American Journal of Health Research
2018; 6(6): 138-149
http://www.sciencepublishinggroup.com/j/ajhr
doi: 10.11648/j.ajhr.20180606.13
ISSN: 2330-8788 (Print); ISSN: 2330-8796 (Online)

The Interplay Between Solar Radiation, Climate Change and Immunotoxicants in Relation to Immune Response Modulation: A Concern for Outdoor Workers' Health

Carlo Grandi, Maria Concetta D'Ovidio*

Department of Occupational and Environmental Medicine, Epidemiology and Hygiene, Italian Workers' Compensation Authority (INAIL), Monte Porzio Catone, Italy

Email address:
ca.grandi@inail.it (C. Grandi), m.dovidio@inail.it (M. C. D'Ovidio)
*Corresponding author

To cite this article:
Carlo Grandi, Maria Concetta D'Ovidio. The Interplay between Solar Radiation, Climate Change and Immunotoxicants in Relation to Immune Response Modulation: A Concern for Outdoor Workers' Health. *American Journal of Health Research*. Vol. 6, No. 6, 2018, pp. 138-149. doi: 10.11648/j.ajhr.20180606.13

Received: October 30, 2018; **Accepted**: November 21, 2018; **Published**: January 3, 2019

Abstract: Immune response may be dysregulated at multiple levels for multiple reasons, spanning from congenital defects to diseases, medical treatments, environmental and occupational exposures. The consequences of immune dysregulation, especially in the case of mild immune dysfunction, are not easy to predict, being dependent on several factors, but may be subtle in most cases. Adverse health outcomes like an increased susceptibility to infections, a higher risk of cancer or the development of autoimmune diseases may occur. Outdoor workers are exposed to several risk factors, partly depending on the working activity or the job performed and partly due to the features and variability of the outdoor environment itself. Outdoor environment generally implies the exposure to severe thermal conditions, meteorological agents, environmental pollutants and solar radiation. Some volatile organic compounds, heavy metals and many pesticide display immunotoxic properties. Solar radiation itself, through the UV component, may induce immunosuppressive effects, both locally and systemically. The ongoing climate change may have a profound impact on the levels of exposure to air pollutants, pesticides, solar radiation, biological agents and disease vectors. A detailed evaluation of the combined exposure to the above-mentioned risk factors is very difficult, given the number of factors involved, the spatial and temporal variability of exposure and the high number of jobs potentially conducted outdoor, but may contribute to the definition of the "exposome" for outdoor workers. The net effect on the immune response modulation and the occurrence of the related potential adverse health outcomes are hard to predict, but this topic is of great importance for a full implementation of occupational health and safety regulation in the case of outdoor workers. This implies an integrated approach in risk assessment, a detailed evaluation of the health status during health surveillance (with particular reference to the immune function) and a careful choice of a suitable combination of preventive and protective measures at individual level.

Keywords: Solar Radiation, Climate Change, Immune Toxicity, Outdoor Workers

1. Introduction

Occupational health and safety involves the assessment and management of all risk factors on the workplaces, both conventional and new/emerging ones. Moreover, workers have to be protected against acute and prolonged combined exposure to potentially highly variable patterns of chemical, physical and biological agents. Depending on the agents involved, their relative concentrations, temporal patterns of exposure and individual susceptibility, additive, synergistic but also antagonistic effects may occur, making the final health outcomes very difficult to predict. In this regard, outdoor workers need a careful consideration, given the exposure to both specific risk factors connected to the job/activity performed and physical, chemical and biological agents commonly found in outdoor settings. They include solar radiation, meteorological factors (e.g. wind, rainfall, high and low temperatures and humidity) as well as urban air chemical pollutants. Climate change may exert a profound effect on environmental exposures and represents an issue of growing importance in public and occupational health [1-3].

This paper stresses the question of occupational exposure of the outdoor workers to xenobiotics with immune-modulating properties (immunotoxicants), with particular attention to the interplay between immunotoxicants, solar radiation and climate change. It must be emphasized that the last one is not an agent affecting workers' health in combinations with others but a feature able to modulate in a complex manner the exposure to many other risk factors encountered outdoor. As immune modulation is affected by individual factors (including diseases, lifestyles, use of immunosuppressive drugs) as well as by co-exposure to several physical, chemical and biological agents (a non-exhaustive view is given in figure 1) the individual balance in terms of health outcomes is hard to determine.

