Health risks

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Abstract

The health risks associated with ozone depletion will principally be those due to increased ultraviolet B (UV-B) radiation in the environment, i.e., increased damage to the eyes, the immune system, and the skin. Some new risks may also be introduced with the increased use of alternatives to the ozone-depleting substances (ODSs). Quantitative risk estimates are available for some of the UV-B-associated effects, e.g., cataract and skin cancer; however, the data are insufficient to develop similar estimates for effects such as immunosuppression and the toxicity of alternatives. Ocular damage from UV exposure includes effects on the cornea, lens, iris, and associated epithelial and conjunctival tissues. The most common acute ocular effect of environmental ultraviolet radiation (UVR) is photokeratitis. Also known as snowblindness in skiers, this condition also occurs in other outdoor recreationists. Chronic eye conditions likely to increase with ozone depletion include cataract, squamous cell carcinoma, ocular melanoma, and a variety of cornet/conjunctival effects, e.g., pterygium and pinguecula. Suppression of local (at the site of UV exposure) and systemic (at a distant, unexposed site) immune responses to a variety of antigens has been demonstrated in both humans and animals exposed to UV-B. In experiments with animals these effects have been shown to worsen the course/outcome of some infectious diseases and cancers. There is reasonably good evidence that such immunosuppression plays a role in human carcinogenesis; however, the implications of such immunosuppression for human infectious diseases are still unknown. In light-skinned populations, exposure to solar UVR appears to be the most important environmental risk factor for basal and squamous cell carcinomas and cutaneous melanoma. Originally it was believed that total accumulated exposure to UVR was the most important environmental factor in determining risk for these tumors. Recent information now suggests that only squamous cell carcinoma risk is related to total exposure. In the cases of both basal cell carcinoma and melanoma, new information suggests that increases in risk are tied to early exposures (before about age 15), particularly those leading to severe sunburns. Testing of a number of the chlorofluorocarbons (CFC) alternatives indicates that most of these chemicals have low acute toxicity, and low to moderate chronic toxicity. Some chemicals that were originally proposed as alternatives have been dropped from consideration because these tests raised concerns about toxicity and/or manufacturing difficulties. In one instance, high accidental occupational exposure was associated with liver damage, underlining the need for care in the use of these substitutes. Recent quantitative risk estimates have been developed for cataract, melanoma, and all skin cancers combined. These estimates indicate that under the Montreal Adjustments, cataract and skin-cancer incidence will peak mid-century at additional incidences of just under 3 per 100 000 and about 7 per 100 000, respectively. © 1998 UNEP. Published by Elsevier Science S.A. All rights reserved.

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1. Introduction

Nearly everyone and indeed every living thing is likely to be exposed to sunlight and the UV-B it contains for various periods during their life. In humans and animals, exposure is principally via the eyes and skin, with effects occurring as a result of the absorption of solar energy by molecules (termed chromophores) present in the tissues/cells of these organs. As displayed in Fig. 1, the absorption of light energy leads to changes in these molecules that eventually can result in a biological effect.
Chromophores absorb light energy at various wavelengths with differing efficiencies. This pattern of absorption is called an absorption spectrum and is characteristic of the type of molecule involved. Fig. 2 shows absorption spectra for five of the chromophores present in skin and eye tissues that are thought to be important to the biological effects of UV-B in humans and animals. These are DNA, tyrosine and tryptophan (two amino acids that are largely responsible for the UV absorbance of proteins), trans-urocanic acid (a molecule present in large amounts in the outermost layer of skin), and melanin (the principal pigment of the skin). The gray area in Fig. 2 marks that part of the UV spectrum, wavelengths under 290 nm, which is not present in terrestrial energy. Thus only those portions of these absorption spectra appearing in the white area (above 290 nm) are likely to be of any relevance to the effects associated with environmental exposures. As Fig. 2 indicates, for all of the molecules except melanin, absorption efficiency drops rapidly within the terrestrial UV-B spectral region with little or no absorbance in the UVA spectral region (above 320 nm). Thus the increase in UV-B that accompanies ozone depletion will increase the amount of biologically active radiation present in ambient sunlight. While it is difficult to predict quantitatively exactly how these increases will be distributed globally, such increases have been observed in a variety of sites across the world. Because of the biological activity of UV-B, such increases are likely to have marked consequences for humans as well as other living creatures. Some of these consequences could be beneficial, e.g., a greater production of vitamin D in the skin of humans, but far more are likely to be detrimental.

This paper presents an overview of the consequences likely to accompany increases in UV-B. It will focus on the possible health risks and only briefly mention possible beneficial effects when these might offset adverse effects or when concerns about them might modify adaptive strategies. The paper’s design is adapted from a four-step risk-assessment approach. It first identifies the hazards. Secondly, it discusses a variety of factors that can modify exposure or susceptibility. Thirdly, it presents quantitative and qualitative estimates of risk with their attendant uncertainties, and fourthly, it ends with a brief discussion of potential risks associated with several of the strategies being adopted to manage or mitigate risk.

2. Hazards for humans

Humans have three major organ systems whose cells and tissues are commonly exposed to sunlight: the eye, the immune system, and the skin, and it is in these three systems that the effects of sunlight on health have been documented. The cells/tissues exposed in the eye are principally those associated with the cornea, the iris, and the lens; those of the skin include the outermost layer of the skin, the stratum corneum, and the epidermis; and those of the immune system are the Langerhans (or antigen-presenting) cells that reside in, or migrate through, the epidermis.

Each of the different types of UV-exposed tissues contains a collection of chemical substances the light-absorbing properties of which can contribute to the process shown in Fig. 1. Furthermore, the organ systems are structured such that some tissues/cells will absorb part of the UV energy before it reaches others. Thus the spectrum of light that first hits the surface of an organ such as the skin is not the same as that reaching tissues/cells located deeper, e.g., in the basal layer of the epidermis. As a result, the wavelength dependence, or action spectrum, of a particular end-point of concern rarely looks exactly like the absorption spectrum of a particular chromophore. Fig. 3 shows action spectra for several of the more important effects, sunburn, DNA damage (dimers), and carcinogenesis, that will be discussed in detail below. Note again that only absorbance above 290 nm is relevant to environmental exposures.

2.1. Effects on the eye

As indicated above, the eyes are a principal route of exposure to ultraviolet radiation (UVR). As illustrated in Fig. 4, when sunlight (and the UVR it contains) impinges on the
normal eye, the cornea is encountered first, then the lens, the vitreous humor, and the retina. Studies indicate that due to its absorption by various molecules in the cornea and the lens, most UVR never reaches the retina in the normal adult eye. In the case of ambient UVR (i.e., UV-B and UV-A), the shorter wavelengths are absorbed preferentially, with the cornea absorbing most of the radiation below 300 nm, and the lens absorbing almost all of the rest of the UVR below about 370 nm [1]. Lens removal (as for the treatment of cataract) does place the retina at risk for UV damage; it is for this reason that many artificial replacement lenses are made with UV-absorbing materials.

2.1.1. Effects on the cornea/conjunctiva

The ocular effect most directly attributable to environmental exposures to UVR is photokeratitis. The ocular equivalent of sunburn, this effect occurs after an acute, i.e., short-term, exposure and is characterized by reddening (inflammation) of the eyeball, gritty feeling of severe pain, tearing, photophobia (avoidance of light), and blepharospasm (twitching). Frequently diagnosed in skiers as ‘snowblindness’, photokeratitis is also seen in beach-goers and others involved in outdoor recreation [2]. Mechanistic studies have revealed that human corneal stromal cells when exposed to low doses (10–100 mJ cm$^{-2}$) either in vitro or in situ show significant increases in the production of a number of biologically active chemicals, i.e., cytokines. The cytokines detected, interleukin (IL) -1, IL-6, IL-8, and tumor necrosis factor alpha (TNFα), are pro-inflammatory and may be responsible for the inflammation that accompanies photokeratitis [3].

