CLIMATE CHANGE, SOLAR RADIATION AND IMMUNE FUNCTION: BIOLOGICAL CONSIDERATIONS AND HEALTH CONCERNS FOR OUTDOOR WORKERS

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INTRODUCTION
Climate change has a significant impact on the outdoor thermal environment, but may potentially affect the environmental and occupational exposure to several physical, chemical and biological agents (IPCC, 2014; Applebaum et al., 2016), among which solar radiation (SR) is of primary importance, especially its ultraviolet component (Bais et al., 2015; Lucas et al., 2015). Exposure to SR may be modified by climate change, both directly and indirectly, although the net effects is difficult to predict. Geographical and meteorological factors are involved as well as cultural and behavioral ones; moreover, a mutual influence between climate and stratospheric ozone dynamics (the last one affecting the total amount of UVB radiation reaching the ground) does exist. SR includes 45% of visible radiation (400 – 780 nm), 50% of infrared radiation (780 nm – 1 mm) and ~ 5% of ultraviolet radiation (UVR). The last one covers the spectral range between 100 and 400 nm and includes the sub-bands UVC (100 – 280 nm), UVB (280 – 315 nm) and UVA (315 – 400 nm). UVR represents about the 5% of the SR at the ground level and the UV component includes, at noon, 95% of UVA and 5% of UVB (UVC is completely absorbed by the ozone layer). The UV component of SR at the earth surface is highly variable, depending on time of day, season, latitude, altitude and cloudiness. Moreover, the human exposure is greatly affected by type of the surrounding surfaces. For instance, water surfaces and the fresh snow, as well as metal surfaces, reflect a great proportion (up to 100%) of the incident UVR, determining high exposures. On the opposite, trees and vegetation in general may shield at various degree the UVR. The human exposure is largely affected by the time spent outdoor and the type of activity. Single parts of the body are differentially exposed to solar UVR, depending on posture, movements and type of garments worn (Godar, 2005; Milon et al., 2007; IARC, 2012).

As UVR does not penetrate deeply the living tissues, skin and eye represent its biological target. UVB may reach the basal layer of the epidermis and UVA, more penetrating, may join the dermal tissue. At the eye level, UVB is completely blocked by the corneal tissues, while a significant proportion of UVA crosses the cornea and is absorbed by the lens. About 1% of the UVA incident to the eye surface may reach the retinal tissue. UVR may exert both acute and long-term effects on skin and eye, depending on dose, dose-rate and duration of exposure (see for instance Svobodova and Vostalova, 2010; Lehmann and Schwarz, 2011; Behar-Cohen et al., 2014). Acute effects include erythema of the skin and photokeratitis, as well as phototoxic and photoallergic reactions, while the long lasting ones are represented by skin
carcinogenesis, photoaging, pterygium, cataract and (perhaps) age-related macular degeneration. Solar UVR also exerts beneficial effects to health, among which the most studied is the synthesis of vitamin D (Lo Piccolo and Lim, 2010), albeit some potential beneficial effects (e.g. lowering blood pressure or reducing the occurrence of certain internal neoplasms) seem to be, at least in part, vitamin D independent (Hoel et al., 2016). The debate of adverse vs beneficial (the last ones mediated or not by the vitamin D) effects of sunlight is still ongoing (see for instance Wright and Weller, 2015; Hoel et al., 2016; Holick, 2016).

EFFECTS OF UVR ON THE IMMUNE SYSTEM

UVR modulates immune function (see for instance Norval, 2006; Matthews et al., 2010; Halliday et al., 2011; Norval and Halliday, 2011; Monteiro et al., 2016). In the UV-induced erythema, for instance, UVR may trigger synthesis and secretion of proinflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α and other cytokines) by immune cells and keratinocytes. Abnormal immune responses elicited by UVR-induced modifications on skin molecular components may contribute to the occurrence of clinical features characterizing some types of photodermatoses (e.g. the polymorphous light eruption); moreover, UVR may be responsible of photoallergic reaction if local or systemic exposure to certain chemicals, drugs in particular, occurs in susceptible individuals, as after irradiation the chemical may give a photoproduct acting as an hapten or a complete antigen.

