects of UV radiation on infectious disease, we are still in the early, '*Is there a problem?*' phase. We cannot give any quantitative estimate and it would be inappropriate to propose action on UV irradiance change solely because of possible effects on infectious disease.

Having started in the middle of my story so that I could introduce the hero, let's go back to the beginning.

TRENDS IN STRATOSPHERIC OZONE AND UV RADIATION AT THE SURFACE OF THE EARTH

Incident UV radiation from the sun must first run the gauntlet of backscattering into space, absorption in the atmosphere and absorption on the ground before it can strike a human being and produce some effect.[10] From the biological point of view, the most important of these predators on solar UV radiation is stratospheric ozone. Ninety per cent of atmospheric ozone is in the stratosphere, it absorbs all UV radiation less than about 290 nm, 90% under 304 nm, 50% at about 314 nm and 1% at about 339 nm. Thus it removes or attenuates the more biologically active, shorter wavelengths of UV radiation. Without it, life on earth as we know it would not exist.

By convention, UV radiation is divided between three wavelength bands: UVC, 100 to 280 nm, UVB, 280–315 nm and UVA, 315–400 nm. Visible light lies in the 400–780 nm wavelength band. Because of stratospheric ozone, only radiation in the UVB and UVA bands of UV radiation reaches the surface of the earth. The bulk of harm to human health probably comes from UVB. This is the band most strongly influenced in intensity by the amount of atmospheric ozone.

Stratospheric ozone concentrations are falling and have been since the mid-1970s[11] (Figure 2). The average summer trends from the world network of ground-based, Dobson spectrophotometers for the period 1970–1991 were –1.7% per decade over North America, –1.2% over Europe and –1.2% over the Far East (Figure 2). For the more recent part of the period, 1978–1991, they were –4.0%, –4.0% and –2.1% respectively. For southern hemisphere stations in Australia, New Zealand and Macquarie Island (Antarctica), the average long-term trend in summer was –1.1% per decade and the trend from 1978 to 1991 was –5.8% per

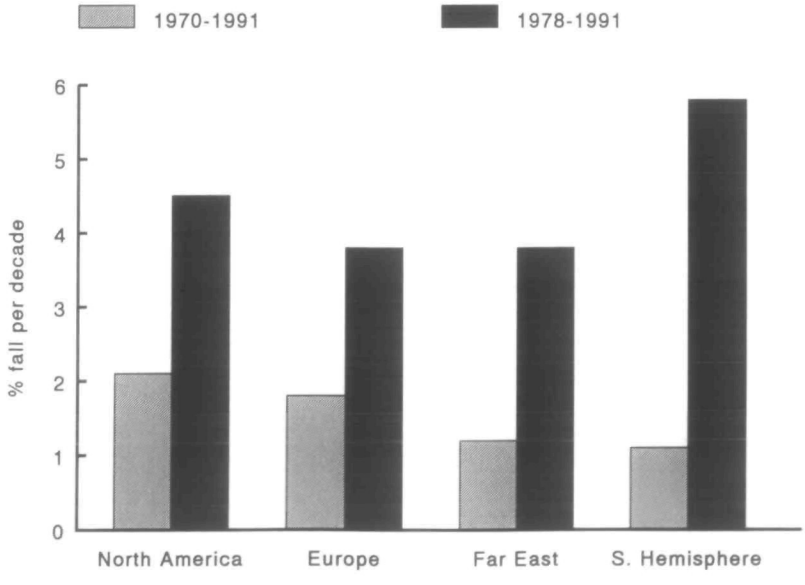

FIGURE 2 *Average trends in total column ozone in North America, Europe and the Far East as measured by a ground-based network of Dobson spectrophotometers from 1970 to 1991 (prepared from data in Stolarski et al.[11])*

decade. Little net change in ozone concentration was seen near the equator. Similar results were obtained for the period 1978–1990 from a different and global source, readings of the Total Ozone Mapping Spectrometer (TOMS) mounted on the Nimbus 7 satellite.[11] The downward trend in ozone continued in 1992.[12]

Why is stratospheric ozone depleting? While not without its detractors, the dominant theory asserts destruction of ozone by chemical reactions involving halocarbons. Halocarbons are long-lived, man-made chemicals, such as chlorofluorocarbons or CFCs, which have been used as aerosol propellants, refrigerants, foam expanders, solvents, etc. They slowly make their way to the stratosphere where, on the surface of polar stratospheric clouds, highly reactive chemical species such as ClO (chlorine monoxide) are formed which, in the presence of sunlight, react with ozone to convert it back to molecular oxygen. A single chlorine or bromine atom may destroy many molecules of ozone.