Additional ocular effects on the cornea/conjunctiva attributed to solar exposure are climatic droplet keratopathy (CDK), pinguecula, pterygium, and squamous cell carcinoma (SCC) of the cornea and conjunctiva. CDK is a degeneration of the fibrous layer of the cornea with the accumulation of droplet-shaped deposits. Pterygium results from an outgrowth of the conjunctiva (outermost mucous layer) over the cornea, which results in the loss of transparency, pinguecula is a raised opaque mass just adjacent to the cornea [4], and SCC is a malignant neoplasm similar to those found on sun-exposed skin. Data supporting the relationship between solar exposure and disease are strongest with CDK and pterygium; epidemiological studies indicate that chronic exposure to the sun, and, most probably UV-B, is an important factor in the development of these diseases. Both are associated with outdoor living or working in environments with high surface reflectance, e.g., water, sand, concrete [4–6]. Interestingly, in a recent study of pterygium, a much-increased risk (36-fold) was found in people with early, intense exposures (residing at 30°S latitude or less for the first five years of life). This was independent of the almost 40-fold increase in risk associated with a work environment below 30°S between the ages of 20 and 29 [6]. Data linking pinguecula to solar exposure are largely anecdotal or based on case reports [7], although Taylor et al. [5] found a weak association between pinguecula and UVR exposure in the Maryland Watermen study.
A recent study of SCC of the eye [8] examined incidence data from across the world in order to assess whether solar UVR is a risk factor for this disease. The study focused on conjunctival and corneal lesions, excluding those on the eyelid, and developed estimated daily UV-B exposures weighted using the erythemal action spectrum. Because HIV infection increases the risk of conjunctival SCC, and two African centers have seen substantial increases in this tumor in the past 5–10 years, the analysis looked at two data sets, one including data from Africa and one excluding these data. With the African data, the study found an increase in incidence of SCC of the eye with UV-B exposure that is equivalent to almost a 50% increase in incidence for every 10° decrease in latitude. Without the African data, an equivalent 40% decline was found for each 10° increase in latitude.

2.1.2. Effects on the uveal tract

The uveal tract consists of the iris, ciliary body, and choroid. Malignant melanoma of the uveal tract is the most commonly occurring primary ocular malignancy. Rare in Blacks, in white patients it most commonly occurs in the choroid [9], but also occurs in the iris. Several epidemiological studies [10] found an increased risk of intraocular melanomas associated with sensitivity to UV. In these studies, sensitivity to sunburn was associated with almost a two-fold increase in risk of intense UV exposures, e.g., prior history of a welding burn or snow blindness, was associated with more than a seven-fold increase in risk. Others have found the evidence less than compelling [11,12]. The latter analysis, however, examined only the hypothesis of a direct effect of UV on the affected cells (i.e., a DNA-damaging effect) and did not evaluate the role of indirect effects that might contribute to carcinogenesis, such as immunosuppression associated with increased production of cytokines [3]. That such processes can occur following UV exposure of the eyes is suggested by the recent finding that in mice, high ocular doses of UV-B can produce systemic immunosuppression equivalent to that obtained by skin irradiation. Furthermore, severing the optic nerve prevented this immunosuppression [13].

2.1.3. Effects on the lens

Of all of the ocular diseases associated with solar exposure, that which affects the lens, cataract, is by far the most important from a public health perspective. Characterized by a gradual loss in the transparency of the lens (due to the accumulation of oxidized lens proteins) [2], the end result is frequently blindness, unless the affected lens is surgically removed.

Several different kinds of cataract are distinguished based on their location in the lens. Cortical cataracts develop in the outer layers of lens protein, commonly called the cortex of the lens. Nuclear cataracts occur in the inner layers of lens protein, i.e., the nucleus of the lens. Posterior subcapsular cataracts (PSCs) occur at the back (posterior) interface of the lens and its epithelial capsule. A fourth form of cataract is mixed, i.e., combining elements of two or more of the aforementioned forms. In a recent Italian-American case-control study of individuals aged 45–79 years, pure cortical cataract accounted for slightly less than 50% of cases, pure nuclear cataract accounted for about 10%, pure PSC for less than 3%, and mixed for about 40%, with the majority of the mixed having a cortical component [14,15].

The epidemiological evidence identifying exposure to UV-B as a risk factor for cataract suggests that the risk may be limited to pure or mixed cortical cataracts and PSC with the exception of the nuclear/cortical combination [15]. In the case of cortical cataract, a number of studies have indicated that the relative risk associated with increased sun exposure is between about one- and three-fold [14,16–18]. In the Beaver Dam Eye Study, this places heavy sun exposure about on a par with diabetes or heavy drinking as a risk factor [16].

The economic and social importance of cataract is enormous. It is the leading cause of blindness in the world [17], with public health-care costs for cataract surgery in the US exceeding $3 billion in 1992. With the prevalence of cataract after age 30 approximately doubling each decade, anything that accelerates onset by 10 years (e.g., the increase in UV achieved in moving from the northernmost to the southernmost regions of the US) would double the number of operations [19].

2.2. Effects on the immune system

In humans, the skin is the principal barrier to the outside world, and thus the first line of defense against foreign agents that may threaten health. In order to fulfill this role, the skin hosts a number of cells from the immune system that can mount or modify immune responses against such ‘foreign invaders’ or against skin cells that have become ‘strange’, e.g., by virus infection or transformation into a cancer cell. However, to function optimally, the immune system needs to be able to discriminate between ‘self’ and ‘strange’ or ‘non-self’, and eliminate only the latter, especially if it is (potentially) harmful.

2.2.1. Immunosuppression

As mentioned above, the skin contains a wide range of molecules, including both proteins and DNA, which undergo photochemical reactions upon absorbing UVR. It is quite likely that a great many of the cell-surface proteins that are used to determine ‘self’ are modified in such photochemical reactions so that at certain UV doses, the skin becomes swamped with ‘non-self’ cells. Were the immune system to react to all of these cells, the resulting inflammatory response might compromise other important skin functions. For this reason, it is believed that the decreased immune responses observed after UV irradiation serve to prevent excessive inflammation and damage to the skin that has been exposed to the sun. The drawback of this postulated beneficial physiological response is that it may be detrimental when it coincides with the entry of an infectious agent, or the development of a cancer cell, against which a forceful immune reaction
needs to be mounted. These immunosuppressive effects of UV exposure can thus result in adverse circumstances: i.e., implants of UV-induced tumors between genetically identical mice are rejected in a naive, unexposed host, but they fail to be rejected in a UV-exposed host [20]. Such a UV-induced immune suppression has also been found for contact hypersensitivity (CH) reactions (a type of immune reaction seen following skin contact with certain reactive chemicals, e.g., poison ivy) [21–23]. It is also seen in delayed-type hypersensitivity (DTH) reactions (the kind of immune response made against virus-infected cells and certain microorganisms) [24]. Fig. 5 shows the two phases of the contact allergy response. UV irradiation can decrease both the induction of new responses through immunization and the elicitation of established immunity. Furthermore, immune suppression can occur locally, within UV-irradiated skin, or systemically at distant sites, depending on the dose of UV and the type of immune response.

Clearly, the switch from an immune reaction to UV-induced suppression of it needs to be well tuned; at one extreme, too much suppression could render an individual susceptible to infections, whereas at the other extreme, too little could result in skin-damaging inflammatory reactions upon UV exposure. The latter would resemble what has commonly been referred to as an allergic reaction to sunlight (a ‘sun allergy’), that a physician would diagnose as a photodermatosis, e.g., UV-B-induced polymorphic light eruption, PLE. This disease can often be treated successfully by subjecting the skin to a series of gradually increasing UV-B irradiations, which are thought to permit the skin to adapt slowly to the effects of UVB [25]. Thus, PLE patients appear to suffer from a compromised adaptation response; their immune response can adapt to small changes in UV-B, but is overwhelmed by large ones. This could explain why PLE is more common toward the poles [26], where the seasonal UV modulation is greatest. If, as projected, large decreases in ozone occur during the wintertime at higher latitudes, one would expect to see a decrease in the seasonal UV modulation at these locations and a lowered incidence of PLE.

