CHAPTER 8

Stratospheric ozone depletion, ultraviolet radiation and health

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Introduction

To our forebears the sky was the realm of the gods, inaccessible to mere humans. Only 100 years ago, the few scientists studying environmental problems would have been incredulous at suggestions that, by the late twentieth century, humankind would have begun to change the composition and function of the stratosphere. Yet this has happened. After 8000 generations of *Homo sapiens*, this generation has witnessed the onset of the remarkable process of human-induced depletion of stratospheric ozone.

By the usual definition, stratospheric ozone depletion is not an integral part of the process of "global climate change". The latter process results from the accrual of greenhouse gases in the troposphere, physically separate from the stratosphere. The stratosphere extends from around 10 to 50 km altitude (see Figure 8.1). It is distinguishable from the lower atmosphere (troposphere) and the outer atmosphere (mesosphere and thermosphere). In particular, most of the atmosphere's ozone resides within the stratosphere. The ozone layer absorbs much of the incoming solar ultraviolet radiation (UVR) and thus offers substantial protection from this radiation to all organisms living at, or near to, Earth's surface.

Intriguingly, atmospheric ozone is not part of the planet's original system but a product of life on Earth, which began around 3.5 billion years ago. Until a half billion years ago, living organisms could not inhabit the land surface. Life was confined to the world's oceans and waterways, relatively protected from the intense unfiltered solar ultraviolet radiation. About 2 billion years ago as photosynthesising organisms emitted oxygen (O_2), a waste gas (ozone–O_3) gradually began to form within the atmosphere (*1*). From around 400 million years ago aqueous plants were able to migrate onto the now-protected land and evolve into terrestrial plants, followed by animal life that ate the plants. So the succession has evolved, via several evolutionary paths, through herbivorous and carnivorous dinosaurs, mammals and omnivorous humans. Today, terrestrial species are shielded by Earth's recently acquired mantle of ozone in the stratosphere that absorbs much of the solar ultraviolet.

Unintentionally, the human species has now reversed some of that stratospheric ozone accumulation. Surprisingly, various industrial halogenated chemicals such as the chlorofluorocarbons (CFCs, used in refrigeration, insulated

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packaging and spray-can propellants), inert at ambient temperatures, react with ozone in the extreme cold of the polar stratospheric late winter and early spring. This time of year combines cold stratospheric temperatures with the "polar dawn", as solar ultraviolet radiation begins to reach the polar stratosphere, where it causes photolytic destruction of human-made gases in the stratosphere, such as the CFCs, methyl bromide and nitrous oxide. This, in turn, generates reactive "free radicals" that destroy stratospheric ozone.

The Montreal Protocol—noticing and responding to ozone depletion

Colour-enhanced pictures of the winter-spring polar "ozone hole" on the United States NASA web-site depict an overall loss which had crept up to around one-third of total Antarctic ozone, by the late 1990s, relative to the pre-1975 figure. Winter-spring losses in the Arctic are smaller because local stratospheric temperatures are less cold than in the Antarctic. During the 1980s and 1990s at northern mid-latitudes (such as Europe), the average year-round ozone concentration declined by around 4% per decade: over the southern regions of Australia, New Zealand, Argentina and South Africa, the figure has approximated 6–7%. Long-term decreases in summertime ozone over New Zealand have been associated with significant increases in ground level UVR, particularly in the DNA-damaging waveband (*2*). Ozone depletion is one of several factors, including cloud cover and solar elevation, which affect ground level UV radiation. An examination of atmospheric changes in Australia from 1979 to 1992 has shown that the deseasonalised time series of UVR exposures were a linear function of ozone and cloud cover anomalies. In tropical Australia a trend analysis indicated a significant increase in UVR, estimated from satellite observations, of 10% per decade in summer associated with reduced ozone (1–2% per decade) and reduced cloud cover (15–30% per decade). In southern regions, a significant trend for UVR over time was not observed, partially due to increased cloud cover. Thus, in Tasmania, despite a significant ozone reduction of 2.1% per decade, measures of ground level UVR have not increased (*3*).

Estimating the resultant changes in actual ground-level ultraviolet radiation remains technically complex. Further, the methods and equipment used mostly have not been standardised either over place or time. While there is good agreement between similarly calibrated spectroradiometers, this may not be true when comparing different types of instruments—spectroradiometers, broad-band meters, filter radiometers. There is little or no reliable evidence on levels of UV radiation prior to concerns related to ozone depletion (pre-1980s) due to maintenance and calibration difficulties with these older instruments. The advent of satellite measuring systems allowed reliable measurement of UVR. However, satellite measurements may not accurately reflect ground level UVR due to failure to take adequate account of lower atmospheric changes. For example, satellite estimates suggest that the difference in summertime erythemal UV irradiances between northern and southern hemispheres is around 10–15%. However, ground level measurements indicate that this difference may be even higher, probably due to lesser atmospheric pollution in the southern hemisphere.

It is clear that under cloud-free skies there is a strong correlation between ground level erythemal UV radiation and levels of atmospheric ozone (*4*). Yet the effects of clouds, increasing tropospheric ozone and aerosol pollution of the lower atmosphere modify this relationship making the detection of long-term trends in UVR related to ozone depletion difficult to elucidate. Long-term pre-

dictions are uncertain since they involve assumptions about not only future ozone levels but also future variations in cloud cover, tropospheric ozone and lower atmospheric pollution. However, exposures at northern mid-latitudes are projected to peak around 2020, entailing an estimated 10% increase in effective ultraviolet radiation relative to 1980s levels (*5*).

Fears of ozone depletion due to human activities first emerged in the late 1960s. A decade of denial and debate followed with eventual acceptance by scientists and policy-makers that ozone depletion was likely to occur and would represent a global environmental crisis. In the mid-1980s governments responded with alacrity to the emerging problem of ozone destruction. The Montreal Protocol of 1987 was adopted, widely ratified and the phasing out of major ozone-destroying gases began. The protocol was tightened further in the 1990s. At first sight, the solution to this particular global environmental change appears to be unusually simple: a substitution of particular industrial and agricultural gases for others. However, the problem has not yet been definitely solved. First, there is a large range of human-made ozone-destroying gases, including some of those chemicals developed to replace the early CFCs. Second, compliance with the international agreement remains patchy. Third, scientists did not foresee the interplay (see below) between a warming lower atmosphere and an ozone-depleted stratosphere. Nevertheless, scientists anticipate that there will be slow but near-complete recovery of stratospheric ozone during the middle third of the twenty-first century.