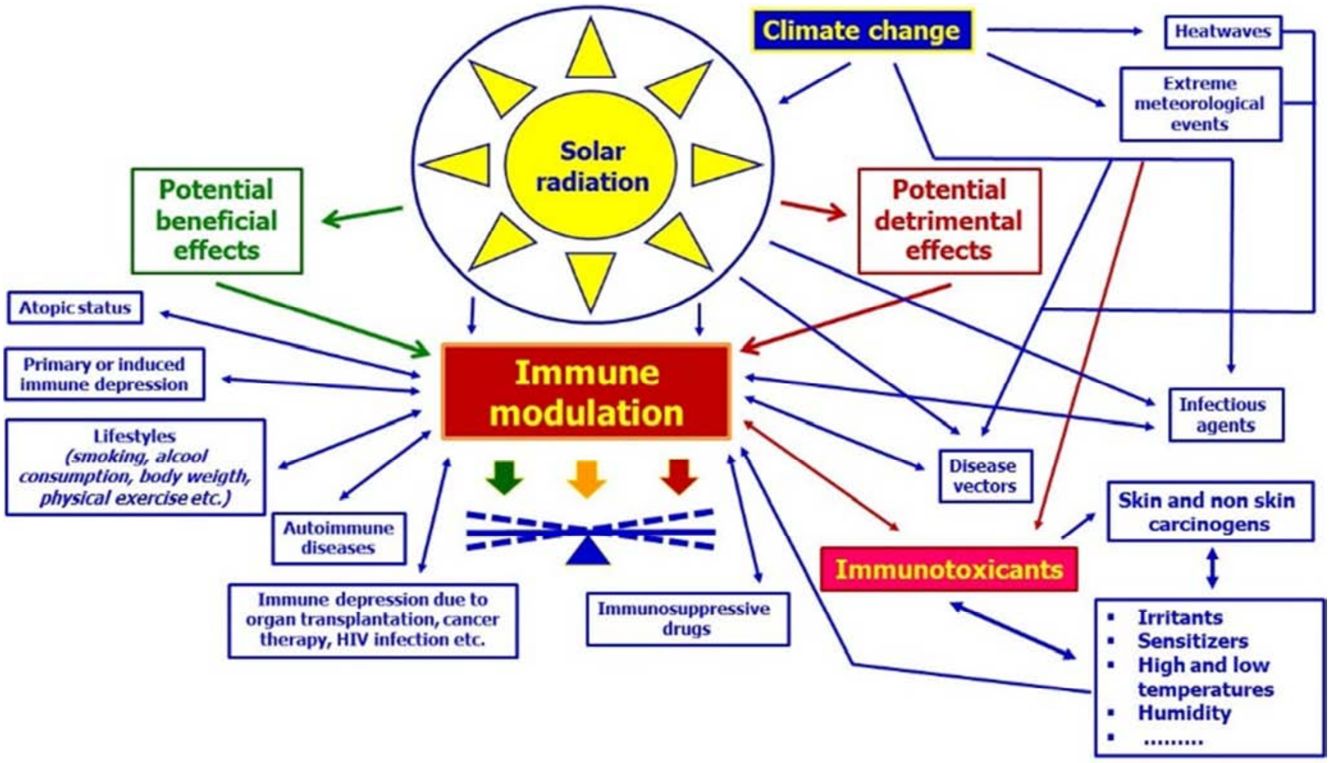

Figure 1. *A simplified picture of the complex interplay between solar radiation, climate change, immunotoxicants, individual physiological and pathological conditions as well as medical treatments and lifestyles involving or affecting the immune response. Which individual balance?*

The more general purpose of this paper is to contribute to the development of a conceptual and operative framework for the assessment and management of outdoor workers' health and safety.

2. A Profile of Factors Involved in a Complex Interplay

2.1. Immunotoxicants

Immune response may be innate or acquired (adaptive) and a lot of different specialized cells are involved. It requires a complex network of intercellular messengers (especially cytokines) and may be elicited at different levels against a highly heterogeneous set of antigens (both exogenous and endogenous). Immune system interacts with and is regulated by other physiological systems, primarily the endocrine and nervous ones, but a growing body of scientific evidence indicates that the microbiome plays a crucial role in regulating the immune response [4-6].