2.2.2. Mechanisms

Immunological reactions tend to be rather complex because they involve multiple simultaneous processes that can act in concert or in opposition to one another. The impact of UV irradiation appears principally to be on cellular immune responses that are mediated through direct cell contact; usually it does not affect humoral immunity that is mediated through blood-borne proteins, e.g., so-called ‘antibodies’. However, within the cellular immune response, there are multiple reactive sub-pathways that are affected differently by UV radiation. Current research on UV immunosuppression has had to recognize and account for these differences in order to understand the many, some of them seemingly contradictory, results. It is beyond the scope of this paper to deal with this matter in any great detail. However, some of this information, in particular, the relevant action spectra, the role of antigen-presenting cells, and the genetic factors that can modify these responses, are necessary to the development of risk-management strategies and so is briefly summarized here.

A critical first step in understanding UV-induced immunosuppression is a knowledge of the important chromophore(s). Unfortunately, recent research has increased rather than decreased the list of possibilities. Initially, there appeared to be two major chromophores of interest, urocanic acid (UCA) [27] and DNA [28], each playing a distinct role in the immune response. Findings from a number of different groups now contribute to the conclusion that both UCA and DNA are important to UV-induced systemic immunosuppression, and that under ambient exposures involving both UV-A and UV-B, a number of interacting events probably contribute to the final outcome (for recent summaries, see Refs. [29,30]). In addition, interest is now focused on chromophores that (perhaps through oxidation) alter cell-membrane components (affecting internal cell signal-transduction pathways [31]), as well as on provitamin D3 that, through its active metabolite (1,25-dihydroxyvitamin D3 [32]) may become immunosuppressive.

Much of the interest in the roles of DNA damage and UCA isomerization in immune suppression relates to the fact that these events affect the production or expression of a variety of biologically active chemicals that can modify immune reactions. Some are released into circulation, i.e., cytokines, while others are displayed on the cell surface, e.g., cell-surface receptors; however, they are key candidates for the development of interventions.

The most prominent cellular target involved in the immunosuppressive action of UVR appears to be the Langerhans cell or antigen-presenting cell (APC). Large numbers of APCs reside in the epidermis and act as the skin’s security force, catching and processing foreign intruders, e.g., antigens, microorganisms, then migrating to the draining lymph nodes to activate the T lymphocytes that will mount the final
immune response. Like cis-UCA, UV irradiation diminishes the number of Langerhans cells in the epidermis, and disturbs the proper priming of T cells, often leading to the generation of suppressor T cells that can specifically block the development of an effective immune response against the invading agent. These suppressive cells induce a lasting tolerance toward the invading agent (i.e., the immune system is rendered ‘blind’ for this specific agent). Recent research suggests that for these aspects of UV-induced immunosuppression two cytokines, TNF-α and IL-10, are responsible for the induction of the transient and persistent tolerances, respectively [33].

Finally, there is good evidence that susceptibility to UV-induced immunosuppression is under some degree of genetic control. Animal experiments initially demonstrated certain mouse strains to be resistant to UV-induced immunosuppression [34,35]. Subsequent work indicated that this distinction was based on relatively high doses of antigen; with lower doses all animals became susceptible [36]. Humans also show differences in sensitivity to local suppression of the CH response [23], which are largely independent of skin pigmentation. In fact, pigmentation provides surprisingly little protection against UV-induced immune suppression [37]. These findings suggest that vaccination programs carried out under conditions of high UV may want to evaluate their dosage regimens carefully in order to avoid providing doses that induce tolerance instead of immunity.

2.2.3. Infectious diseases

Because of the experimental evidence that UV affected cellular immunity, concern arose about the implications of UV-induced immunosuppression for infectious diseases. Cellular immune responses are of paramount importance in the defense against a wide variety of infections. The 1903 Nobel laureate Niels Finsen first reported that UVR could heal skin tuberculosis (Lupus vulgaris) but adversely affected smallpox [38], and others later found that lung tuberculosis was also adversely affected. Much more recent work using animal models of human diseases has confirmed that UV-B can affect different infectious diseases (and even differing manifestations of the same diseases) differently, as well as indicating that certain diseases, e.g., schistosomiasis [39], are unaffected.

Human infectious diseases that in animal models have shown an effect of UV-B include herpes, tuberculosis, leprosy, trichinella, candidiasis, leishmaniasis, listeriosis, and Lyme disease. Reported effects have included suppression of immune responses to the organisms or their antigens, reactivation of latent infections, increased body burdens of organisms, decreased resistance to re-infection, and reduced survival [24,40–43].

UV-B has been shown to activate viruses such as herpes, HIV, and human papilloma viruses (HPV) [44–46] as well as to affect the immune response to herpes [47]. In animal models of human tuberculosis, leprosy, listeriosis, trichinosis, and Lyme disease, UV-B treatments suppressed DTH responses to the organisms, depressed clearance of the organisms, and, in certain instances, increased mortality [42,43,48].

The information summarized above has raised concerns that UV-induced immune suppression could adversely affect the course of some infectious diseases in human populations. However, with the exception of HIV infection, there appear to be no recent published studies that have explored this issue through epidemiological analysis. In the case of HIV infection, a recent report from the Multicenter AIDS Cohort Study [49] found no evidence that solar UV exposure exacerbated HIV infections in white homosexual males. Indeed, it was found that in men who were HIV positive at baseline, those who purposely sought sun exposure were less likely to have progressed to AIDS. As these authors noted, however, these findings need to be confirmed in a large, prospective study of HIV-infected individuals before any conclusions are made as to the beneficial effects of solar exposure on AIDS progression [49].

2.3. Lupus and other autoimmune diseases

The impact of UV-B exposures on APCs, and on the production and release of cytokines, opens up the possibility that increases in UV-B could either exacerbate or ameliorate autoimmune diseases. Data exist in support of both possibilities and seem to suggest that diseases likely to be exacerbated will be those involving aberrant humoral immunity, e.g., systemic lupus erythematosus (SLE), whereas those likely to be ameliorated will be those involving aberrant cellular immunity, e.g., multiple sclerosis (MS) and psoriasis. In the case of SLE, it has long been known that UV-B exposures can exacerbate certain symptoms, probably in part due to the production of TNFα [50].

More recent studies of SLE, however, also suggest that exposures to UV-B could not only exacerbate SLE, but might even serve as initiating events. First, studies of SLE have demonstrated a spectrum of APC and T-cell defects consistent with loss of the cytokines that help regulate cell-mediated responses [51] — exactly what is observed following UV exposures [52,53]. The loss of cytokines also removes a regulatory constraint on the cells important to humoral immunity, thereby leading to an increase in the production of antibodies of the type implicated in the pathogenesis of SLE [52]. Secondly, although the SLE antigens are mostly derived from internal components of the cell (e.g., the nucleus and the cytoplasm), the autoimmune response that is made to them is of the type normally reserved for components found outside the cell or on the cell membrane. This paradoxical finding may be explained by a recent observation that several of the nuclear and cytoplasmic autoantigens important to SLE pathogenesis are found on the surfaces of dying (apoptotic) skin cells, but not of normal cells. If this means that these antigens are now presented to APCs as if they were membrane components [54], this could explain the anomalous immune response seen in SLE. Since induc-
tion of apoptosis in keratinocytes is a consequence of UV exposure [55], increases in UV could provide greater opportunities for encouraging an SLE-type immune response.

In the case of MS, a degenerative disease of the nervous system with autoimmune characteristics, it has long been recognized that there is a latitude gradient for the disease, with incidence increasing with increasing distance from the equator (exactly the opposite of what is found for skin cancer). More than a decade ago, it was proposed that this could be explained as a result of the immunosuppressive effect of sunlight, and cross-reactivity between melanocyte antigens and those of the nervous system important to MS development [56]. Subsequent work has strengthened the hypothesis that a sunlight-mediated immunosuppression may explain the latitude gradient, although it is now thought that the important antigen(s) are viral proteins that are cross-reactive with myelin basic protein [57].