Apart from the very strong basis that it has in chemistry, there is evidence of the 'smoking gun' kind that the halocarbons really are the culprits. There is a remarkably strong correlation in time and place between the presence of ClO in the stratosphere over Antarctica and the development and location of the Antarctic ozone hole.[13,14] Similar observations have been made over the Arctic polar vortex.[15] While halocarbons are not the only source of chlorine in the stratosphere, they are believed to contribute about 80% of the present total.[16]

On the basis of the measured fall in stratospheric ozone, it is possible to estimate by way of a radiative transfer model (i.e. a model of the way UV radiation passes through the earth's atmosphere and the factors which influence it[10]) what the resulting changes in UV irradiance at the surface of the earth will be. Because ozone absorbs only short-wave UVB radiation, these estimates have generally been made with reference to a specific biological action spectrum, i.e. a spectrum that describes, by wavelength, the effectiveness of UV radiation in producing a particular biological effect. The validity of the radiative transfer model is supported by the demonstration empirically of relationships between total column ozone and biologically effective UV radiation. Such relationships have been shown, for example, in simultaneous measurements of ozone and spectral UV radiation over the course of a year at Lauder in New Zealand and in relation to the development of the seasonal Antarctic ozone hole at Ushuaia in southern Argentina (55°S).[17,18]

Estimates of UV irradiance trends, modelled from satellite-based, TOMS measurements of ozone made between 1979 and 1992,[19] suggest that erythemal UV irradiance in populated parts of the southern hemisphere has increased from between 0% per decade at the equator to about 5% per decade at latitude 45° (Figure 3). In the

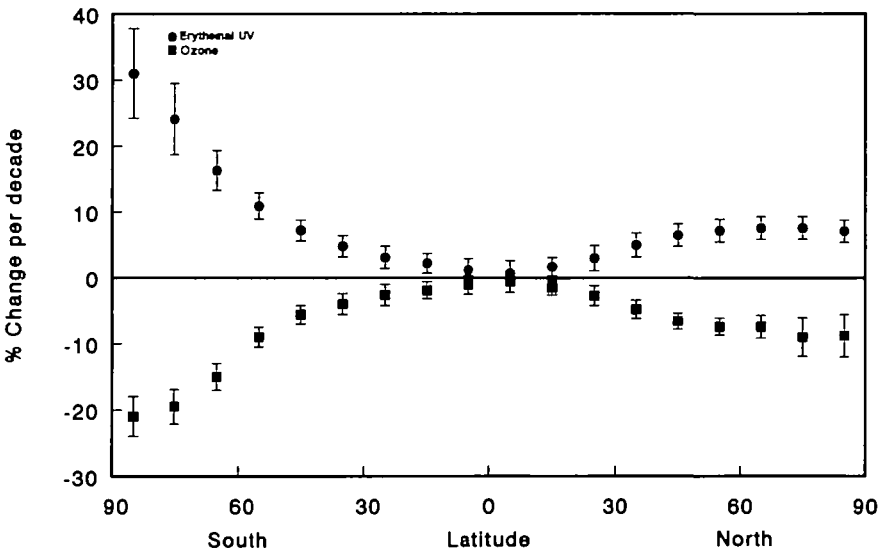

FIGURE 3 *Estimated average trends in erythemal UV irradiance at ground level by latitude between 1979 and 1992 with the corresponding trends in average measurements made by the Total Ozone Mapping Spectrometer (TOMS) on the Nimbus 7 satellite from which the UV radiation trends were estimated (prepared from data in Madronich and de Gruijl[19]). The bars show 1 SD on either side of each estimated average value*

northern hemisphere the corresponding range was from 0% to about 5.5%, at latitude 65°. These proportional increases represent, at their maxima, absolute increases of around 450 J/m^2 in November and December at latitude 45°S and 350 J/m^2 in May at latitude 45°N.

These estimates of UV irradiance trends assume cloud-free and aerosol-free skies. Thus, depending, for example, on parallel trends in climate and pollution in the lower atmosphere, the actual UV radiation trends could be quite different. Ideally, there would be corresponding measurements of trends in UV irradiance at the surface of the earth. In fact, there are few well-collected sets of data on UV irradiance trends and, so far, none of them has been the subject of an adequate analysis. Thus while there have been reports of rising, falling, or both rising and falling UV irradiance at the earth's surface,[20–22] it is not possible at present to be certain of what the true trend has been anywhere.[23,24]

What about the Future?