Moreover, at least some features of the immune response are shown to be affected by circadian rhythmicity and dysregulation of the last one may potentially alter immune function [7-8], though little is known in this regard until now. A fine regulation of the immune response is essential to protect body against infections, for early detection and elimination of transformed cells as well as to prevent autoimmune phenomena.

Immune system is immature at birth, maturates during childhood, but the full immunocompetence is established in the adolescence, while ageing is accompanied by a certain degree of immune impairment, whose consequences are not easy to determine, but are dependent on individual features as well as concomitant diseases and medical treatments. Immune response in adults is susceptible to be affected by some types of exposures during prenatal life or in the first postnatal period, although there is no still solid evidence in this regard.

Congenital or acquired immune deficits make the body more susceptible to infections as well as to the development of certain types of cancer. On the opposite, a dysregulation of the immune response is the leading cause of autoimmune diseases. However, outcomes due to immune dysregulation may be highly variable, spanning from severe to mild immunodeficiency and subtle effects or, on the opposite, to autoimmune reactions and diseases as well as to a higher cancer risk. In some cases, immune dysregulation may result into beneficial effects for health (see the simplified scheme reported in figure 2).

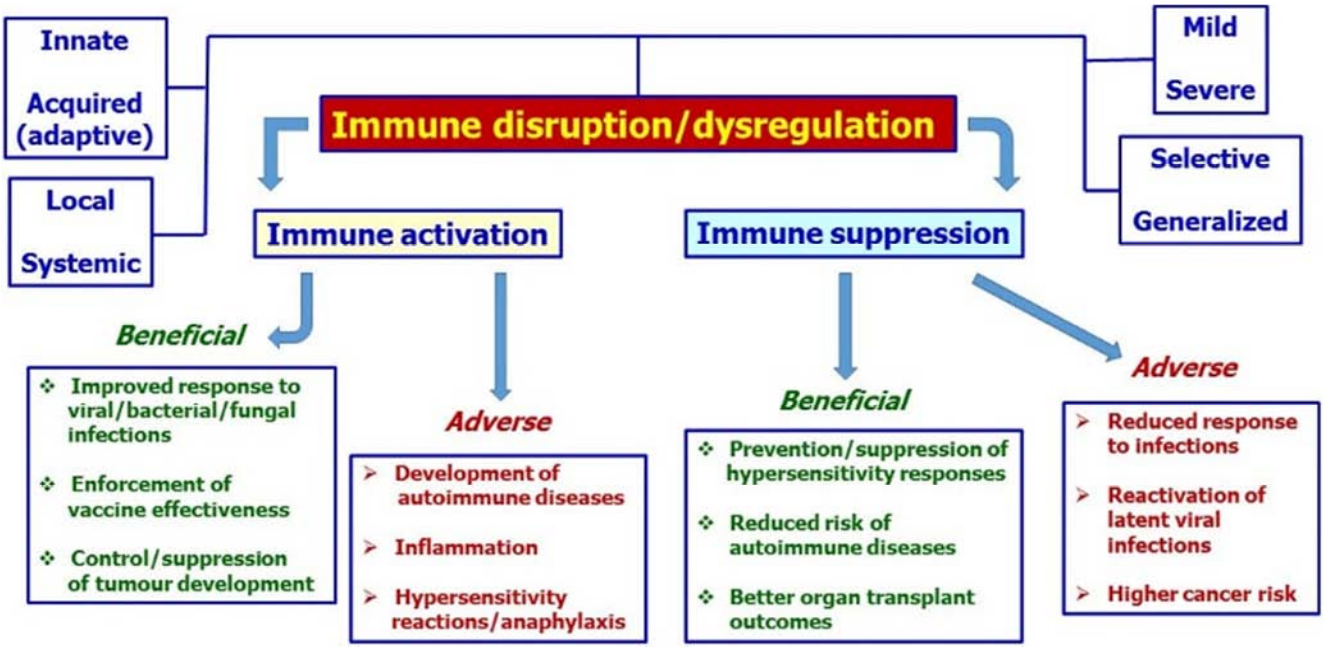

Figure 2. *An overview of the consequences due to immune disruption/dysregulation. Potential adverse or beneficial health outcomes are summarized in the lower boxes.*

Due to complexity and redundancy of the immune response, type/s and extent of the alteration/s involved, individual susceptibility, exposure to immune active agents, lifestyles, concomitant diseases, environmental and occupational exposures etc. all contribute to shape the health outcomes. Drugs and other xenobiotics may interfere with mechanisms involved in the immune response at different levels, with variable overlapping for different chemicals, and the identification of suitable biomarkers of exposure/effect/susceptibility is a concern of increasing importance (see for instance [9-11]).