3. Effects on the skin

3.1. Sunburn

Sunburn is probably the most widely experienced form of acute solar damage to the skin. A reddening of the skin, which in severe cases leads to blistering, sunburn is a delayed erythema initially characterized by the appearance of ‘sunburn cells’, the depletion of APCs, and the infiltration of the epidermis and dermis by a variety of inflammatory cells, e.g., mast cells, monocytes, and lymphocytes. Subsequently the skin responds with hyperproliferation [58]. Sensitivity to sunburn varies based on pigmentation, with heavily pigmented individuals generally being much less sensitive than lightly pigmented ones.

Sensitivity to sunburn, along with tanning ability, has been used to develop a classification system of six skin phototypes. The most sensitive individuals (skin type I) develop a moderate to severe sunburn after a short-term (an hour or less) exposure in the summer, rarely tan even after repeated exposure and generally have very fair, often freckled skin, red or blond hair, and blue eyes. The most resistant individuals (skin type VI) are darkly pigmented without exposure and become even more deeply pigmented upon exposure [59]. These classes have been widely used to classify individuals within a population according to skin type; from such efforts we have come the conclusion that sensitivity to sunburn is a risk factor for skin cancer (discussed in more detail below).

3.2. Photoaging

Aging of the skin is a well-documented consequence of exposure to sunlight. Characterized by wrinkles, altered pigmentation and loss of elasticity, such ‘photoaged’ skin is associated with overgrowth of abnormal elastic fibers in the dermis, and a decrease of collagens [60]. Reactive oxygen species (ROS) have been implicated in the etiology of photoaging [61]; however, mechanistic studies suggest that UV-B is much more effective than UV-A at inducing the over-production of precursor molecules [62]. Furthermore, the combination of UV-B and UV-A was slightly less effective than UV-B alone in the induction of these effects [62]. Since UV-A is generally considered more effective at ROS generation, these results suggest that the exact mechanism of these effects is yet to be determined. Given these uncertainties, photoaging must be considered as one of the effects that may increase with stratospheric ozone depletion.

3.3. Skin cancer

Among light-skinned populations, skin cancers associated with exposure to solar radiation are the most common kind of cancer. Three types of skin cancers comprise this group: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and cutaneous melanoma (CM). The first two are often collectively referred to as non-melanoma skin cancer (NMSC). BCC and SCC both result from the malignant transformation of keratinocytes, the major structural cell of the skin. CM, on the other hand, results from the malignant transformation of melanocytes, which are the skin’s pigment-producing cells.

These tumors share some traits and differ in others. Shared traits include an increased risk of developing these tumors with increased exposure to sunlight, and a pigment-related variation in susceptibility, with darker skinned races and individuals being at less risk of developing skin cancer for a given amount of exposure than those with lighter skin. As discussed in detail below, although these tumors share certain features, their biological behavior and relationships to solar exposure are qualitatively and quantitatively different; thus, they are discussed individually.

Epidemiological studies are a primary source of information for assessing the relevance of solar UV exposure to the etiology of diseases such as skin cancer. Even though there has been considerable improvement in study design, epidemiological findings in this research area still suffer from two principal flaws. First, because of the lack of an independent metric of exposure, e.g., a biomarker of cumulative UV exposure, epidemiological studies currently base their exposure estimates on patient and control recall of exposure much of which occurred decades ago, and thus are subject to ‘recall bias’. Secondly, there are inevitable correlations between what may be independent risk factors, e.g., sun sensitivity is directly related to the numbers of actual sunburns or the use of sunscreens. These in turn relate not only to intermittent exposure but also to sun-seeking behavior that also increases the overall level of exposure.

3.3.1. Basal cell carcinoma

BCC is the predominant form of NMSC among white populations [63]; in the USA it represents about 80% of the NMSC diagnosed [64]. Susceptibility varies according to skin type, with the most sensitive individuals being those
with fair skin and a marginal to poor tanning ability (i.e., skin types I and II). In contrast to SCC and CM, BCC has no unique precursor lesion, although recent studies have identified a gene associated with nevoid BCC syndrome, which is associated with susceptibility to BCC in the general population. Alterations in this gene (termed 'patched') occur in 90% of BCCs examined, and about 50% of these alterations are mutations caused by UV-B radiation, based on the pattern of base changes in this gene. This provides direct molecular evidence for a role of UV-B in BCC.

The incidence rate of BCC among various white populations has been increasing recently, albeit more significantly in some locations than others. In Albuquerque, NM, an evaluation by a major health-care provider of the change in age-standardized rates of BCC between 1978 and 1991 found an increase of about 13% per year [65] (BCC showed little change in rate.) In contrast, a survey done in Australia showed only about a 2% annual change between 1985 and 1990 [66].

Because early studies in the USA showed that the majority of BCCs (almost 80%) occurred on the most heavily exposed sites (head, neck, and extremities), the risk of BCC was once thought to be directly related to life-time cumulative sunlight exposure [67]. However, recent epidemiological data suggest that this conclusion is too simplistic. In two recent epidemiological studies from Australia, Kricker and her colleagues [68, 69] examined several interesting aspects of BCC. In the first report these authors found that the risks of BCC occurring on heavily exposed sites (head, neck, and extremities) decreased with increasing total exposure, whereas the risks of BCC occurring on an intermittently exposed site (the trunk) showed the opposite pattern: increasing risk with increasing exposure. In the second report these authors concluded that intermittent exposure, especially in youth (between the ages of 15 and 19), may be important in explaining BCC. These data are consistent with two hypotheses. Kricker et al. [68] suggest there is a plateau in BCC risk at higher levels of exposure, in accord with that postulated by others who had observed a similar pattern [70]. Gallagher et al. [63] suggest that it is only childhood exposures that are important. Unfortunately distinguishing between these two hypotheses is difficult, since a majority of an individual’s life-time UV dose is accumulated by age 18 [71], and operationally they are the same: one represents a time threshold and the other a dose threshold.

Kricker and her colleagues [68, 69] also looked at BCC risk based on skin type and found differing dose-response relationships for those who tan well as compared to those who tan poorly. For good tanners, the risk of BCC increased with increasing sun exposure, whereas for the poor tanners the risk was initially flat and then fell with increasing exposure. Assuming the plateau hypothesis is correct, these observations suggest that good tanners get a lower effective dose per hour of solar exposure (probably due to the effect of tanning and skin thickening) than the poor tanners and thus their keratinocytes achieve this plateau later in their lifetime.

The presence of a plateau also suggests that in order to reduce risk, particularly in those who tan poorly, substantial reductions in exposure will be required.

3.3.2. Squamous cell carcinoma

SCC, although much less common than BCC, is almost an order of magnitude more common than CM in the USA. In The Netherlands, however, the ratio is almost 1:1. More than for any other skin cancer, epidemiological data on SCC implicate lifetime cumulative UV exposure as a critical risk factor. In line with earlier studies, the multicenter Helios study in southern Europe showed that the risk of SCC goes up with lifetime exposure [72]. A smaller, but very thorough, Canadian study [73] on 180 SCC patients treated in 1983 and 1984 did not find any significant increase in risk related to life-time exposure, but rather, increased risk was associated with chronic occupational exposure over the decade prior to diagnosis of the tumor. As the authors point out, these findings may be hampered by random errors in recall and by a correction for body area exposed. Besides introducing a new source of error, the correction for exposed body area may not be appropriate for SCC since risk is primarily determined by the genotoxic damage at the site of occurrence. That persistent UV exposure in the final stages of tumor development is important can be inferred from the observation that avoiding sun exposure, including the use of sunscreens, reduces formation of actinic keratoses (AK), precursor lesions of SCC [74]. The Canadian study also found an increase in risk in relation to regular over-exposure (sunburns) during childhood. The latter correlation with childhood sunburns has also been found in other studies [75, 76]. However, as pointed out above and by Armstrong et al. [77], this may primarily imply that a high level of childhood exposure, rather than sunburns per se, is the dominant risk factor. Considering the presently available epidemiological data, it appears prudent to conclude that UV exposure contributes to SCC risk both in early and late stages of tumor development.