On the other side, UVR may suppress both local and systemic immunity, as observed in experimental animals and human volunteers for contact hypersensitivity and delayed-type hypersensitivity reactions due to antigens applied on irradiated vs non-irradiated skin. Mechanisms involved in UV-induced immunosuppression are not completely defined, but a lot of molecular and cellular events (often interrelated) may be involved: DNA lesions, reactive oxygen species synthesis, cis-urocanic acid isomerization, NO synthesis and release, modulation of NF-κB pathway, cytokines release (IL-10 in particular), interference with chemotaxis and antigen processing by Langerhans cells, activation of T- and B- regulatory cells, effects on mast cells, draining of Langerhans cells into regional lymph nodes, vitamin D3 mediated immunomodulation etc.

UV-induced immunosuppressive effects are due to both UVB and UVA radiation. Regarding the dose-response relationship, this is linear in the case of UVB radiation: an increasing dose (up to levels inducing a moderate erythemal effect) progressively
increases the level of immunosuppression. For UVA the dose-response relationship is bell-shaped, as evidenced in experimental studies on both contact and delayed-type hypersensitivity reactions. Action spectrum of UVR induced immunosuppression displays a peak at 310 nm (UVB) and a second peak around 370 nm (UVA). Considering the solar spectrum at the ground level it may be argued that for exposures equivalent to 15 – 20 minutes at noon during the summer period the UVA contributes to the overall immunosuppressive effect of solar UVR about 3 times more than UVB, while for higher exposures the UVA contribution falls rapidly due to the bell-shaped dose-response relationship and the UVB becomes predominant in this regard. UVA doses too high or too low to be immunosuppressive by alone may interact with the UVB radiation to induce and enforce immunosuppressive effects. The time of induction is about 24 h for UVB, 48 h for UVA and 72 h in the case of UVB-UVA combination.

Experimental studies conducted with animal models of infectious diseases show that UV irradiation administered before or after the infection determines a significant suppression of the immune response (T lymphocytes activity in particular), leading to an increased microbial load or to a more serious symptoms. This is true for microorganisms responsible for both skin and systemic infections, belonging to viruses, bacteria, fungi, protozoa and nematodes. Until now epidemiological studies give, at best, only suggestions of an increase of symptomatic infections or of more severe clinical outcomes in relation to UVR exposure. The only proven effect in humans is the reactivation of latent herpes simplex infections because of solar UVR exposure. Little evidence is still available with regard to other infectious agents, including varicella-zoster virus, papillomavirus, polioma virus, M. leprae, L. donovani. The discrepancy between experimental and epidemiological data may be partly due to differences in species and infectious charge, but may also be attributed to a lack of ad hoc epidemiological investigations. Moreover, epidemiological surveillance of the infectious and communicable diseases generally does not include data on solar UVR. In addition, it is possible that environmental UVR modifies some biological features of the microorganism before the infective contact occurs.

UVR may reduce the immunostimulating effects of vaccines in animal models, but human data do not allow conclusions, although suggestions of a decreased vaccine efficacy due to exposure to SR or UVR are available in humans for influenza, measles, TBC and hepatitis B. However, large and well-conducted studies are lacking and results may be sometimes explained by confounding factors.
In any case, a growing body of data allowed a new discipline to arise in the contexts of immunological sciences, the *photoimmunology* (Ullrich e Byrne, 2012; Gallo and Bernard, 2014; Elmets et al., 2014), and the framework of the UV-induced immune effects displays and increasing complexity and is still far from a complete and detailed description. For instance, a role of skin microbiome in modulating immune UV effects is emerging (Patra et al., 2016) and an immunomodulatory action may not be exclusive of the solar UVR but could also be exerted (by alone or in combination with UVR) by visible (blue light) and near infrared (780 – 1.400 nm) radiation of the solar spectrum (Gonzales Maglio et al., 2016).