Among xenobiotics, a growing number of pollutants in living and working settings are potentially able to modulate one or more molecular and cellular pathways eliciting the immune response (see for instance [9, 12-13]). Mechanisms include the alteration of the cytokines secretion pattern by one or more types of immunocompetent cells. Both humoral and cell mediated immunity may be affected, including pathways regulating the strength and duration of the immune response. Moreover, some immunotoxicants may interfere with the response to mitogens by immunocompetent cells or may induce a direct toxic damage to lymphoid organs.

In this paper, the term "immunotoxicant" is used in reference to a chemical agent able to interfere with the immune function in a wide sense, resulting in a potential activation or suppression, at different degrees, of one or more features of the immune response. In this regard, the terms immunotoxicity and immunomodulation as well as similar ones, although not overlapping (for instance immunomodulation may or may not result in immunotoxicity depending on concomitant factors and boundary conditions), may conceptually be used in an interchangeable way. Sensitizers (e.g. allergens) are a special case of immune active physical, chemical and biological agents and are not included in the present discussion. The following examples indicate compounds (or classes of compounds) for which, based primarily on *in vitro* and *in vivo* studies, an immunomodulatory action (potentially resulting in immunotoxicity) was shown to some extent and at any level of the overall immune function.

(1) Metals like arsenic, lead and mercury [14-16].
(2) Polycyclic Aromatic Hydrocarbons (PAHs) [17-18].
(3) Ozone [19].
(4) Benzene, trichloroethylene, tetrachloroethylene, toluene, styrene [20].
(5) Diesel exhausts [20].
(6) Crystalline silica [20].
(7) Welding fumes [20].
(8) Pesticides belonging to carbamates, organophosphorus compounds, organochlorines, pyrethroids [9, 12], including those with estrogenic activity reported in the following point of this list.
(9) Environmental estrogens. Phytoestrogens in food (like ginestein and zearalenone), bisphenol-A, 2,3,7,8-tetrachloodibenzo-p-dioxin (2,3,7,8-TCDD) and estrogenic pesticides (insecticides like DDT, metoxychlor and chlordane, herbicides like exachlorobenzene, fungicides like pentachlorophenol and nematocides like aldicarb) are included [21].
(10) Nanoparticles and nanomaterials (silica nanoparticles, TiO_2, carbon nanotubes, fullerenes, nanoparticles in general) [22-24].

Target tissue(s)/organ(s) of an immunotoxicant may be the skin or the respiratory tract for local immunomodulatory actions (with or without a systemic immunologic involvement) or immunocompetent cells/tissues (e.g lymph nodes) when a systemic absorption occurs. Multiple approaches and methods were developed over time to assess the immunotoxic properties of a chemical, but an integrated and validated approach is not still available (see for instance [25]), especially for topics like developmental immunotoxicity. Experimental and epidemiological evidence about immunotoxicants is growing but still insufficient and, jointly with other critical issues, does not allow to predict the health outcome/s given a certain pattern of individual exposure to one or more compounds with immune modulating properties, especially in occupational settings (a schematic view of the concerns in this regard is reported in table 1).

Table 1. *Occupational exposure to immune-modulating agents: challenges in risk assessment.*

Action mechanism/s	Multiple molecular and cellular pathways of interference with immune response, depending on the chemical involved. In some cases a chemical exerts its immunomodulatory effects through several action mechanisms
Threshold of effect	Variable, but in most cases potentially low or very low: doses necessary to induce immunomodulatory effects vary on the basis of compound, action mechanism/s, molecular/cellular pathways affected, absorption route/s and outcome/s considered
Dose-response relationship	Not fully assessed in most cases. A well characterized dose-response relationship between an immunotoxic chemical and a given immune endpoint or a given set of immune responses is often not flanked by a clear relationship between the level of immune impairment and the occurrence/severity of a health outcome
Types of effect	Likely to be subtle in most cases, but with potential long-lasting severe health consequences
Occupational exposure	Extremely variable, but often at low levels for a prolonged time
Interactions	Possible synergy between two or more immune modulating agents. Immunotoxicity potentially modulated by co-exposure to irritants, sensitizers, radiation, severe thermal environments etc.