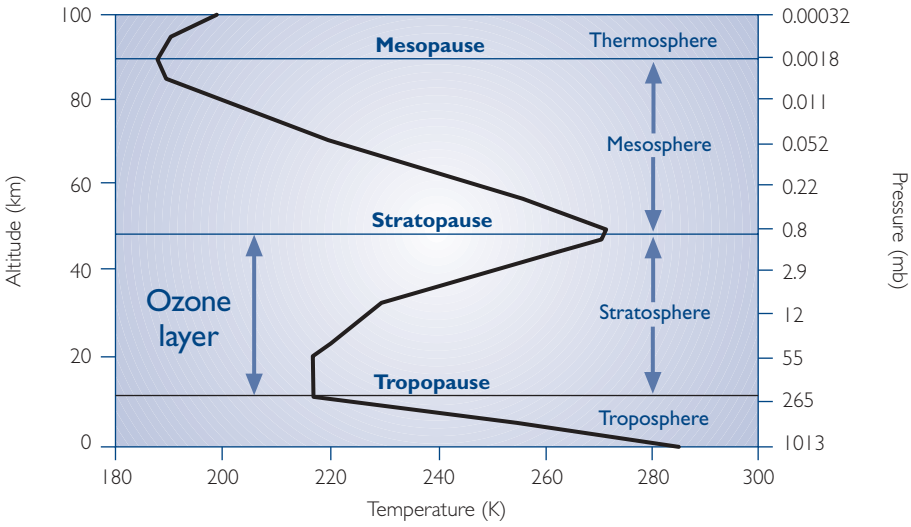
Difference between stratospheric ozone depletion and human-enhanced greenhouse effect

Stratospheric ozone destruction is an essentially separate process from greenhouse gas (GHG) accumulation in the lower atmosphere (see Figure 8.1), although there are several important and interesting connections. First, several of the anthropogenic greenhouse gases (e.g. CFCs and N_2O) are also ozone-depleting gases. Second, tropospheric warming apparently induces stratospheric cooling that exacerbates ozone destruction (*6*, *7*). As more of Earth's radiant heat is trapped in the lower atmosphere, the stratosphere cools further, enhancing the catalytic destruction of ozone. Further, that loss of ozone itself augments the cooling of the stratosphere. Interactions between climate change and stratospheric ozone may delay recovery of the ozone layer by 15–20 years (*5*).

Third, depletion of stratospheric ozone and global warming due to the build-up of greenhouse gases interact to alter UVR related effects on health. In a warmer world, patterns of personal exposure to solar radiation (e.g. sun-bathing in temperate climates) are likely to change, resulting in increased UVR exposure. This may be offset by changes in cloud cover and cloud optical thickness as a result of global climate change. Predictions of future UVR exposures based on ozone depletion, behavioural changes and climate change are uncertain. A recent analysis of trends in Europe reports a likely increase of 5–10% in yearly UV doses received over the past two decades (*5*).

Stratospheric ozone depletion has further indirect health effects. One important effect is that ozone depletion in the stratosphere increases the formation of photochemical smog, including ozone accumulation, in the lower troposphere. That is, ozone depletion in the upper atmosphere will allow more ultraviolet radiation to reach the troposphere where photochemical smog forms via a UVR-mediated breakdown of nitrogen dioxide (a common fossil fuel pollutant) and

FIGURE 8.1 Layers of the Earth's atmosphere. *Source: reproduced from reference 8.*



other products. Photochemical smog is a complex chemical mixture containing nitric acid (HNO_3); peroxyacyl nitrates (PANs), aldehydes (e.g. formaldehyde) ozone (O_3) and other substances. It has been estimated that the concentration of tropospheric ozone has increased from 10 ppb 100 years ago to 20–30 ppb in some locations today, with peaks of >100 ppb reported in some centres (*9*). The ozone component of photochemical smog acts as a respiratory irritant, causing oxidant damage to the respiratory epithelium and possibly enhancing allergen-induced airway inflammation.

Solar UVR measurement

Sunlight consists of solar rays of differing wavelengths. Visible light ranges from 400 nm (violet) to 700 nm (red). Infrared radiation, or heat, has longer wavelengths than visible light; ultraviolet radiation has shorter wavelengths than visible light. UVR is further divided into UVA (315–400 nm), UVB (280–315 nm) and UV-C (<280 nm). Almost all incoming solar UVC and 90% of UVB are absorbed by stratospheric ozone, while most UVA passes through the atmosphere unchanged. Although UVA penetrates human skin more deeply than UVB, the action spectra from biological responses indicate that it is radiation in the UVB range that is absorbed by DNA—subsequent damage to DNA appears to be a key factor in the initiation of the carcinogenic process in skin (*10*).

The amount of ambient UVB experienced by an individual outdoors with skin exposed directly to the sky is dependent on the following:

(i) stratospheric ozone levels
(ii) solar elevation
(iii) regional pollution
(iv) altitude of the individual
(v) cloud cover
(vi) presence of reflective environmental surfaces such as water, sand or snow.

The amount of received UVR exposure can be measured in terms of the energy of the transmitted photons, often expressed as energy per unit area irradiated (e.g. joules per square metre).

To examine the health effects of solar UVR, it is necessary also to consider measurement in the biological dimension. Hence, UVR also is described in units of erythemal (sunburn) efficacy. To this end, exposure is spectrally weighted over the relevant wavelengths according to erythemal impact (using the Commission Internationale de l'Éclairage {CIE} (*11*) erythemal standard action spectrum (*12*)). Thus, standard erythemal doses (SEDs) can be defined (*13*) by which daily, monthly or annual UV exposures can be quantified. A UV index also has been defined to express the daily maximum in biologically effective UVR, reached around midday.

Main types of health impacts

There is a range of certain or possible health impacts of stratospheric ozone depletion. These are listed in Table 8.1.