Serious international action to protect stratospheric ozone got underway in September 1987, with the signing of the first Montreal Protocol on Substances that Deplete the Ozone Layer.[25] The requirements of the protocol have since been toughened twice as concern about stratospheric ozone has increased.[26,27] From a requirement in the 1987 protocol of a reduction to 50% of 1986 production and consumption of chlorofluorocarbons by 1 July 1998, the 1992 amendment has moved to a requirement of zero production and consumption by 1 January 1996. Similar provisions apply to other halocarbons that may deplete stratospheric ozone.

The success of these measures will depend on adherence by the signatory nations, which are estimated to represent about 93% of global consumption and production of controlled chemicals,[28] to the requirements of the Montreal Protocol and on there being no substantial increase in production and use of these chemicals by non-signatory nations. The latter is by no means certain because of the cost of substitute chemicals for use in refrigeration, for example. Projections of stratospheric chlorine loadings made on the assumption of full compliance with the initial Protocol and its two amendments[29] suggest that chlorine loadings will return to the level of 1970 in about the year 2080 (Figure 4). The rates of growth of measured atmospheric concentrations of CFC-11 and CFC-12 did indeed begin to fall in 1989.[30]

What are the likely corresponding trends in UV irradiance? Dr Sasha Madronich (personal communication) of the US National Center for Atmospheric Research has made projections, by use of a radiative transfer model, on the assumption that the consumption and production of CFCs will be reduced to 95% of their 1986 values between 1996 and 2000. These projections suggest that peak UV irradiances will be reached in about 2000 in the southern hemisphere and a bit later, about 2010, in the northern hemisphere. These peak levels, representing 5–30% increases in annual UV irradiance over their 1970s levels in the populated temperate and cold climates of both the northern and southern hemispheres, are projected to change little until some time after 2040. In the tropics, UV irradiance increases will be modest at between 0% and 5%.

Apart from a very uncertain increase in the incidence of infectious disease, what other effects on health might, say, a total increase in ambient UV irradiance of 15% above 1970s levels extending over at least the next 50 years be expected to produce in human populations?

EFFECTS OF UV RADIATION ON THE EYES

Like effects on the immune system, the effects of UV radiation on the eyes probably have little respect for race or colour. There are at least eight categories of harmful effects (Table 1); the evidence that any of them, except acute photokeratitis, photoconjunctivitis and solar retinopathy, really are caused by solar UV radiation is not sufficient to give a confident 'yes' to the question: Is there a problem? For acute photokeratitis, photoconjunctivitis and solar retinopathy the evidence is almost entirely of the immediate cause and effect kind; that is, high exposure is followed within a

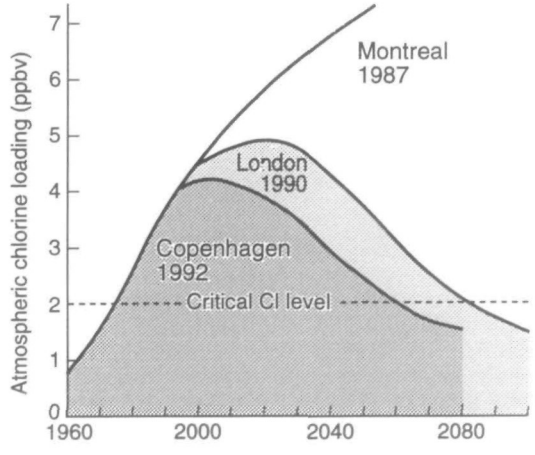

FIGURE 4 *Estimates and projections of stratospheric chlorine loadings from the 1960s to the year 2080 on the assumption of full implementation of the control measures introduced with the 1987 Montreal Protocol and its 1990 and 1992 amendments (reproduced with permission from the World Meteorological Organization[29])*

short time (12–24 hours) by onset of acute disease, classically in the situations of 'snow blindness', which is acute photokeratitis resulting from the almost 100% reflection of UV radiation from snow, and blindness following 'sungazing', the viewing of solar eclipses and, occasionally, simple sunbathing.[31]

A question mark has been placed against solar retinopathy because of uncertainty about its attribution to UV radiation. While the retina appears to be most sensitive to shorter wavelengths in the solar spectrum,[32] the absorptive power of the cornea and the lens combine, in adults, to prevent almost all radiation below 400 nm reaching it.[33] However, the lens is more transparent in children allowing up to 4% of radiation in the range 300–340 nm to reach the retina.[33] Thus an increase in UV irradiance could increase the risk of acute solar retinopathy in children at least, and perhaps also in adults because a small amount of UV radiation probably does get through.