As an example, beside the question of the dose-response relationship between an immunotoxic chemical and a specific immune response a more complex question is to assess the relationship between the level of immune dysregulation on one side and, for instance, the quantification of the increased susceptibility to infections on the other side [26]. The same is conceptually valid in the case of cancer and autoimmune diseases. In any case, dose-response relationship and threshold/s of effect depend not only on the agent involved, but also on exposure route, previous immune features, individual susceptibility and co-exposures.

2.2. Solar Radiation

Solar radiation (SR) includes ultraviolet (UV), visible and infrared (IR) radiation. UV radiation includes UVC (100 - 280 nm), UVB (280 - 315 nm) and UVA (315 - 380 nm), the last one subdivided into UVA1 (320 - 340 nm) and UVA2 (340 - 400 nm), visible radiation spans from 380 to 780 nm, while IR radiation covers the spectral range 780 nm - 1 mm. Three IR sub-bands are recognized: IRA (780 - 1.400 nm), IRB (1.400 - 3.000 nm) and IRC (3.000 - 1 mm). The SR composition at the ground is different from that at the upper limit of the atmosphere, as the ozone layer completely blocks UVC band and largely absorbs UVB. So, at the ground SR includes 5-6% UV (of which up to 95% UVA), about 45% visible radiation and 50% IR (the IRA band alone is over 30% of the solar spectrum) [27-29]. Biological and health effects of SR mostly involve the skin and the eye and are largely due to UV radiation. However, a growing body of experimental evidence indicates that visible radiation and IRA, by alone or synergizing with UV radiation, may exert a biological action resulting in potential adverse effects on skin and eye (for instance cancer, accelerated photoageing, cataract or retinal damage) for long-term exposures [30-31]. UV radiation may induce both acute and long-lasting effects on skin (including erythema, melanoma and non-melanoma skin cancer, photoageing) and eye (keratitis, *pterygium*, cataract and macular degeneration) [32]. SR as a whole and the single UV bands (UVA, UVB and UVC) are recognized to be carcinogenic to humans (group 1 of the International Agency for Research on Cancer classification of the carcinogenic evidence of an agent [28]). The action mechanism includes DNA damage and reactive oxygen species (ROS) production in the target cells and tissues. The biological effectiveness of UV radiation varies greatly with the wavelength, being maximum around 300 nm and falling rapidly as we move toward greater wavelengths. Action spectra differ in relation to the biological effect concerned, but for many effects, there is a substantial overlapping. For instance, the action spectrum of erythema is regarded as valid also for some long-term effects like actinic keratosis and squamous cell carcinoma of the skin. Solar UV but also the visible band of SR may induce phototoxic and/or photoallergic reactions when photosensitizers are present into the skin or eye tissues. Beside adverse effects, UV radiation may exert proven (e.g. vitamin D3 synthesis) or supposed (e.g. a reduced risk of some internal cancers, blood pressure lowering) beneficial effects. Melanin synthesis and skin thickening may be viewed as defence mechanisms or adaptive responses to UV exposure, whose effectiveness is highly variable among individuals, depending on biological features (*in primis* the phototype). A peculiar effect linked to UV exposure is immune suppression, which involves Langerhans and other immunocompetent cells in the skin, as well as keratinocytes, and may lead to a local but also a systemic depression of the immune response, the last one due to immune cell migration to regional lymph nodes as well as to cytokines production and release. UV immunosuppressive effects recognize several action mechanisms at molecular and cellular level, not yet completely elucidated but with an increasing evidence of crosstalk between biochemical cascades [33]. UV-induced immune suppression was repeatedly shown in the last decades in experimental animals in terms of inhibition of delayed type immune reactions or sensitization reactions, but the epidemiological evidence is still lacking or largely insufficient. The action spectrum of UV immune suppression displays a peak at 300 nm and additional peak into the UVA2 range (370 nm) [34-35]. Moreover, the dose-response relationship for immunosuppressive effects seems to be bell-shaped for UVA and linear with a plateau for UVB. Consequently, the relative importance of the two bands in inducing immunosuppressive responses for individuals exposed to solar UV radiation is dependent on time of exposure, prevailing UVA effects for exposures of short duration (minutes or tens of minutes) and UVB action for more prolonged exposures. Immunomodulating effects of UV, whose study is included in the relatively new discipline of *photoimmunology* [36], may be involved in the carcinogenic action of SR and it is speculated that UV immune suppression may increase the susceptibility to infectious agents in human populations and may reduce the effectiveness of vaccines [37-38]. An overview of health effects due (or likely to be due) to SR is reported in figure 3.