Many epidemiological studies have implicated solar radiation as a cause of skin cancer (melanoma and other types) in fair-skinned humans (*14*, *15*). The most recent assessment by the United Nations Environment Program (1998) projected significant increases in skin cancer incidence due to stratospheric ozone depletion (*16*). The assessment anticipates that for at least the first half of the twenty-first century (and subject to changes in individual behaviours) additional ultraviolet radiation exposure will augment the severity of sunburn and incidence of skin cancer.

High intensity UVR also damages the eye's outer tissues causing "snow blindness", the ocular equivalent of sunburn. Chronic exposure to UVR is linked to conditions such as pterygium (*17*). UVB's role in cataract formation is complex but some subtypes, especially cortical and subcapsular cataracts, appear to be associated with UVR exposure while others (nuclear cataracts) do not.

In humans and experimental animals, UVR exposure causes both local and whole-body immunosuppression (*16*). Cellular immunity is affected by variation in the ambient dose of UVR (*18*). UVR-induced immunosuppression therefore could influence patterns of infectious disease and may also influence the occurrence and progression of various autoimmune diseases. Nevertheless, little direct evidence exists for such effects in humans, and uncertainties remain about the underlying biological processes.

Finally, there is an ecological dimension to consider. Ultraviolet radiation impairs the molecular chemistry of photosynthesis both on land (terrestrial plants) and at sea (phytoplankton). This could affect world food production, at least marginally, and thus contribute to nutritional and health problems in food-insecure populations. However, as yet there is little information about this less direct impact pathway.

Disorders of the skin

Since the 1850s it has been known that excessive exposure to sunlight can cause skin damage. Observation of boatmen, fishermen, lightermen, agricultural labourers and farmers revealed that skin cancer developed on areas most frequently exposed (e.g. hands, neck and face) (*19*). The exact process by which

TABLE 8.1 Summary of possible effects of solar ultraviolet radiation on the health of human beings.

Effects on skin
- Malignant melanoma
- Non-melanocytic skin cancer—basal cell carcinoma, squamous cell carcinoma
- Sunburn
- Chronic sun damage
- Photodermatoses.

Effects on the eye
- Acute photokeratitis and photoconjunctivitis
- Climatic droplet keratopathy
- Pterygium
- Cancer of the cornea and conjunctiva
- Lens opacity (cataract)—cortical, posterior subcapsular
- Uveal melanoma
- Acute solar retinopathy
- Macular degeneration.

Effect on immunity and infection
- Suppression of cell mediated immunity
- Increased susceptibility to infection
- Impairment of prophylactic immunization
- Activation of latent virus infection.

Other effects
- Cutaneous vitamin D production
  - — prevention of rickets, osteomalacia and osteoporosis
  - — possible benefit for hypertension, ischaemic heart disease and tuberculosis
  - — possible decreased risk for schizophrenia, breast cancer, prostate cancer
  - — possible prevention of Type 1 (usually insulin dependent) diabetes
- Non-Hodgkin's lymphoma
- Altered general well-being
  - — sleep/wake cycles
  - — seasonal affective disorder
  - — mood.

Indirect effects
- Effects on climate, food supply, infectious disease vectors, air pollution, etc.

exposure to sunlight causes skin cancer was not understood until relatively recently.

The incidence of skin cancer, especially cutaneous malignant melanoma, has been increasing steadily in white populations over the past few decades (*20*). This is particularly evident in areas of high UVR exposure such as South Africa, Australia and New Zealand. Human skin pigmentation has evolved over hundreds of thousands of years, probably to meet the competing demands of protection from the deleterious effects of UVR and maximization of the beneficial effects of UVR. Skin pigmentation shows a clear, though imperfect, latitudinal gradient in indigenous populations (*21*). Over the last few hundred years, however, there has been rapid migration of predominantly European populations away from their traditional habitats into areas where there is a mismatch of pigmentation and UVR. The groups most vulnerable to skin cancer are white Caucasians, especially those of Celtic descent (see Box 8.1) living in areas of high UVR. Further, behavioural changes particularly in fair-skinned populations, have led to much higher UV exposure through sun-bathing and skin-tanning. The

marked increase in skin cancers in these populations over recent decades reflects, predominantly, the combination of post-migration geographical vulnerability and modern behavioural patterns. It remains too early to identify any adverse effect of stratospheric ozone depletion upon skin cancer risk.

UVR and skin cancer

UVR exposure was first linked experimentally to skin cancer in the 1920s (*19*). Using a mercury-vapour lamp as a source of UVR, Findlay exposed mice experimentally to daily doses of UVR over 58 weeks. Malignant tumours developed in four of the six mice that developed tumours, leading to the conclusion that exposure to UVR could result in skin cancer (*19*). Epidemiologists' interest in this association was further stimulated by the possibility of human-induced damage to stratospheric ozone, first theorized in the 1970s. The International Agency for Research on Cancer in 1992 concluded that solar radiation is a cause of skin cancer (*14*). A summary of the evidence appears in Box 8.1.

Within the ultraviolet radiation waveband, the highest risk of skin cancer is related to UVB exposure. UVB is much more effective than UVA at causing biological damage, contributing about 80% towards sunburn while UVA contributes the remaining 20% (*22*). UVB exposure (from both sunlight and artificial sources) has been linked conclusively to cutaneous malignant melanoma (CMM) and non-melanoma skin cancer (NMSC) (*23*, *24*). Figure 8.2 shows diagrammatically the UV spectrum and the erythemal effectiveness of solar radiation in humans.

There is a strong relationship between the incidence (and mortality) of all types of skin cancer and latitude, at least within homogeneous populations. Latitude approximately reflects the amount of UVR reaching the earth's surface (*24*).

BOX 8.1 Evidence linking skin cancer to solar radiation

- Skin cancer—cutaneous malignant melanoma (CMM) and non-melanoma skin cancer (NMSC)—occurs predominantly in white populations. It is uncommon in populations with protective melanin pigmentation of the skin, e.g. Africans, Asians, Hispanics, etc.
- Especially common in fair complexioned individuals who freckle and sunburn easily, notably those of Celtic ancestry, e.g. Irish, Welsh, etc.
- Occurs primarily on parts of the body most often exposed to sunlight.
- Incidence of skin cancer is inversely correlated with latitude and shows a positive relation to estimated or measured levels of UVR.
- Outdoor workers with chronic sun exposure are at greater risk than indoor workers for NMSC. Indoor workers with intermittent sun intensive exposure appear more prone to CMM.
- Risk of skin cancer is associated with various measures of solar skin damage.
- Individuals with certain genetic skin diseases, such as albinism, are prone to skin cancer by virtue of their sensitivity to UVR.
- Experimental animals develop skin cancer with repeated doses of UVR (especially UVB).
- Most SCC and BCC have highly specific mutations of the tumour supressor gene p53 that are characteristic of UV-induced changes in model systems.