Brash [78] and his colleagues [79] found UV-related mutations in the p53 tumor suppressor gene in the majority of SCCs as well as BCCs. In addition, this group found that about 60% of AK bear such mutations [80]. These mutations were also found in experimentally UV-B-induced murine skin cancers, first in low percentages [81] but later in the majority [82, 83]. In samples from normal skin of the shoulders of Australians who had skin cancers removed, cells with a specific UV-related p53 mutation could be detected, while they were virtually absent in unexposed buttock skin [84]. In mouse experiments, microscopic clusters of cells with high levels of mutant p53 protein were observed long before the UV-induced macroscopic skin tumors appeared [85]. Such microscopic clusters have also been found in human skin from surgical resections [86, 87]. Hence, it appears that mutations in the p53 gene occur at a very early stage of the development of SCC (in contrast to other tumors, like colon cancer, where it marks a late conversion to malignancy).
In addition to earlier experiments in which SCCs were induced in hairless mouse skin by chronic UV-B exposure, it has recently been reported that SCC can be similarly induced in normal human skin grafted onto immune-deficient mice [88]. These experiments clearly show that the human skin taken out of its own environment can develop AK and SCC within one to two years of daily UV-B exposure, although the yield of frank SCC was low. This may provide an important new model to investigate quantitative and wavelength relationships between skin-cancer induction and UV exposure.

3.3.3. Cutaneous melanoma

CM differs significantly from NMSC in terms of incidence, biological behavior and relationship to UV-B. CM is a far rarer tumor and is generally much more aggressive than either BCC or SCC. Although in the USA CM probably accounts for only 2–3% of those skin cancers associated with solar exposure, it accounts for most of the mortality.

As with BCC, the risk of CM does not appear to be directly linked to cumulative life-time UV exposure. CM frequently occurs at anatomical locations that are not the most heavily sun-exposed. Furthermore, as noted in a recent review of almost 30 epidemiological studies, an increased risk of melanoma is associated principally with an increase in intense exposures of the intermittent type, e.g., such as those received by areas exposed only during outdoor recreational activities [89].

There is also considerable evidence that exposures in early childhood area may be important. A number of epidemiological studies have also found higher melanoma risk with increasing sun exposure in individuals who lived in sunny areas during their childhood [90–92]. Attwell and Doré [92] also found that sun exposure during childhood may in some instances constitute a significant risk factor for melanoma only if there is also substantial sun exposure during adult life, i.e., that childhood and adult exposures act interdependently.

An additional risk factor for CM revealed by epidemiological studies is the presence of one or more forms of pigmented lesions on the skin — either freckles or moles (which are also known as melanocytic nevi). In a number of studies, prevalence of nevi was the single most important determinant of melanoma risk, a finding that was later confirmed by clinical studies [93]. Pathological examination of melanomas frequently reveals histological evidence of a pre-existing nevus [94], leading to the suspicion that at least some nevi may be precursor lesions for melanoma. Since nevi exist in a gradient of premalignancy, with the common melanocytic nevus being the most benign and the dysplastic nevus being the least benign, some effort has been spent in evaluating the relative risk associated with various kinds of nevi. In a number of well-conducted epidemiological studies, it has been found that having a large number of moles is associated with a higher risk of melanoma [95,96].

A recently described action spectrum for melanoma in fish [97], unlike that developed in mice for SCC [98] (and the rest of the action spectra in Fig. 3), appears to have a strong UV-A dependence. Work in the South American opossum provides some support to the notion that exposure to UV-A may be important to CM. In that animal model UV-A treatments alone induced melanocytic hyperplasia, a precursor to melanoma in these animals [99]. To date, however, these lesions have not progressed to malignant melanoma. These findings suggest that the etiology of melanoma is probably complex and likely involves a multistep process of both UV-B- and UV-A-induced changes in a variety of different molecules [100].

4. Hazards for domestic animals

SCC associated with ambient solar exposure has been reported in cattle, horses, cats, sheep, goats, and dogs [101–103]. These tumors occur principally in poorly pigmented skin unprotected by hair, and thus are frequently found on eyelids, nose, ears, tails, and the mucocutaneous junctions of the eyes and anogenital regions [103]. The incidence of these tumors is generally very low, although occasionally herds of susceptible cattle or sheep can demonstrate incidences as high as 20% [102].

Other effects in domestic animals that may increase under ozone depletion include exacerbation of infectious bovine keratoconjunctivitis in cattle [104], and skin lesions and cataract in farm-raised fish [105], both of which have been associated with significant economic losses. Concerns have also been raised with regard to cataract and eye infections in sheep herds raised under the ozone hole in Chile; however, an investigation into this issue found no evidence to support such a concern [106].

5. Factors modifying exposure and susceptibility

As already intimated, the risks to humans and domestic animals of developing the effects described above depend on a number of factors besides the ambient UV exposures, including such things as the degree of skin pigmentation, sun-seeking behavior, age at exposure, etc. This section briefly reviews what is known about a number of these factors because of the importance of this information to the development of risk-management strategies.

5.1. Genetics

A number of genetic differences have been described that influence susceptibility to the adverse effects of solar exposure. These include variations in genes determining: (1) quantitative and qualitative differences in pigmentation; (2) the repair of UV-induced damage to DNA and other molecules; (3) the ability to make an immune response to certain types of antigens; and (4) the expression of oncogenes or growth-promoting substances, e.g., cytokines. In some cases,
these variations may lead to differences in the dose of UV-B delivered to the target cell, whereas others may influence the kinds and amounts of damage, and still others the repair or the consequences of damage. To date, no single genetic change has been identified that confers absolute susceptibility to these effects; rather each of these genes appears either to demonstrate a number of different alleles or a variety of different mutations that are associated with greater or lesser responses to the effects of UV-B. Furthermore, it is becoming clear, at least in the case of skin cancer, that multiple processes must be compromised in order for adverse effects to occur.

One of the most overarching sets of such genetic differences is that conferring high or low degrees of pigmentation. Numerous studies have indicated that, in general, those of Negroid ancestry show a very much lower incidence of skin cancer (100 fold for NMSC, 10 fold for CM) than those of Caucasoid ancestry [67]. A more recent series of reports from Hawaii extended this observation to other races and found that Caucasians on the island of Kauai have about a 10 times higher incidence of NMSC compared to those of Japanese ancestry, who in turn have a five-fold higher incidence than those of Philippine or Hawaiian ancestry [107,108]. Interestingly, a similar degree of protection is not conferred by pigmentation either for cataract [109] or the immunological effects of solar exposure [37].

Among the light-skinned races, certain qualitative differences in pigment also appear to be important to sun sensitivity, as well as to skin-cancer risk. In particular, those with higher ratios of pheomelanin (the yellow/orange melanin found in red hair) to eumelanin (the brown/black melanin of brown/black hair), who rarely tan and almost always burn, appear to be at greatest risk [67,73,91]. Pheomelanin is known to generate ROS when irradiated with UV-B, whereas eumelanin appears to act protectively against ROS; it has been postulated that this difference may be the reason for the increased susceptibility to skin cancer of those with fair skin and red hair [94]. Recent information suggests, however, that multiple factors are important to susceptibility, and that different genes may be important for poor tanning ability and UV sensitivity. In the case of poor tanning ability, it has been shown that people with a poor tanning response show variations in a gene important to eumelanin synthesis in melanocytes [110]. Furthermore, some of these genetic variations may be associated with increased risk of melanoma [111]. In the case of sensitivity to the erythemal effects of UV-B, it has recently been shown that individuals showing the greatest inflammatory response to UV-B exposures lack a key detoxification enzyme for ROS [112].