For public health, the greatest importance should be attached to the possibility that an increase in UV irradiance would increase the incidence of cataracts. Cataracts affect all populations and account for visual loss in an estimated 17 million people, 13 million in developing countries and 4 million in developed countries.[34] With ageing of the world's population, this total is expected to grow to 40 million by the year 2025. In a survey of a general US population 43–84 years of age, visually significant lens opacity was observed in 14.1% of subjects when the worst eye was considered and 5.0% when the best eye was considered.[35] An additional 3.6% of subjects had received prior cataract surgery to the right eye, thus nearly 10% suffered or had suffered visual disability from cataracts.

There is a geographical relationship between cataract and solar UV irradiance. Worldwide, prevalence tends to increase with increasing proximity to the equator[36] and increasing prevalence has been observed with increasing ambient UV radiation in the USA,[37] among aborigines in Australia,[38,39] in China[40] and in Nepal.[41] These associations may be confounded by associations between diet and other lifestyle factors and cataract.

A number of studies have examined the relationship between prevalence of lens opacity or clinical incidence of cataracts and measures of personal exposure to the sun. In these studies, the strongest evidence of causation by sun exposure has been observed for one particular type of cataract, cortical cataract. Three out of nine cross-sectional or case-control studies of all cataracts or cortical cataracts alone have found statistically significant positive associations with some measure of sun exposure (Table 2). The best of these studies[44] was carried out in Chesapeake Bay fishermen, traditionally called watermen, and included a very comprehensive measure of cumulative adult exposure of the eyes to the sun. It showed a monotonic, increasing dose–response relationship for cortical cataract across quartiles of estimated exposure to UVB. There is some evidence that the more visually disabling but rarer posterior subcapsular cataracts are also caused by

TABLE 2 *Summary of studies in which incidence of clinical cataract or prevalence of lens opacity of varying degrees of severity have been studied in relation to a measure of personal sun exposure. (Results shown are those for cortical opacities, where these were analysed separately, or all opacities together)*

Authors	Numbers of lens opacities/ all subjects	Types of lens opacities	Measure of sun exposure	OR (95% CI) for highest exposure category	*P* value
Chatterjee *et al.*[42]	87/601	All	Outdoor work	0.7 (0.5–1.1)	>0.05
Collman *et al.*[43]	113/274	Cortical	Total cumulative	1.5 (0.2–7.2)	>0.05
Taylor *et al.*[44]	340/838	Cortical	Total cumulative	3.3 (0.9–10)	0.03
Mohan *et al.*[45]	1441/1990	All	Outdoor work	NS[a]	<0.05
Bhatnagar *et al.*[46]	181/421	All	Outdoor work	2.1 (1.2–3.6)	<0.05
Leske *et al.*[47]	995/1430	Cortical	Outdoor work	0.9 (0.6–1.2)	>0.05
Italian-American Study Group[48]	1008/1475	Cortical + mixed	Outdoor work	1.8 (1.2–2.6)	<0.05
			Outdoor leisure	1.4 (1.1–1.9)	<0.05
Cruickshanks *et al.*[49]	766/4728	Cortical	Outdoor leisure in summer	1.0 (0.8–1.3)	>0.05
			Outdoor work	1.1 (0 8–1.3)	>0.05
Wong *et al.*[50]	34[b]/339	All	Cumulative occupational exposure	2.1 (0.6–7.9)	>0.05

[a] NS = not stated, direction of effect also not stated.
[b] Grades III–V lens opacity.

sun exposure.[51] There is no evidence that UV radiation causes what is probably the commonest kind of cataract, nuclear cataract.

While the evidence of epidemiology is not sufficient on its own, taken with sufficient evidence that exposure to UV radiation, and more specifically UVB, causes cataract in experimental animals,[52–54] it can be concluded that UV radiation probably does cause cataract in humans.

EFFECTS OF UV RADIATION ON THE SKIN

UV radiation also causes mainly harmful effects on the skin (Table 1); although some of the photodermatoses could be improved by an increase in winter UVB resulting from stratospheric ozone depletion because they are made worse by loss of adaptation to UV radiation.[55] Some skin effects of UV radiation, such as the various types of benign chronic sun damage, may appear to be trivial but are important cosmetically and lead to emotional if not physical morbidity and substantial cost, as from the purchase of cosmetics and recourse to cosmetic surgery.