Source: adapted from reference 23

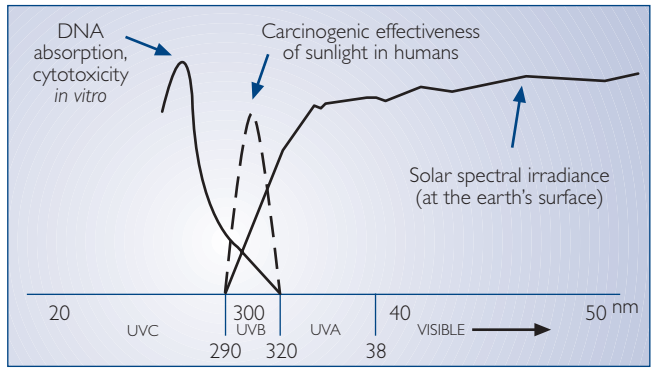


FIGURE 8.2 Biologically active UV radiation. Diagrammatic representation of the range of ultraviolet and visible radiation, the relative incidence of different wavelenghts (in nanometres) at Earth's surface, and the predicted source of cancer risk (carcinogenic effectiveness) as the product of both incident radiation and the experimentally-shown "action spectrum" for DNA damage (*25*). Source: reference 26.

This is due partly to the differing thickness of the ozone layer at different latitudes, and partly to the angle at which solar radiation passes through the atmosphere.

In response to UVB exposure the epidermis thickens via an increase in the number of cell layers (epidermal hyperplasia). This occurs particularly in people who do not tan readily. This thickening reduces the amount of UVB penetration to the basal layer providing partial natural protection against the harmful effects of UVR (*27*). Animal experiments indicate that despite this epidermal protection, further UVB exposure can act as a potent tumour promoter on damaged basal cells (*28*).

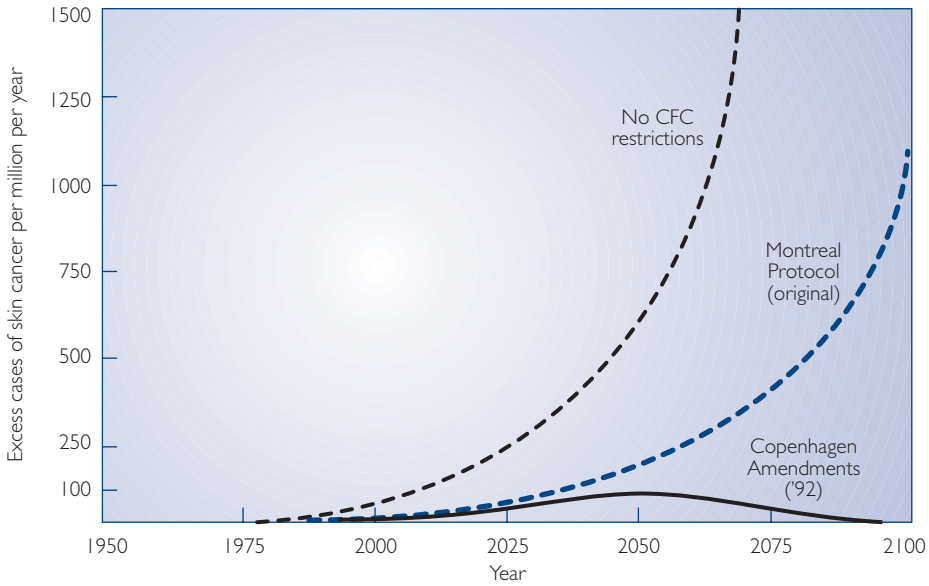
Ozone depletion and skin cancer

Scientists expect the combined effect of recent stratospheric ozone depletion, and its continuation over the next one to two decades, to be (via the cumulation of additional UVB exposure) an increase in skin cancer incidence in fair-skinned populations living at mid to high latitudes (*29*).

Future impacts of ozone depletion on skin cancer incidence in European and North American populations have been modelled (*30*). Figure 8.3 summarizes the estimates for the expected excess skin cancer incidence in the US white population, following three scenarios of ozone depletion. The first entails no restrictions on CFC emissions. The second, reflecting the original Montreal protocol of 1987, entails a 50% reduction in the production of the five most important ozone-destroying chemicals by the end of 1999. In the third scenario, under the Copenhagen amendments to that protocol, the production of 21 ozone-depleting chemicals is reduced to zero by the end of 1995. This (vertically integrated) modelling study estimated that, for the third scenario, by 2050 there would be a park relative increase in total skin cancer incidence of 5–10% in "European" populations living between 40°N and 52°N (based on a 1996 baseline of 2,000 cases of skin cancer per million per year in the United States and 1,000 cases per million per year in northwest Europen). The figure would be higher, if allowing for the ageing of the population. The equivalent estimation for the United States' population is a 10% increase in skin cancer incidence by around 2050.

It must be remembered that all such modelling makes simplifying assumptions and entails a substantial range of uncertainty. Not only is the shape of the UVR-cancer (dose-response) relationship poorly described in human populations, but also there is inevitable uncertainty about actual future gaseous emissions; the physical interaction between human-induced disturbances of the lower and

FIGURE 8.3 Estimates of ozone depletion and skin cancer incidence to examine the Montreal Protocol achievements. *Adapted from reference 30.*



middle atmospheres (including changes in cloud cover under conditions of climate change); and future changes in patterns of human exposure-related behaviours.

Eye disorders

Both age related macular degeneration (AMD) and cataract show associations with low or depleted antioxidant status and higher oxidative stress (smoking), suggesting common aetiological factors. Approximately 50% of incident UVA and 3% of UVB penetrates the cornea, where a further 1% of UVB is absorbed by the aqueous humor (*31*). Remaining UVR is absorbed by the lens, hence the UVR association with lens opacities is the most plausible. There is some evidence that sunlight exposure (possibly the blue light component) may be implicated in macular degeneration (*32*).