Another set of genes important for understanding susceptibility to the effects of solar exposures are those associated with repair of UV-B-induced alterations in DNA. Patients with xeroderma pigmentosum (XP), a rare genetic disease characterized by poor repair of UV-induced DNA damage, have a 2000-fold increased risk of developing skin cancer before the age of 20 [113]. It has been suggested that many skin-cancer patients suffer from similar albeit much less severe defects in DNA repair [114,115]; however, these findings have not been universal [116] and require additional investigation.

One interesting finding with regard to repair-deficiency syndromes and skin cancer is the discrepancy observed between two such syndromes in the development of skin cancer. Trichothiodystrophy (TDD) is a DNA-repair-deficiency syndrome with many similarities to XP; indeed one form of XP, XP-D, has mutations in the same gene as that affected in TDD. However, only XP-D individuals are at increased risk of skin cancer. An explanation for this anomaly may be that cells from XP-D patients, but not from TDD patients, are more susceptible to one of the steps in UV-B-induced immunosuppression [117]. Thus, in addition to a faulty DNA-repair process, XP-D patients also have a compromised immune response. The conclusion from this study is that faulty DNA repair alone may not be sufficient to cause the observed increase in skin cancer; it may need to be accompanied by a compromised ability to respond to UV-induced immunosuppression [117].

Two additional sets of genes which appear to be able to influence the development of UV-B-induced neoplastic responses are (1) those that affect the immune response and (2) those that act as growth regulators, either stimulating uncontrolled growth, e.g., proto-oncogenes, or restraining such growth, e.g., suppressor genes. In the case of those that influence the immune response, as demonstrated by the finding with XP-D patients, the immune response to UV-induced tumors may be compromised. In the case of growth regulators, a host of genes have been identified which when mutated (by UV or another insult) can result in the development of a tumor. Chief among these is the gene for p53 that has been discussed above in some detail. Mutations in p53 appear to be key to the development of both BCC and SCC, but not CM [87]. Another gene, that which codes for cyclin-dependent kinase inhibitor 2 (CDKN2) or p16, has been found to be very important in CM. Recent information suggests that CDKN2 is a melanoma tumor suppressor gene located on chromosome 9 which is particularly important to familial melanoma but may also have a role in sporadic melanoma [118,119].

5.2. Behavior

There are a number of behavioral choices that can significantly affect the risks associated with ozone depletion. The largest of these is undoubtedly 'sun-seeking' behavior. Numerous epidemiological studies have demonstrated the importance of various exposure patterns. Thus high cumulative exposure is a risk for SCC and many of the ocular effects, most notably cataract [63,120]. Childhood and intermittent exposures, particularly those leading to sunburns, appear to be important to BCC and CM [63,90,91.96], and intense exposures appear to be important for sunburn, melanoma, BCC, snowblindness, pinguecula, CDK, and pterygium [6,68,69,100]. Clearly those who avoid such behaviors will
reduce their risk. Such avoidance can be achieved in a number of different ways, e.g., modifying time of exposure, avoiding exposure during the peak solar hours (10 am to 2 pm in the Northern Hemisphere), wearing protective clothing such as hats, sunglasses, and densely woven materials; staying in the shade and off highly reflective surfaces, and foregoing sunny vacations.

5.3. Diet

Numerous studies have explored the impact of various nutritional variables on the expression of UV-associated adverse effects. Information has come from experimental as well as epidemiological studies. However, for the most part what appears to be clear cut in experimental systems is found to be far from clear-cut in epidemiological studies. In the case of cataract, for example, Varma et al. [121] indicate that the experimental evidence for the protective effect of antioxidants for cataract is quite compelling. In contrast, a parallel review of the epidemiological evidence by Hodge et al. [120] indicates that the information is difficult ‘to unravel’. These latter authors conclude that nutrition is clearly important in the case of nutritionally deprived communities, but also conclude that these findings are difficult to generalize to more affluent communities because the relevant studies provided conflicting results. Even in nutritionally deprived populations, however, the protective role of adequate nutrition in the form of adequate protein consumption or additional nutritional supplements (only the riboflavin/niacin complex demonstrated any effect) did not apply to cortical cataracts, the major form of UV-induced cataract [120].

In the case of skin cancer, the epidemiological evidence also appears to be somewhat conflicting. A summary of the information on NMSC presented in one recent review indicates that while one study found a protective effect of dietary factors, other studies found no significant benefit [122]. In the case of melanoma, a number of different studies have examined either the consumption or serum levels of vitamin E, α-tocopherol, or β-carotene consumption and related them to risk. The results have been highly variable; e.g., in the case of consumption, vitamin E in foods, but not in supplements, was protective [96]. In the case of serum levels, some results suggest that low serum concentrations of α-tocopherol or β-carotene were associated with higher risk [123], whereas others studies found that plasma levels of α-tocopherol were not related to risk. Taken collectively, these results suggest that dietary interventions may be of little help in preventing or managing the risks of cataract and skin cancer from UV-B.

5.4. Medical treatment/status

A number of factors related to health status have shown an association with increased risks from UV exposures. From a risk-assessment perspective, these factors often identify sensitive subpopulations whose reactions may occur earlier or to a higher degree than those of a normal population, thus providing information helpful to the understanding of mechanisms needed for risk management. From a risk-management point of view, such populations may require special handling in the development of appropriate management strategies.

Given the importance of the immune response to the development of skin cancer, it was hypothesized early on that immunosuppression would have an impact on tumor development. Studies in renal transplant patients (whose immune responses are suppressed in order to prevent rejection of a kidney transplant) confirmed this hypothesis by revealing a dramatic increase in warts and SCC on sun-exposed skin of these patients [124]. The warts are known to be associated with HPV, but the carcinomas and precursor lesions in these patients were also found to bear a great variety of HPV [125], not generally found in SCC [126]. It has, however, recently been found that HPV are commonly detectable in hair plucked from eye brows [127]. The question now is whether the HPV is merely a hitchhiker in proliferating carcinoma cells or whether it really plays a causal role in the development of these tumors. The skin carcinomas in people with renal transplants were also found to contain UV-related p53 gene mutations [128]. These findings clearly show that a good immune system prevents the development of potential carcinomas on sun-exposed skin. As discussed above, the UVR from the sun can also exert immunosuppressive action and thus enhance the development of skin carcinomas.

Besides SCC, non-Hodgkin’s lymphoma occurs much more frequently in people on immunosuppressive medication [129]. The risks of non-Hodgkin’s lymphoma and skin cancer appear to be associated; people who were treated for skin carcinomas have an increased risk of non-Hodgkin’s lymphoma [130,131] and vice versa, i.e., people treated for non-Hodgkin’s lymphoma have an increased risk of skin cancer [132]. The persistent increase in non-Hodgkin’s lymphoma over the last four to five decades parallels increases in skin-cancer incidence and it is hypothesized that both these trends are due to increased exposure to sunlight [133]. It has been speculated that the common factor in the etiologies of these cancers is the UV-induced immunosuppression [134] or, more specifically, that cytokines released upon UV exposure may stimulate the outgrowth of precursor cells of B lymphocytes to develop into a non-Hodgkin’s lymphoma [135]. Non-Hodgkin’s lymphomas have been reported to occur more frequently in the sunniest parts of Great Britain [136], but in contrast to skin carcinomas, there is no increase in non-Hodgkin’s lymphomas toward the south in North America [137]. Interestingly, mice developed lymphomas as a consequence of exposure to UV radiation and a chemical carcinogen (7,12-dimethylbenz(a)anthracene), whereas treatment with each of these factors separately did not induce lymphomas [138]. In sum, there appears to be an association between the risk of skin carcinomas and non-Hodgkin’s lymphomas, but whether UV radiation is a risk factor for non-Hodgkin’s lymphomas is not clear. More data are required to negate or
confirm a direct relationship between UV radiation and non-Hodgkin's lymphoma.

The immune system can be compromised in many different ways, e.g., through medication or infections. An additional UV-induced suppression might then have more devastating impact than normal. A very timely topical example of an affliction that cripples the immune system is AIDS (caused by HIV), and these patients could run an increased risk from UV exposures. However, AIDS patients with psoriasis have been treated with UV radiation and no aggravation of the AIDS was found [139,140]. This result could be offset by the fact that psoriasis itself activates the immune system on which UV radiation then exerts a first dampening effect without further diminishing the resistance to HIV.