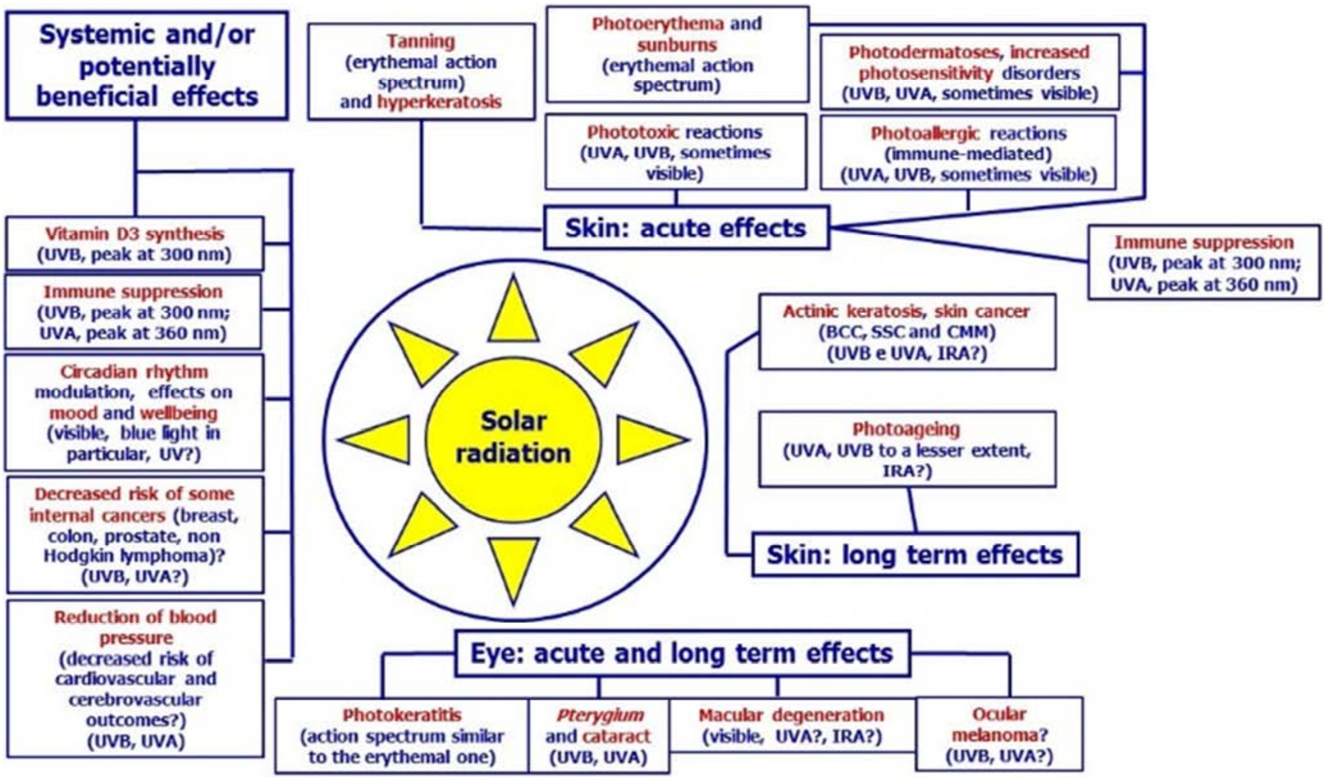

Figure 3. *Summary of the biological/health effects, both adverse and beneficial (proven or speculated), due to exposure to solar radiation. Some additional details in the text.*