Solar radiation and risk of lens opacities: current level of evidence

The shorter wavelength constituents of solar radiation (notably UVA, UVB and UVC) are more damaging to biological molecules than is visible light. Although UVB is only 3% of the UVR that reaches the earth, it is much more biologically active than UVA.

In vivo and in vitro laboratory studies demonstrate that exposure to UVR, in particular to UVB, in various mammalian species induces lens opacification (*33*). The actual mechanisms remain unclear but a range of adverse effects is observed as a result of free radical generation from UVR energised electrons. There has been criticism that UVR doses in laboratory studies are much higher than those encountered in natural conditions (*34*). However, based on ambient UVA and UVB fluxes in the north-eastern United States, it has been estimated that 26 hours of continuous UVA exposure or 245 hours of continuous UVB exposures at those ambient levels would exceed the rabbit lens threshold for lens damage (*31*). While direct extrapolation from animal studies to humans is not possible it

is plausible that in humans, with much longer age spans than laboratory animals, cumulative damage to the lens from UVR could explain the high prevalence of lens opacities in elderly people.

There is mixed evidence for UVR's role in lens opacities in human populations (*35*). Cataracts are more common in some (but not all) countries with high UVR levels. However, few studies have examined whether UVR can explain differences between populations in the prevalence of lens opacities. One study of cataract surgical rates in the United States' Medicare programme estimated a 3% increase in the occurrence of cataract surgery for each 1° decrease in latitude across the United States (*36*). However, surgery rates are not a good measure of the prevalence of opacities in the population; they are influenced by service access and differences in the thresholds for eligibility for surgery. Studies in non-Western populations have provided some weak evidence for opacities being higher in areas with greater UVB radiation. These studies based on eye examinations included surveys among Australian Aboriginal populations (*37*); rural Chinese populations (*38*); and across areas of Nepal (*39*). These associations may have been confounded by other unmeasured lifestyle factors, such as diet.

Studies measuring UVR or outdoor exposure in individuals have shown inconsistent results. The strongest evidence is provided by a study of a high UVR-exposed group (fishermen), in the Chesapeake Bay Watermen Study in the United States (*40*, *41*), which showed an association between adult UVR dose and risk of cortical and posterior subcapsular opacities. In general population studies in the United States, UVR exposure was related to cortical opacities in one study (*42*) but not in another (*43*), or has been observed in men but not in women (*44*). Further support for the association with cortical opacities and UVR comes from mannikin studies showing the largest doses of UVR to be received by the lower and inner (nasal) lens—the site where cortical opacities predominate (*45*). Cortical opacities are rare in the upper lens. However, it has been suggested that the lack of an association between UVR and nuclear opacities may reflect failure to measure exposures occurring in earlier life (*46*). Since the nuclear material is the oldest in the lens capsule, the most relevant exposures are those that occur in early life. In India, where rates of lens opacities are higher than in Western populations, estimated lifetime sunlight exposure was associated with all types of lens opacities, including nuclear (*47*).

Few studies have been conducted in European populations. A hospital-based case control study conducted in Parma, northern Italy showed an increased risk of cortical cataracts with a four point scaled estimate of time spent outdoors (*48*). In a small population based study in the north of Finland, working outdoors was a risk factor for cortical cataracts in women, but not men (*49*). The POLA (Pathologies Oculaires Liées à l'Age) study showed a significant association between annual ambient solar radiation and cortical and mixed (mainly cortical and nuclear) cataracts, with a modest trend also in nuclear-only cataracts (*50*). The POLA study was undertaken in a small town in the south of France close to the sea where there were high levels of outdoor professional and leisure activities. The study also showed an excess risk of posterior subcapsular cataracts for people who were professionally exposed to sunlight (eg fishing, agriculture, building industry). Of the European studies, only that of POLA attempted to measure ambient UVR. Such measurements of UVR exposure (i.e. taking account of occupation, leisure and residence) rarely have been made in other European populations.

The Reykjavik Eye Study, a population-based study in Iceland, found a positive relationship between cortical cataract and time spent outside on weekdays (*51*). In Australia, the Melbourne Visual Impairment Project demonstrated a relationship between UVR and cortical cataract, as well as an interaction between ocular UVB exposure and vitamin E for nuclear cataract (*52*).

An evaluation of the possible risk from UVR must take account of both confounding factors and factors that may modify the association. Factors that may increase susceptibility to UVR-induced damage include poor nutrition and smoking. Smoking may act as an additional source of oxidative stress and consistently has been shown to increase the risk of cataract. Antioxidant micronutrients may enhance the free radical scavenging defence system of the eye. There is some evidence that low dietary intakes of vitamins C, E and carotenoids increase cataract risk (*53*, *54*).

Solar radiation effects on the cornea and conjunctiva

Acute exposure of the eye to high levels of UVR, particularly in settings of high light reflectance such as snow-covered surroundings, can cause painful inflammation of the cornea or conjunctiva. Commonly called snow-blindness, photokeratitis and photoconjunctivitis are the ocular equivalent of acute sunburn.

Pterygium is a common condition that usually affects the nasal conjunctiva, sometimes with extension to the cornea. It is particularly common in populations in areas of high UVR or high exposure to particulate matter. Studies of the Chesapeake Bay watermen showed a dose-response relationship between history of exposure to UVR and risk of pterygium (*55*). Others have found measures of UV exposure to be strongly related to pterygium risk (*56*, *57*). In a large population-based study in Melbourne, almost half of the risk of pterygium was attributable to sun exposure (*58*).

Effects on the retina

Other eye disorders associated with UVR are uncommon but cause significant morbidity to affected individuals. Acute solar retinopathy, or eclipse retinopathy, usually presents to medical attention soon after a solar eclipse when individuals have looked directly at the sun. Effectively this is a solar burn to the retina. Usually the resulting scotoma resolves but there may be permanent minor field defects. Several cases of solar retinopathy in young adults, possibly related to sun-gazing during a period of low stratospheric ozone in the United States, have been described (*59*, *60*).