By far the most important of the cutaneous effects of UV radiation are the skin cancers. Here there is little doubt of causation by UV radiation. A group of experts convened in February 1992 by the International Agency for Research on Cancer, concluded that 'there is sufficient evidence in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and non-melanocytic skin cancer.' That at least the non-melanocytic skin cancers are caused by UVB specifically is suggested by the action spectrum for induction of non-melanocytic skin cancer by UV radiation in hairless albino mice, which has its main peak at about 300 nm[56] and the action spectrum in human skin for the main kind of UV radiation-induced DNA damage (i.e. formation of cyclobutylpyrimidine dimers) which also peaks at about 300 nm.[57]

The link between the cyclobutylpyrimidine dimers and non-melanocytic skin cancer is made through observations that mutations of the p53 tumour suppressor gene are found in some 50% of basal and squamous cell carcinomas,[58,59] and that these mutations show a pattern of base changes similar to what would be expected if they were a result of dimers caused by UV radiation.[58]

That the UVB wavelength band is mainly responsible for melanoma is much less certain. The only action spectrum describing the wavelength dependence of production of melanoma in experimental animals comes from studies of hybrids of two species of small fish (genus *Xiphophorus*), platyfish and swordtails. This action spectrum shows much higher relative activity in the UVA band than is seen in the action spectrum for non-melanocytic skin cancer in mice.[60] If this action spectrum were to apply to melanoma in humans it would mean that most cases of the disease are now caused by UVA rather than UVB and, therefore, that a 15% increase in ambient UVB would lead to a substantially smaller proportionate increase in melanoma incidence. There is currently no evidence for UV-specific mutation patterns of oncogenes or tumour suppressor genes in human melanoma

RELATIONSHIP BETWEEN UV IRRADIANCE CHANGE AND CHANGE IN THE INCIDENCE OF SKIN CANCER AND PREVALENCE OF CATARACT

Estimates have been made of the extent to which incidence of skin cancer will increase as a result of an increase in UV irradiance due to depletion of stratospheric ozone. They have been based on analysis of the rates of change of skin cancer incidence with latitude-related changes in UV irradiance; that is, by a geographical correlation approach. The best known and most commonly used geographical relationships are those established from data on non-melanocytic skin cancer collected in a special survey in the USA in 1977 and 1978 and UV radiation measurements collected through the US network of Robertson–Berger meters.[61] Corresponding relationships were later established between melanoma incidence measured by the US SEER cancer registries and the Robertson–Berger meter data[62] (Figure 5).

The results of these analyses have commonly been expressed in terms of the biological amplification factor (BAF) which is defined as follows:[63]

$$BAF = (dI/I)/(dD/D)$$

where dI is 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 ambient level, D, of solar radiation (i.e. spectral dose weighted by the action spectrum for production of skin cancer). By biologically effective here, I mean the spectral dose weighted by the action spectrum for production of skin cancer. The biological amplification factor is commonly conceptualized as the percentage increase in incidence of skin cancer (or some other biological effect) that would result from a 1% increase in ambient UV irradiance. The values obtained for melanoma from Figure 5 were 0.7 in males and 0.8 in females, the estimated slopes of the regression lines.