The balance between potential beneficial and adverse effects of solar UV radiation depends on dose, dose-rate, cumulative exposure and individual susceptibility. Exposure to SR may be highly variable, depending on both environmental and individual features. It varies with time of day, latitude, altitude, cloudiness, atmospheric pollution, environmental albedo (an example is given by the reflecting power of surfaces surrounding the exposed individual), time spent outdoor, shadow, individual protection by the use of clothing, hats, sunglasses and sunscreen [28, 39-40]. Individual exposure may be measured by personal dosimeters or through adequate modelling. However, several concerns and limitations occur, making difficult the assessment of the total dose for a give tissue or body district, especially for long-term or lifetime cumulative exposures [41-42].

2.3. Climate Change

The ongoing climate change (CC) may deeply affect both natural environments and human communities. Trends and effects of a changing climate are periodically analyzed and monitored (see for instance [43]) and the impact on human health is largely discussed since many years. The focus is mainly on public health [44-47], with an increasing interest in occupational health [48-49]. It is generally recognized that CC, by alone or in combination with other environmental factors (e.g. stratospheric ozone dynamics), potentially affects environmental exposure to several physical, chemical and biological agents as well as disease vectors [3, 32, 50-56]. Exposure to volatile organic compounds (some of them with immunotoxic properties), pesticide (including the immunotoxic ones) and particulate matter (the last one containing or not in different amounts immunotoxic metals or other immunotoxic compounds) may increase or decrease, depending on local weather conditions, solar irradiation, personal habits, degree of personal protection and other individual and environmental factors, making the net result in terms of spatial and temporal patterns of exposure very difficult to predict [57] (see figure 4).