Immune system function and immune-related disorders

Although most of the available evidence comes from studies of experimental animals, it appears that ultraviolet radiation suppresses components of both local and systemic immune functioning. An increase in ultraviolet radiation exposure therefore may increase the occurrence and severity of infectious diseases and, in contrast, reduce the incidence and severity of various autoimmune disorders. The damping down of the T lymphocyte (helper cell type 1), or "T_H1", component of the immune system may alleviate diseases such as multiple sclerosis, rheumatoid arthritis and insulin-dependent (Type 1) diabetes. Undifferentiated T_H0 cells are immunologically primed to develop into either T_H1 or T_H2 cells; in animals these two groups are thought to be mutually antagonistic (*61*). Thus UVR

exposure theoretically could worsen T_H2-mediated disease by suppressing T_H1 cell function (*62*), however, more recent work has shed some doubt on this notion. In mice UVR exposure is associated with decreased systemic T_H2 as well as T_H1 immune responses (*63*). UVR leads to increased secretion of the cytokine, interleukin (IL)-10 (*64*) appears to suppress T_H1 and T_H2 cytokine responses to external antigens (*65*). Much remains unknown. Partly in response to questions about the biological impacts of stratospheric ozone depletion, among scientists there is new interest in assessing the influence of ultraviolet radiation upon immune system function, vitamin D metabolism (see Box 8.2) and the consequences for human disease risks.

Recent research suggests that UVR exposure can weaken T_H1-mediated immune responses through several mechanisms:

- UVR can cause local epidermal immunosuppression and a reduction in contact hypersensitivity (CH) and delayed type hypersensitivity (DTH) (*62*);
- UVR acts to convert urocanic acid (UCA) from the *trans*-UCA form to its isomer, the *cis*-UCA form, within the stratum corneum (*64*). This process induces changes in epidermal cytokine profiles from a wide range of cell types. UVR-induced DNA damage also alters cytokine profiles, leading to immunosuppression (*64*). Liposome therapy with a DNA repair enzyme can prevent UVR-induced cytokine alterations such as the upregulation of IL-10 (*66*). Importantly, subepidermal cytokine signalling alterations also can induce soluble products that can exert systemic immunosuppression (*61*);
- sunlight suppresses secretion of the hormone melatonin. Activation of melatonin receptors on T helper cells appears to enhance T lymphocyte priming and the release of T_H1 type cytokines such as interferon gamma (*67*);
- a role for UVR in promoting the secretion of melanocyte stimulating hormone (MSH), which may suppress T_H1 cell activity, also has been proposed (*68*);
- the active form of vitamin D ($1,25(OH)_2D_3$), derived from UVR-supported biosynthesis has well-documented immunomodulatory effects. Peripheral monocytes and activated T helper cells have vitamin D receptors, vitamin D or its analogues can down-regulate T helper cell activity (*69*).

Overall, these findings indicate that UVR suppresses T_H1-mediated immune activity. It is important to note that part of this effect occurs independently of vitamin D.

Possible effect on human infectious disease patterns

Higher UVR exposure could suppress the immune responses to infection of the human host (*70*). The total UVR dose required for immune suppression is likely to be less than that required for skin cancer induction but direct human data are not available. In animals, high UVR exposure has been shown to decrease host resistance to viruses such as influenza and cytomegalovirus, parasites such as malaria and other infections such as *Listeria monocytogenes* and *Trichinella spiralis* (*71*). However, significant inter-species variation in UVR-induced immune suppression and other differences in host response to infection limit direct extrapolation of these findings to humans.

Recently, data from these animal studies have been used to develop a model to predict the possible changes in infection patterns in humans due to increased UVR resulting from stratosphere ozone depletion (*72*). Importantly, the model did account for likely inter-species variation in susceptibility to UVR-induced

TABLE 8.2 Predicted effects of stratospheric ozone decreases on the biologically effective ultraviolet irradiance, and hence, on suppression of the specific cellular immune responses to Listeria bacteria (local noon, clear skies, southern Europe).

Latitude (month)	Decrease in ozone (%)	Ozone (dobson units)	Biologically Effective irradiance (W/m^2)	Increase in BE_{imm} %	RAF_{imm}	Calculated time (min) for 50% immunosuppression[a]
40 °N	0	335.6	0.073	0.0	—	350
January	5	318.8	0.075	3.0	0.60	340
	10	302.0	0.078	6.3	0.63	327
	20	268.5	0.083	13.5	0.68	307
40 °N	0	307.9	0.278	0.0	—	92
July	5	292.5	0.285	2.5	0.50	90
	10	277.1	0.292	5.3	0.53	87
	20	246.3	0.310	11.5	0.58	82

Abbreviations: BEI_{imm}, biological effective irradiance for immunosupression: RAF_{imm}, radiation amplification factor for immunosupression.

[a] Lymphocyte proliferation in response to Listeria bacteria.

Source: adapted from reference 72.

immunosuppression. The theoretical model demonstrated that outdoor UVB exposure levels could affect the cellular immune response to the bacteria *Listeria monocytogenes* in humans. Using a worst-case scenario (sun-sensitive individuals with no UVR adaptation), ninety minutes of noontime solar exposure in mid-summer at 40 °N was predicted to lead to a 50% suppression of human host lymphocyte responses against *Listeria monocytogenes*. A 5% decrease in ozone layer thickness might shorten this exposure time by about 2.5% (*72*) (Table 8.2).

Human epidemiological studies are required to confirm the findings from laboratory or animal studies. They also are needed to provide clearer risk assessments of the adverse immunosuppressive effect of increased UVR exposure. Such studies also should consider the role of vitamin D in host resistance to infection.

Personal UVR exposure in humans has been demonstrated to increase the number and severity of orolabial herpes simplex lesions (i.e. around the mouth). Recent questions have been raised about the potential adverse consequences of UVR-induced immunosuppression for HIV-infected individuals. A 1999 review concluded that despite experimental evidence in laboratory animal studies demonstrating HIV viral activation following UV radiation, there were no data in humans that consistently showed clinically significant immunosuppression in HIV-positive patients receiving UVB or PUVA therapy (*73*). A small follow-up study of HIV-positive individuals failed to detect any association between sun exposure and HIV disease progression. However, the review concluded that larger follow-up studies were required to assess fully this important issue (*73*).

Increased UVR exposure: a possible effect to reduce vaccine efficacy?