Certain medical treatments may add to the cancer risk from (solar) UV exposures, e.g., immunosuppression radiation therapies for cancer [96] and PUVA (a combination of UV-A and oral dosing with 8-methoxypsoralen) treatments for psoriasis [141].

The PUVA treatment of psoriasis has become very widely used but has been found to be associated with a substantial increase in skin-cancer risk in a long-term follow-up. Recently, it has been reported that in the long run the risk of melanoma is also significantly increased [142]. The SCCs found on the PUVA-treated individuals occurred frequently on skin areas that are exposed in the PUVA treatment but are not regularly exposed to the sun, e.g., the legs, where they do not commonly occur in the general public. Curiously enough, many of the skin carcinomas taken from PUVA-treated patients were found to have mutations in the p53 gene that pointed at UV-B radiation instead of the PUVA treatment as the direct cause [143]. This would indicate that UV-B radiation may even have contributed to the development of these clearly PUVA-related skin tumors. Clearly, there are a number of factors that can amplify the risks of UV exposure, and vice versa. Identifying high-risk populations will open up the possibility for well-targeted mitigating strategies.

6. Risk assessment

Quantitative risk assessment of the effects of ozone depletion is a data-intensive process which until recently has only been done for a few effects, most notably those affecting human health for which there are adequate data, i.e., cataract and skin cancer. With the exception of the 1987 USEPA risk assessment [94] and regulatory impact assessment (RIA) [144], the impact of increases in ambient UV-B on these diseases has previously been quantified principally by comparing two stationary situations: one with an ozone concentration constantly at a normal level and the other constantly at a lower level [145–147]. The corresponding disease incidences were estimated in two steps from the constant level of increased ambient UV radiation to the increased incidences: the first step is represented by the radiation amplification factor, RAF = (percentage increase in carcinogenic UV) per (percentage decrease in ozone), and the second step by the biological amplification factor, BAF = (percentage increase in incidence) per (percentage increase in carcinogenic UV radiation) [148]. The overall increase in incidence per percentage ozone depletion is then represented by the amplification factor, AF = RAF × BAF.

The future projections of ozone-depleting substances (ODSs) in the atmosphere made in recent years have invited scenario studies on future ozone density and corresponding levels of ambient UVR. These in turn are now being translated into assessments of the risks to the biosphere in order to assess the importance of such atmospheric changes. It cannot be over-emphasized, however, that these scenario studies should not be taken as genuine forecasts. They are, at best, idealized computations on the effects of the changes in a small subset of factors leaving all other relevant modifying factors undisturbed. In the real world many of the other relevant factors may change and diminish or aggravate the effects (e.g., increased or decreased cloudiness). Nevertheless, these scenario studies serve the purpose of quantifying and comparing the potential effects of certain policies.

As indicated above, it is not currently possible to develop quantitative risk assessments for all of the health effects expected from ozone depletion. Presented below, therefore, is a mixture of quantitative and qualitative information that assesses to the extent possible the likely impacts of ozone depletion on human health.

6.1. Cataract

In Chapter 2 of the 1989 UNEP Environmental Effects Panel Report [149], a static estimate was developed of the cataract risk of ozone depletion. In that effort it was estimated that the world’s population, if subjected to a sustained 1% decrease in the ozone layer, would develop between 100 000 and 150 000 additional cases annually. More recently, the US Environmental Protection Agency (USEPA) has updated the work developed for their earlier Regulatory Impact Analysis [144] using a quantitative model that incorporates the ozone-depletion scenarios developed by the Scientific Assessment Panel [150]. Fig. 6 presents the results of that effort [151]. Although these estimates were developed on the basis of USA data, they should be applicable to similar populations, i.e., those that are adequately nourished, worldwide. As discussed above, under-nourished populations may be a greater risk.

6.2. Sunburn

Exposure to sunlight may lead to a reddened and painful skin. This ‘sunburn’ is mainly caused by the UV-B radiation in sunlight. Exposures to more UV-B give more severe sunburns. An increase of sunburns by ozone depletion would be more than a nuisance; sunburn is also considered to be a risk factor for more serious effects, such as melanoma.

Analysis of available knowledge leads to the conclusion that sunburns will not appreciably increase under a decreasing
ozone layer; this is due to a powerful adaptation of the skin [26]. A gradual thinning of the ozone layer would, for instance, lead to 20% more UV-B in 10 years’ time. The skin is equipped with an adaptation that can even cope with the changes in UV-B with the seasons. These are much more drastic; in mid-latitudes, the UV-B irradiance in summer is typically 10 times larger than in winter.

Experience with phototherapy of skin diseases shows that one UV-B exposure, sufficient to cause a slight reddening, decreases the sensitivity of the skin by about 20%. In a series of exposures, this can be repeated many times. That is how the skin adapts to the UV-B changes with the seasons. A calculation shows that adaptation from winter to summer irradiance requires 13 such steps of 20% each. This will not change much under a UV-B irradiance increased by 20% due to ozone depletion. It will in fact become a bit easier, as the winter irradiance increases more than that in summer, so that the difference becomes a bit smaller.

It is certainly possible to think of situations where adaptation cannot work in this way. For instance, if a totally unadapted skin is suddenly exposed to full sunlight, more UV-B in the sunlight will increase the likelihood of sunburn. Persons going on an expedition to the Antarctic ozone hole have reported experiences in this line. But such conditions are quite exceptional. By far the most sunburns arise from lack of care in going through the adaptation process. Such sunburns will not increase.

6.3. Skin cancer

Using the process described above, the amplification factors for SCC and BCC have been determined to be 3 and 1.7, respectively. As discussed above in Section 3.3.1, the AF for SCC has a greater degree of certainty than that for BCC. Melanoma, because of uncertainties in its action spectrum, could have an RAF equivalent to that of the carcinomas (1.2) or closer to 0.1 (if the process is mainly UV-A-driven). A third possibility is that the development of melanoma can involve at least two different UV-driven processes, each with a substantially different wavelength dependence: e.g.,

UV-A-driven initiation of transformed cells and UV-B-driven immune suppressive episodes that promote the development of the tumor, or vice versa. Thus any quantitative model for the UV induction of melanoma will have significantly more uncertainty than that for SCC and probably more than that for BCC as well.

Recent risk-assessment efforts with a quantitative model that incorporates ozone-depletion scenarios from the Scientific Assessment Panel provide estimates of the additional cancer risks in populations annually based on the estimated changes in UV-B over time [152,153]. It should be noted, however, that such efforts are not just a matter of including information on the changing concentration of ozone (and UV-B) with time. There are also a number of issues that need to be addressed with regard to the assumptions chosen for the dose–response models used to approximate the relationship between exposure and effect. The process of disease development has to be dissected in phases (steps) that are either UV-driven or not, and it should be known at which stage in the development (early or late, or both) UV is important. From experimental data and epidemiology, it can be inferred that chronic accumulation of UV exposures is important throughout the development of SCC. In contrast, for BCC and CM, acute intense exposures, particularly those acquired in childhood, may be the critical dose metric; although, as discussed above, this may be true in the case of CM only if adulthood exposures are also substantial [92].

Several groups are developing risk estimates using such scenario-based approaches; unpublished data from two of them developed for this assessment are presented here. Fig. 7 is a summary graphic from the Dutch group [152]. Calculations for skin-cancer risks are performed for five scenarios applying the UV-chain methodology developed by Slaper et al. [152], and assuming full worldwide compliance with the agreed protocols within the Vienna Convention.

The calculations are based on the production and depletion scenarios used in the WMO/UNEP scientific assessment of ozone depletion [154]. Skin-cancer risks are calculated for the zonal average ozone depletion observed at 45°N (as reported in Ref. [154]) assuming a population with the sen-
sitivity and age distribution as in the USA (risk in 1980 estimated at 2000 skin cancer cases per million per year). Excess cases refer to additional cases due to ozone depletion. The majority of the excess cases are non-melanoma, and the lethality is approximately 2% of the incidence. The risks are probably conservative estimates, because:

- full compliance with restrictions is assumed, throughout the world
- aging of the population will probably increase the excess risks by 60%
- probable increases in exposure due to changes in behavior are not accounted for.