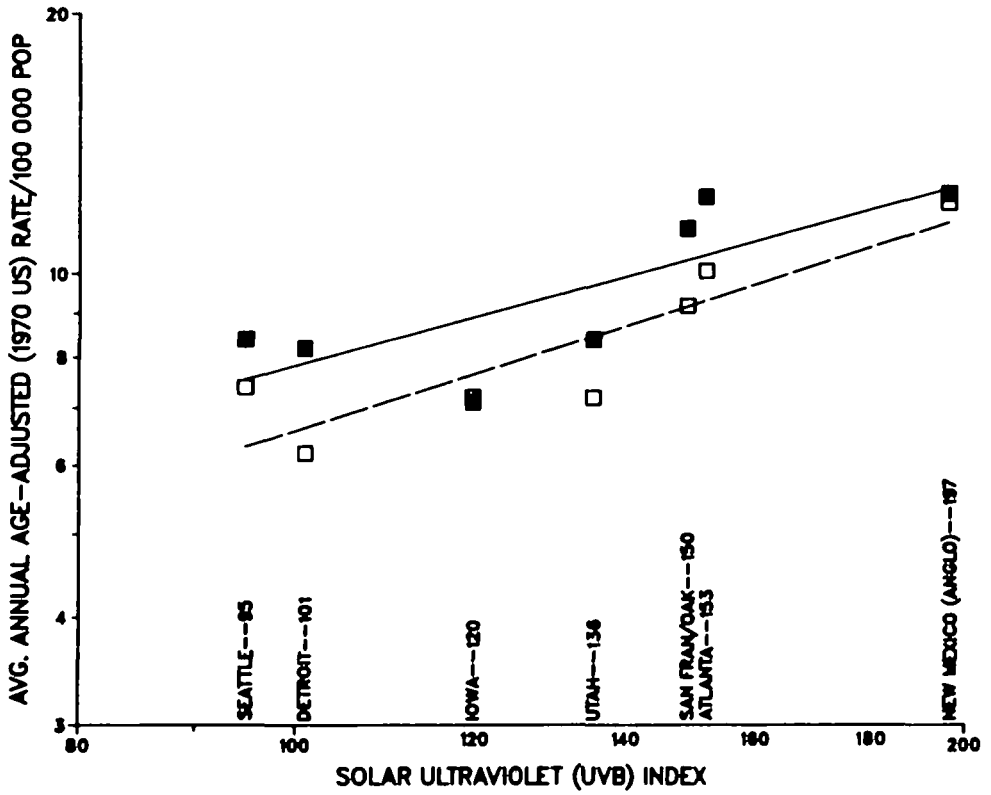

FIGURE 5 *Relationship of the logarithm of age-adjusted incidence of melanoma in seven population groups in the USA to the logarithm of UV irradiance as measured by Robertson–Berger meters (reproduced with permission from Scotto and Fears[62])*

The most recent estimates of the biological amplification factors for non-melanocytic skin cancer and cutaneous melanoma have been based on data from the USA and Scandinavia (Table 3). Generally, the estimates of the biological amplification factor for basal cell carcinoma (BCC) lie between about 1.5 and 2.0. For squamous cell carcinoma (SCC) and melanoma, there is much greater variation in estimates. Those for squamous cell carcinoma are between about 2.0 and 4.0 when based on the US data but between 1.0 and 2.0 when based on Norwegian data. For melanoma, they are between 0.3 and 0.5 when based on US data but between about 1.0 and 3.0 when based on Scandinavian data. While attempts were made to adjust the melanoma estimates from the USA for confounding with constitutional sensitivity to the sun and sun-related behaviour, even the unadjusted estimates (ranging from 0.6 to 1.0[61,66]) are considerably less than those from Scandinavia. The most likely reasons for the differences between the estimates is differences in their error.

This approach to estimation of dose–response has assumed, among other things, that: the correct action spectrum has been used to weight spectral UV irradiance when producing a single figure for ground level UV radiation in each area; all members of the populations giving rise to the incidence rates have lived their whole lives in the present environment; the skin cancer incidence rates have been measured accurately and, in particular, that their error does not correlate with ambient UV irradiance; and that possible confounding of ambient UV radiation with constitutional sensitivity to the sun and sun-related behaviour is either unimportant or has been adequately taken into account. None of these assumptions is likely to be correct in any of the estimates of biological amplification factor made so far and the estimates may be substantially inaccurate.[68]

Thus while we can be confident that an increase in ambient UV irradiance will increase the incidence of skin cancers over what it would have been had the irradiance increase not occurred, we can give no confident estimate of how large this effect might be.

TABLE 3 *Recent estimates of the biological amplification factors (BAF) for non-melanocytic skin cancer and cutaneous melanoma based on geographical correlations between average annual ambient UV radiation and skin cancer incidence or mortality*

			Non-melanocytic skin cancer	
Authors	Region	Sex	BCC incidence	SCC incidence
Scotto *et al.*[61]	USA 8 centres	M	1.3–2.6[a]	2.1–4.1
		F	1.1–2.1	2.2–4.3
de Gruijl & van der Leun[64,b]	USA 8 centres	MF	1.4	2.5
Moan *et al.*[65]	Norway 6 areas	M	1.5–2 0[a]	1.2–1.5
		F	1.6–2.1	1.6–1.8

			Melanoma	
Authors	Region	Sex	Incidence	Mortality
Scotto & Fear [62]	USA 7 areas	M	0.4[c]	
		F	0.5[c]	
Pitcher & Longstreth[66]	USA 215 SMAs	M		0.4[d]
		F		0 3[d]
Moan & Dahlback[67]	Norway	M	1.9	
		F	3.2	
	Finland	M	1.3	
		F	2.2	
	Sweden	M	1.9	
		F	2.3	

[a] Exponential model used in which the value of the BAF varies with ambient UV radiation, thus range of values given.
[b] Same data as used by Scotto *et al.*[61] except that a power model was used instead of an exponential model and the most recent action spectrum for UV radiation carcinogenesis in mouse skin was assumed.
[c] Adjusted for population estimates of ethnic origin, pigmentary characteristics, use of suncreens, and hours per week of outdoor exposure.
[d] Adjusted for population estimates of ethnic origin, household income, outdoor occupation and education.