**HEALTH CONCERNS FOR OUTDOOR WORKERS**

Exposure to SR is one of the most prominent occupational risk factors for outdoor workers, i.e. worker performing their job outdoor for a significant proportion of their working time. In addition to the variables listed in the introduction, the patterns of exposure of outdoor workers are also dependent on the type and timing of the job performed (including pauses). Climate change may affect the total amount of the individual exposure to SR in an unpredictable manner, overlapping with other factors affecting the exposure (Bais et al., 2015; Lucas et al., 2015; Grandi et al., 2016). If an increased exposure over time occurs, the potential health outcomes may include an increase in sunburns episodes, more frequent and severe clinical features in workers carrying photodermatoses, an increased frequency of phototoxic and photoallergic reactions, accelerated skin ageing, a higher frequency of skin cancer, cataract and, possibly, macular degeneration. The effects on immune system are difficult to predict at present, but in the event of more marked and prolonged patterns of immune suppression of both local and systemic immunity the following may be expected.

- A higher frequency of viral infections and recrudescence of latent infections (e.g. herpes simplex);
- a higher frequency and severity of some bacterial/fungal infections;
- a higher diffusion of infectious/parasitic diseases as a result of the combined effect of a different pattern of diffusion of infectious agents and vectors due to climate change and the UV-induced immunosuppressive effects;
- a higher incidence of skin cancer (specular to a decrease in immune surveillance of neoplastic development), both melanoma and non melanoma;
- a worsening of clinical features of some autoimmune diseases displaying photosensitivity (e.g. lupus).

Moreover, immunomodulating effects of SR may combine with those due to immunosuppressive drugs as a part of therapeutic treatments for autoimmune, inflammatory or neoplastic conditions resulting in a more severe immune depression in subjects under treatment. Besides, a strengthening of immunosuppressive effects of SR by co-exposure to immunotoxic chemicals (heavy metals, some pesticides etc.) in the workplace may not be excluded. However, individuals affected by some conditions where the immune system plays a role in the pathogenesis or in the onset of clinical features might have health benefits from a more pronounced UV-induced immune suppression, regardless vitamin D status:
- subjects affected by asthma;
- atopic subjects;
- subjects with sensitization to one or more chemical/biological agent/s;
- subjects affected by some autoimmune conditions like multiple sclerosis, type one diabetes mellitus, rheumatoid arthritis etc.;
- subjects carrying some dermatological diseases, for instance most of psoriatic patients.

**CONCLUSIONS**

The emerging features on solar UVR and immune system add complexity to the definition of the overall impact of SR on human health, especially in a context of a changing climate. For outdoor workers the framework is further complicated, as additional concerns arise from co-exposure to other occupational hazards. Some of them, such as irritants, sensitizers and barrier disrupting agents (for instance detergents, especially for prolonged unprotected contact), have the skin as a target and may amplify inflammatory/immune effects of the solar UVR. The indications reported above are only suggestive and presently it is not possible to quantify the modulation of immune function by SR and its potential effects on health as a whole in different conditions or for different combinations of conditions. However, these uncertainties highlight the need of a proper preventive and protective measures for outdoor workers regularly exposed to SR (Grandi et al., 2016), with particular reference to the use of adequate clothes, hats, eyeglasses, sunscreens and hand
protection. Personal protection from SR has not to hinder the use of personal protective devices for other occupational hazards and has to comply with thermal comfort of the worker. In view of the implementation of preventive and protective measures in workplaces (as stated by EU regulation) the assessment of the immune function has to be included into the health surveillance schedules for outdoor workers, especially if the last ones are surveyed in relation to multiple occupational hazards. Immune function may be analyzed at different levels, applying basic and/or innovative methodologies (Toda and Ono, 2002; Subramanian et al., 2015; Galli, 2016), depending on the health status of the workers, the level of exposure to SR (especially UVR) and the co-exposure to chemical, physical or biological agents interacting with SR at the level of biological targets or modulating the immune function itself.

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