There has been concern that increased exposure to UVR due to stratospheric ozone depletion could hamper the effectiveness of vaccines, particularly BCG, measles and hepatitis (*70*). BCG vaccine efficacy has a latitudinal gradient with reduced efficacy at lower latitudes. Seasonal differences in vaccine efficacy have been observed for hepatitis B (*74*). While this ecological observation may reflect other latitude-related factors, it is also consistent with UVB depressing an effective host response to intradermally administered vaccines (*75*).

In animal studies, pre-exposure to UVB prior to intradermal vaccination with *Mycobacterium bovis* (BCG) impairs the DTH immune response of the host animal to mycobacterial antigens (*62*). Local UV irradiation of the skin prior to, and following, inoculation decreases the granulomatous reaction to lepromin in sensitised individuals (*76*). Overall these studies indicate that a potential health effect of increased UV exposure could be reduced vaccine efficacy particularly for vaccines that require host immune responses to intradermally administered antigens.

Non-Hodgkin's Lymphoma

The incidence of Non-Hodgkin's Lymphoma (NHL) has increased greatly worldwide in recent decades. The reasons for this increase are not known but high personal UVR exposure has been suggested as a possible contributary factor, for the following reasons:

- NHL incidence in England and Wales is positively associated with higher solar UV radiation by region (*77*);
- patients with NHL also have been noted to have an increased likelihood of non-melanoma skin cancer;
- chronic immunosuppression is an established risk factor for NHL and, as discussed, UVR has immunosuppressive effects on humans.

BOX 8.2 The beneficial role of UVR for Vitamin D synthesis in humans

The active metabolite of Vitamin D ($1,25(OH)_2\ D_3$) is a human hormone with an important role in calcium and phosphorous regulation in humans. It also has other important roles. In 1822, the link between sunlight deprivation and the bone disease rickets was postulated. This link was confirmed in the early 1900s by experiments that showed that sunlight exposure could cure rickets. More recently, vitamin D has been shown to have an important role in the immune system and also may be important in the growth of neural tissue during early life. Furthermore, vitamin D receptors (VDR) have now been located in a variety of cells (e.g. brain, breast and pancreas).

Sunlight exposure is the primary determinant of vitamin D levels in terrestrial vertebrates, including humans. UVB rays enter the epidermis and release energy that changes a pre-existing cholesterol metabolite to previtamin D and its isomer cholecalciferol. Cholecalciferol (25(OH)D) is carried in the blood stream to the liver and then kidney, where, after a series of biological reactions, the active vitamin D hormone ($1,25(OH)D_3$) is formed. Circulating serum 25(OH)D concentration provides an integrated assessment of vitamin D intake and stores (*79*).

The exact dose of UVR exposure for optimal vitamin D levels is not known particularly as the required UVR dose will be influenced by host factors such as skin pigmentation, vitamin D receptor gene allelic status and dietary vitamin D intake. Whole body exposure in a bathing suit to one minimum erythemal dose of UVR is equivalent to ingesting 10 000 international units of vitamin D. It is important to note that while excessive dietary vitamin D can lead to vitamin D toxicity, excessive UVR exposure cannot lead to vitamin D toxicity.

Source: adapted from references 80 and 81

A causal link has not been established (*78*). Nevertheless, NHL is a disease that should be monitored closely because of its possible increase with any future increases in UVR.

Is UVR exposure beneficial for some autoimmune diseases?

Recent developments in photoimmunology and epidemiology suggest that UVR may have a beneficial role in autoimmune diseases such as multiple sclerosis (MS), type 1 diabetes mellitus (IDDM) and rheumatoid arthritis (RA). Each of these autoimmune diseases is characterized by a breakdown in immunological self-tolerance that may be initiated by an inducing agent such as an infectious micro-organism or a foreign antigen (*82*). A cross-reactive auto-immune response occurs and a "self-molecule" is no longer self-tolerated by the immune system. At this stage, the host tissue becomes immunogenic, attracting a T helper cell type 1 (T_H1) mediated immune response resulting in chronic inflammation (*82*). That is, the T_H1 lymphocytes no longer recognise the host tissue as such and instead try to eliminate the host tissue by inflammation.

The well-established gradient of MS increasing with increasing latitude may reflect differential UV-induced immune suppression of autoimmune activity. That is, at lower latitudes where MS prevalence is lower high levels of UVR exposure may dampen down the immune over-activity that occurs in MS. In particular, the autoimmune profile of MS is characterized by disturbances of those T cell-related activities specifically affected by UVB (*83*). A strong inverse association between UVR exposure and MS has been shown. In Australia the negative correlation between regional UVR and MS prevalence is higher than the magnitude observed for the positive correlation between regional UVR and malignant melanoma (*84*).

A recent case-control study found that compared to indoor workers living in a low sunlight region, the odds ratios for an outdoor worker dying from MS in low, medium and high residence sunlight were, respectively, 0.89 (with 95% confidence intervals of 0.64 to 1.22), 0.52 (0.38, 0.71) and 0.24 (0.15, 0.38) (*85*). Thus high residential and occupational solar exposure (in combination) were associated with a reduced likelihood of MS. UVR may affect not only the development of MS but also its clinical course. An ecological study recently has shown a striking inverse correlation between serum 25(OH) D, a metabolite of vitamin D, and high MS lesion activity (*86*).

For type 1 diabetes, a disease resulting from T cell-mediated inflammation with destruction of pancreatic tissue, the epidemiological evidence also suggests a possible beneficial role for UVR. An increasing disease prevalence gradient with increasing latitude has been noted. In a Finnish birth cohort study, vitamin D supplementation in infancy was inversely associated with subsequent type 1 diabetes (relative risk 0.22 {0.05, 0.89}) (*87*). Vitamin D receptor gene allelic status has been found to relate to MS and type 1 diabetes in some populations (*88*). For rheumatoid arthritis, dietary supplementation with vitamin D has been related to lower levels of disease activity (*89*).

Overall, the epidemiological features of these three autoimmune diseases are consistent with a protective effect for high personal UVR exposure. However, the data are not conclusive and further research work is required.

UVR and other diseases with immune dysfunction

Although the three diseases above are characterized by T_H1 cell over-activity, other immune diseases may be characterized by T_H2 cell over-activity or a mixed

T cell over-activity pattern. Systemic lupus erythematosus (SLE) is characterized by a mixed T_H2/T_H1 disturbance. It has been postulated that the immune dysfunction in SLE begins under the skin where UV-induced keratinocytes produce antigens that are recognized by the body to be foreign (*90*). UVR plays a major role in the induction of lesions of patients with the cutaneous form of lupus disease and photo-aggravation of systemic disease may occur in systemic SLE (*91*).