Returning for a moment to cataracts, a similar approach to that used to estimate the biological amplification factors for skin cancer can be used to estimate the biological amplification factor for cortical cataract. Hiller *et al.*[69] found that the relative risk for cortical cataract was 1.45 (95% CI : 1.01–2.11) per 1000 'counts' increase in ambient UVB at the place of residence in the USA. From this value it may be estimated that the biological amplification factor for cataract ranged from 1.0 to 2.3 across the 3.5-fold range in UVB counts observed in the USA in this study. An alternative estimate of 0.7 (95% CI : 0.0–1.4) has been made of the biological amplification factor for cataract based on the dose–response relationship observed between UVB and cortical cataract in the study of Chesapeake Bay watermen.[44,55] By way of comparison, the biological amplification factor at Washington DC can be estimated at 1.2 (95% CI : 0.0–2.4) from the data of Hiller *et al.*[69] Even assuming the lack of major biases from measurement error and confounding, the value of the biological amplification factor for cortical cataract is known, at best, to within a factor of about two.

OTHER EFFECTS OF UV RADIATION ON HEALTH

There is a small list of 'other direct effects' (Table 1), all of which are potentially beneficial. Of these, the best known is the photochemical production of vitamin D_3 from cholesterol in the skin.[70] For most people, dietary vitamin D is not sufficient to meet the body's needs and deficiency would occur but for cutaneous synthesis. Deficiency is observed, for example, in older people who stay indoors most of the time and dark-skinned children living in northern Europe. An increase in UV irradiance would certainly benefit the latter. It would not carry with it the risk of vitamin D intoxication in others because the synthesis of vitamin D in the skin is self-limiting and does not lead to overproduction.

Observations of increasing mortality from cancers of the breast, colon and prostate with increasing latitude have led to suggestions that UV radiation may protect against these cancers, perhaps by proposed anti-carcinogenic actions of vitamin D.[71–73] Variations with latitude in medical care, death certification practices, diet and other lifestyle factors are alternative explanations for the latitude gradients; thus these observations can be taken only as raising hypotheses which require testing by other means. Finally we need to recall the wider environmental effects of UV radiation and the possibility that there may be substantial indirect effects on human health by way of changes in UV irradiance on climate, food supply, atmospheric chemistry, and the like.[74] These indirect effects on health are, as yet, of largely unknown direction and totally unquantified.

RECOMMENDATIONS FOR ACTION ON STRATOSPHERIC OZONE DEPLETION AND HEALTH

We come now to the last of the three questions that the founding members of the International Corresponding Club would have asked and we should ask: *What should be done about it?*

As far as stratospheric ozone depletion is concerned, the answer has already been given and, if the control measures of the Montreal Protocol work as hoped, that problem should no longer be with us 50–100 years hence. From the public health point of view, the action agenda lists mainly data collection and research.

First, there is a need to establish high quality, spectral monitoring of solar UV radiation in populated areas covering the full range of latitudes at which significant numbers of people live in both hemispheres. These data are required to validate further the radiative transfer models used to estimate trends in UV radiation from trends in ozone[75] and to provide reassurance that the situation is, at least, no worse than the models would suggest. It may prove also that trends in UV irradiance will provide the best estimate we can make of trends in health consequences of UV radiation that are caused by environmental change because of the difficulty of measuring trends in these health effects accurately and separating those due to changing environment from those due to changing behaviour.

Second, there is a need to develop some way of measuring trends in the biological consequences of exposure to UV radiation in human beings. The measurements of such trends would provide some assurance that the effects of environmental change are not greater than expected from estimated UV radiation trends or, alternatively, give early warning that they are. At present, it is doubtful whether the incidence of any of the diseases due largely to UV radiation can be measured with sufficient accuracy to allow valid conclusions regarding trends of the size that might be caused by ozone layer depletion.[76] Even the incidence of cutaneous melanoma, which most might think can be measured with reasonable accuracy by cancer registries, now appears to be strongly influenced, at least over short periods, by public and professional attention to the disease.[77]