It should also be noted that certain risk groups (outdoor workers with a fair complexion) probably have much higher excess risks for the non-melanoma skin cancers, and also that in certain areas depletion can be larger than the zonal average used in this evaluation.

6.4. Infections

Although it is now adequately documented that UVR can modulate immune reactions in rodents as well as in humans, the impact of current levels of ambient solar UVR on infections in human populations is still unknown. Currently available epidemiological data are unsuited to ascertain and quantify any such effect [155], and given the fact that scientists have been aware of this lack of data for decades, a well-designed epidemiological study that addresses this issue is long overdue. Consequently, we are still completely ignorant when it comes to quantifying possible effects on infections of ozone depletion.

In developing animal models for the effects of UV radiation on infections, investigators have been measuring changes in fundamental immune reactions that are associated with the course of the infection and that may also be measured in humans. Thus, the aim is to predict UV-induced effects on human resistance to infection by measuring the relevant changes in basic immune responses after UV exposure [156], a so-called 'parallelogram' approach. This approach is in its infancy and requires a thorough and detailed knowledge of the immunological responses that play a role in any particular infection under consideration, in order to identify the relevant measurements. This approach also has certain limitations in that the outcome of such analysis only evaluates host resistance and does not provide complete information on the spread and course of an infection in a population.

The first conjectural calculations demonstrate that physiologically relevant exposures to solar UVR (e.g., 90 min around noon in July at 40°N) may significantly hamper cellular immunity against a bacterial infection (Listeria monocytogenes) in the 5% most sensitive individuals in a population of white Caucasians. This result is in reasonable agreement with direct measurements of the UV-induced suppression of immune reactions against simple chemicals [35,23], where UV-B exposures of the same order of magnitude as those calculated were found to affect a high percentage of people. In spite of these promising developments in indirect methods for assessing UV-related risks of infection, a more direct quantitative assessment of UV-induced enhanced infection remains desirable. A reliable assessment of the magnitude and breadth of effects of current ambient UV levels on infections and on success rates of vaccinations...
appears to be a long way off, and an expansion to include the
effects of an ozone depletion delves even deeper into the
realm of human ignorance.

7. Offsetting risks of mitigation strategies

7.1. CFC substitutes

A large number of chemical substances are now being used
(or proposed) as substitutes for the ODSs that are being
phased out under the Montreal Protocol and its Amendments.
Increased usage of such substances will increase human (and
environmental) exposures to them and may also increase
risks from these compounds to human (and environmental)
populations. A complete assessment of the risks of ozone
depletion thus needs to include not only the risks associated
with increases in UV-B, but also the risks from the replace-
ment substances.

However, it is beyond the scope of this paper to do a
complete life cycle (from production, through use and
release) risk assessment for these chemicals. First, the list
of possible substitutes is growing; secondly, the production and
use information for many of these compounds is constantly
changing and not generally available; and finally, with
the exception of the more or less well-known substitutes such as
the hydrochlorofluorocarbons and other chlorofluorocarbons
(CFCs), the toxicology database for them is inadequate. Thus
in this section, we present only a qualitative assessment of
the toxicity information on some of the better-characterized
substitutes and indicate where readers can find more
information.

Table 1
CFC substitutes

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<th>Common</th>
<th>Chemical name</th>
<th>CAS No</th>
<th>Reference</th>
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<td>355-35-9</td>
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<td>HCFC-225ca</td>
<td>1,1-dichloro-1,1,2,2,3-pentafluoropropane</td>
<td>505-55-1</td>
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</tr>
<tr>
<td>HCFC-225cb</td>
<td>1,3-dichloro-1,1,2,2,3-pentafluoropropane</td>
<td>507-55-1</td>
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<tr>
<td>HFA-132b*</td>
<td>1,2-dichloro-1,1-difluoroethane</td>
<td>1649-08-7</td>
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</tr>
<tr>
<td>HFA-133a</td>
<td>1-chloro-2,2,2-trifluoroethane</td>
<td>75-88-7</td>
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</tr>
<tr>
<td>HFA-142b</td>
<td>chlorodifluorooctane</td>
<td>75-68-3</td>
<td></td>
</tr>
<tr>
<td>HFC-23</td>
<td>trifluoromethane</td>
<td>75-46-4</td>
<td></td>
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<tr>
<td>HFC-32</td>
<td>difluoromethane</td>
<td>75-10-5</td>
<td></td>
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<tr>
<td>HFC-125</td>
<td>pentfluorooctane</td>
<td>354-33-6</td>
<td></td>
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<tr>
<td>HFC-134a</td>
<td>1,1,1,2-tetrafluoroethane</td>
<td>811-97-2</td>
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</tr>
<tr>
<td>HFC-227ea</td>
<td>1,1,1,2,3,3,3-heptafluoropropane</td>
<td>43-89-0</td>
<td></td>
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<tr>
<td></td>
<td>d-limonene</td>
<td>5989-27-5</td>
<td></td>
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<tr>
<td></td>
<td>methylene chloride</td>
<td>75-09-2</td>
<td></td>
</tr>
</tbody>
</table>

All three HFAs, -132b, -133a, and -142b (see Table 1),
demonstrate a low acute inhalation toxicity. HFA-132b
showed a moderate level of toxicity upon repeated exposure
in standard toxicity tests, but demonstrated maternal and fetal
toxicity at all concentrations in a reproductive toxicity study.
For technical and toxicological reasons, it is thus not being
actively pursued as an ODS substitute. HFA-133a demon-
strated moderately high toxicity to most systems upon
repeated exposures with a No Observed Adverse Effect Level
(NOEL) of 24 000 mg m⁻³. However, adverse reproductive
effects were observed in several studies with a NOEL
recommended as 485 mg m⁻³. Company occupational expo-
sure limits have been established between 5 and 24 mg m⁻³.
HFA-142b demonstrates a moderate level of toxicity upon
repeated exposure, with a NOEL for chronic exposure of
82 000 mg m⁻³. There is some evidence of cardiovascular
sensitization potential but only at very high levels (205 000
mg m⁻³) and no evidence of carcinogenic, reproductive or
developmental effects. An 8 h occupational exposure level of
1000 ppm has been proposed.

All three HFCs, -32, -125, and -134a, demonstrated low
toxicity upon acute and repeated inhalation exposure in stan-
dard toxicological testing protocols. None demonstrated any
reproductive toxicity and only one, -134a, demonstrated any
fetotoxicity (NOEL 10 000 ppm in one study and 100 000
ppm in a second, which was also the dose at which maternal
toxicity was observed).

All three HCFCs, -21, -124, and -141b, demonstrate low
acutely toxicity, and HCFC-124 and -141 demonstrate
generally low toxicity overall. The recommended occu-
pational standard for these two HCFCs is 1000 ppm.
HCFC-21 demonstrates greater toxicity than the other two HCFcs, with liver toxicity and cardiac sensitization at relatively low concentrations (15 and 1000 ppm, respectively). The recommended occupational standard for HCFC-21 is 10 ppm.

References


[159] D.A. Stringer (Ed.), Joint Assessment of Commodity Chemicals No. 25. 1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) CAS No. 2873-89-0, European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC), Brussels, Belgium, 1994.

[160] D.A. Stringer (Ed.), Joint Assessment of Commodity Chemicals No.29. 1,1-Dichloro-1-fluoroethane (HCFC-141b) CAS No 1717-00-6, European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC), Brussels, Belgium, 1994.

[161] F.M. Carpanini (ed.), Joint Assessment of Commodity Chemicals No.11. 1,2-Dichloro-1,1-difluoroethene (HFA-132b) CAS:1649-08-7, European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC), 1990, Brussels, Belgium.