Atopic eczema, a disease of immune disturbance that includes T_H2 over-activity, appears to be inversely related to UVR. Strong latitudinal gradients for increasing eczema with increasing latitude have been reported in the Northern Hemisphere (*92*). In a clinical trial, narrow-band UVB therapy significantly improved allergic eczema (*93*). Thus, high UVB exposure appears to have a beneficial effect on the immune disorder of atopic eczema even though this disease is not characterized by a purely T_H1 immune over-activity pattern.

Other diseases that could be exacerbated by decreased UVR exposure, particularly if dietary vitamin D sources were inadequate

Although a detailed discussion is beyond the scope of this chapter, it should be noted that inadequate UVR exposure in the absence of adequate dietary D sources, could lead to vitamin D deficiency. This would increase the likelihood of rickets, osteomalacia, osteoporosis, muscle pain and possibly hypertension (*94*) or ischaemic heart disease (*95*). Certain cancers (e.g. prostate and breast) have been linked to vitamin D deficiency, although not conclusively (*80*). Vitamin D deficiency may increase tuberculosis (TB) risk (*96*). Evidence suggests that the explanation for this may reflect the immunological modulation caused by vitamin D. Vitamin D activates one group of white blood cells, the monocytes, thereby increasing their capacity to resist cell infection by the mycobacterium (*96*). Further, a recent case-control study showed that the combination of vitamin D deficiency and the "high-risk" allele of the vitamin D receptor gene was strongly associated with the occurrence of TB (*97*).

During pregnancy, inadequate maternal UVR exposure in the absence of adequate dietary vitamin D sources will lead to low foetal exposure to vitamin D. As vitamin D appears to be important in neural growth this could influence the developing brain of the foetus. In fact, this has been proposed as an explanation for the finding that winter-born babies appear at increased risk of schizophrenia (*98*). Furthermore, inadequate UVR exposure usually is associated with reduced visible light and a reduction in photoperiod. This will alter melatonin levels, a hormone important in maintaining the rhythm of wake/sleep patterns. Changes in photoperiod also have been related to seasonal affective disorder (*99*). Although not well understood, the relationship between solar radiation and mood is important to consider (*100*).

Public health message re UVR exposure

Encouraging total sun avoidance (with the related notion of solar radiation as a "toxic" exposure) is a simplistic response to the hazards of increased ground level UVR exposure due to stratospheric ozone depletion, and should be avoided. Any public health messages concerned with personal UVR exposure should consider the benefits as well as the adverse effects. The notion that UVR is inherently an adverse exposure to be maximally avoided cannot fully be reconciled with evolutionary heritage. It is a reasonable presumption that levels of skin pigmentation in regional populations originally evolved over many millennia to optimise

the amount of UVR absorbed by the skin in order to balance biological benefits and risks. The possible benefits and adverse effects of UVR exposure on human health therefore should be assessed concurrently (*100*).

Many modern infants and young children already receive less solar radiation than children several decades ago. This reflects an increase in indoor living and medical recommendations promoting sun avoidance advice (*100*). A growing recognition of low winter 25(OH) D levels, particularly among children of Asian origin residing in the United Kingdom, has led to the current United Kingdom recommendation that all pregnant women and children up to age five should have a vitamin D supplement, unless solar and dietary sources are adequate (*101*). Clear guidelines on the optimal age-appropriate solar radiation dose are not yet available (*101*) and are difficult to formulate because the recommended level of appropriate solar radiation depends on host factors as described above. However, the lack of clear recommendations could lead to inappropriate personal solar exposure. For example, a recent case report of severe rickets in a Caucasian child residing in Toronto, Canada, highlighted the possible adverse effects of inadequate UVR exposure in childhood (*102*). The child went outdoors in summer but was always covered by potent sunscreen. The child's rickets subsequently responded well to dietary vitamin D. This case highlights the importance of considering UVR as an exposure that requires titration rather than avoidance.

Although measured UVR exposures are proportional to ambient UVR for similar population groups, there is a wide variation in inter-personal UVR exposure within each of these groups. Some individuals may have only one-tenth of the population average for UVR exposure, others may have an individual UVR exposure of ten times the average (*12*). The factors affecting this large inter-individual variation are not well understood. In addition to the difficulty in quantifying both UVR exposure and inter-individual variation in susceptibility to UVR, this large variation in sun exposure behaviour makes difficult the correct titration of UVR at a population level.

To negate the adverse effects of increased UVR exposure due to ozone depletion, an alternative response to that of careful titration of sun exposure dose is, in theory, to recommend total sun avoidance and large-scale vitamin D supplementation. However this approach:

- runs the possible risk of hypervitaminosis D with resultant hypercalcaemia, a documented cause of infant mortality 40 years ago;
- neglects the possible benefits of UVR exposure than are not mediated via vitamin D;
- neglects that other beneficial factors such as visible light exposure are correlated with UVR exposure.

Conclusions

The occurrence of stratospheric ozone depletion over the past quarter-century, and its anticipated continuation for at least the next several decades, has focused attention on questions about the impact of UVR on human biology and disease risks. This has coincided with a growth of knowledge about some of the basic biological pathways via which UVR affects human biology. In particular, it is evident that a change in levels of UVR exposure will affect the incidence of skin cancer, and is likely to affect the incidence of several ocular disorders, including cataract, and various immune-related diseases and disorders.

Uncertainties remain about the extent to which the loss of stratospheric ozone to date has resulted in increases in ground-level UVR. Environmental monitoring systems often have been unstandardized, non-spectral, and suboptimally located. Climate-related changes in cloud cover appear to have compounded the relationship between ozone depletion and ground-level UVR.

The majority of the known health consequences of increased UVR exposure are detrimental. However, UVR exposure also has some beneficial effects. Therefore, while excessive solar exposure should be avoided—the more so during the current and foreseeable period of stratospheric depletion—so should excessive sun avoidance. Future public health advice about solar exposure should take account of the changing ambient UVR environment and the available knowledge about the health risks and benefits of UVR exposure.

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