Some hope lies in the identification of a stable biological marker of accumulated exposure of the skin to the sun. Colleagues at the International Agency for Research on Cancer have recently developed a method to detect UV radiation-induced mutations in the p53 tumour suppressor gene in normal human skin. We have been able to show that the mutation is commonly present in exposed but not unexposed skin in older Australians.[78] Efforts are being made to make the assay quantitative and its correlation with estimated sun exposure and its capacity to predict risk of skin cancer are being evaluated in case-control studies of non-melanocytic skin cancer and melanoma. Measurement of the prevalence of UV-induced mutations in exposed skin of random samples of, say, 40-year-olds, could be a very accurate measure of their lifetime sun exposure. Repetition of this population measurement on a regular basis could provide an accurate measure of trends in biologically relevant UV radiation exposure. Such a measure would not distinguish trends due to environmental change from trends due to behavioural change. It would be, nonetheless, a powerful and relevant indicator of trends in all factors affecting UV radiation exposure.

Third, there is an urgent need for research into the possible consequences of an increase in UV irradiance for the incidence of infectious disease in humans. Some rather simple designs are possible. For example, the effect of ambient UV radiation on vaccine effectiveness might be addressed by examining seasonal effects on the antibody response to a T-dependent antigen such as the measles vaccine or the development of delayed type hypersensitivity to tuberculin following BCG vaccination. The issue of UV radiation activation of the human immunodeficiency virus might be examined by incorporating measures of sun exposure into new or ongoing follow-up studies of people with asymptomatic human immunodeficiency virus infection and observing their effects on the development of clinical disease.

Fourth, there is a need to confirm the apparently causal association between UV radiation and the development of cataracts and to ascertain the contribution of UV radiation to the burden of visually significant cataract in populations of different ethnic backgrounds, at different levels of ambient UV radiation exposure and at different levels of economic development around the world. Such a study, if conducted, should also endeavour to establish the dose–response relationship between solar UV radiation and cataracts of different types so that better estimates can be made of the likely increase in the world burden of cataract that would result from the expected change in UV irradiance.

Fifth, there remains a need to determine accurately the dose–response relationship between ambient solar UV radiation and the major types of skin cancer. Because of the likely complexity of the interrelationship between amount and pattern of exposure in affecting incidence of skin cancer,[79] such a study would require an ecological approach similar to that adopted by Scotto *et al.*[61] and Scotto and Fears.[62] There are many difficulties in such a study, not least of which are the accurate measurement of incidence of skin cancers and appropriate adjustment for differences between populations in constitutional sensitivity to the sun and sun-related behaviour.[76] It is here, too, that a biological marker might save the day. It may prove possible, for example, to establish the relationship between ambient UV radiation and UV-induced mutations in skin at a

site of the skin for which the effects of sun-related behaviour are fairly easily measured. Measurement, then, of the quantitative relationship between UV-induced mutations and risk of the different types of skin cancer might permit an accurate quantitative risk assessment.

Sixth, we should accept that environmental UV radiation is likely to be, for the next 50 years at least, more damaging to human organisms by 15% or more than it was 20 years ago. We cannot now do more to improve this situation. We can, however, increase our efforts to encourage people to reduce their personal exposure to the sun. Diffy[80] has estimated that, for the average resident of the British Isles, staying indoors for one hour around midday between May and August or wearing a wide-brimmed hat every day during a 2-week summer vacation would reduce UV radiation exposure by the same amount as ozone layer depletion might increase it. These measures are apparently simple but it is important to recall that we need to shift the population averages by these amounts, or more if we want to do something about the existing burden of disease related to UV radiation. Encouragingly, changes in behaviour of greater amounts than this appear to have been achieved by the Sun Smart campaigns conducted in Australia in recent years.[81]

Finally, the International Epidemiological Association should reflect on the lessons that the response to this episode of major environmental change has for it. Epidemiology has been only peripherally involved in providing the data on which public action to deal with ozone layer depletion has been based and there is still a substantial lack of epidemiological data for a complete assessment of the possible impact of this environmental change. While the prescriptions above may help to remedy the latter deficiency, we need to consider how epidemiologists could make a more timely contribution to understanding the impact of a future major change in the global environment. I suggest that when such a change seems possible the Association convene a group of experts to recommend a programme of epidemiological research that would go most directly to estimating and, ultimately, measuring the impact of the possible change. A well-constructed programme, appropriately justified and cogently promoted to concerned governments, research-funding agencies and the epidemiological community, could go a long way to ensuring that the effects on health can be fully and appropriately considered in future responses to global environmental change.

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