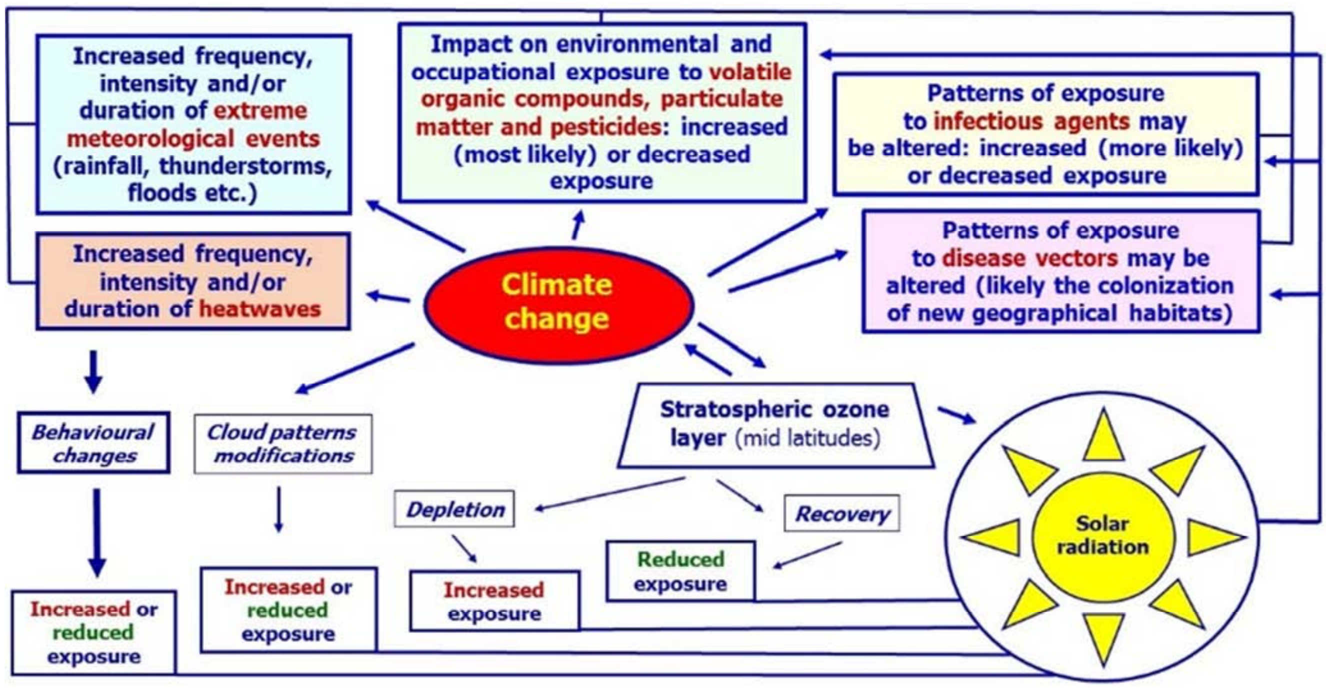

Figure 4. *Interplay between climate change, stratospheric ozone, meteorological features, solar radiation and exposure to chemical and biological agents as well as to disease vectors. See text for references.*

Consequently, health outcomes are even more difficult to determine at individual and group level.

2.4. Outdoor Workers

Several working activities are conducted outdoor, exposing workers to variable (but generally severe) microclimatic conditions, to variable (but generally high) levels of SR and to a pattern of pollutants qualitatively and quantitatively variable, depending on location, time of day, season, atmospheric conditions, distance from environmental sources of pollution, type of job/activity performed etc.

The overall number of exposed workers is very difficult to quantify and one reason is that presently there is no a robust and shared definition of "outdoor worker". For instance, there is no agreement on the minimum working time spent daily or weekly outdoor to define a worker as an outdoor worker. Moreover, while many activities are conducted outdoor or predominantly outdoor, others are mixed (partly outdoor and partly indoor). In addition, a lot of indoor activities may expose workers to risk factors typical of the outdoor environment, e.g. SR through windows and other transparent barriers. Another example deals with outdoor biological agents and allergens moving inside through doors/windows opening and/or by active or passive transport due to human, animal or non-living matrices [58-65].

Even with these limitations, it is possible to identify working activities or categories, reported in the following not exhaustive list, for which the outdoor component is prevailing (or in any case not negligible): asphalt workers, beach workers, construction workers, drivers (trucks, public transports etc.), farmers and forestry workers, fishing activities, fuel station workers, green areas maintenance workers, offshore workers, open sky miners, outdoor loading and unloading workers, outdoor security activities, outdoor sport instructors, postmen, power lines and water pipes workers, ski instructors and other outdoor winter workers, street vendors.

3. Results

Metals, solvents, some pesticides, dioxins and other chemicals or classes of chemicals, used or produced during working activities, or in any case present in the workplaces, display *in vivo* and *in vitro* immunotoxic properties, regardless their possible sensitizing properties. Outdoor workers may be simultaneously and chronically exposed to immunotoxic chemicals and SR; the ongoing CC may, depending on the specific environmental and/or working conditions, increase or (on the opposite) decrease exposure to these substances and to SR. The net effect on the immune response regarded as a whole is, once again, very difficult to predict. In fact, it depends on the combination and levels of the exposures involved, as well as on the individual health status and the health outcome/s considered (immune response to viral, bacterial or fungal pathogens, reactivation of the latent viral infections, autoimmune diseases, cancer). Moreover, a specific agent may display a bimodal or multimodal action on the immune response, based on the level and modes of exposure.

Even for a well-known physical agent like temperature, whose immunomodulating action is recognized long since, a considerable level of uncertainty does still exist. Temperature rise, for instance due to fever, increases the effectiveness of the immune response as a whole and this has a clear evolutionary significance in terms of response to infections. For core temperatures higher than 40 °C immune function tends to decline. However, excluding fever, the available evidence has not still clearly addressed the effects of different patterns of temperature elevation, suggesting that degree, duration and frequency of temperature variation, as well as local vs systemic heating, may be important in determining the final outcome/s (see for instance [66]). Moreover, the immune function might be differently affected in terms of acute or long-term responses.

EU directives on occupational health and safety (starting from the framework directive 89/391/EC [67]) establish the assessment of "all" risk factors existing in the workplace and, to reduce or eliminate risks, the adoption of suitable preventive and protective measures (both collective and individual, whose modulation is dependent on types and levels of the risk/s involved). Existing European regulation repeatedly stresses the question of "workers" at particular risk, i.e. workers that, for physiological features, pathological conditions, lifestyles or co-exposures, may be more susceptible to the adverse health effects induced by the exposure to a given risk factor, for instance a chemical or a physical agent.

In these cases, thresholds of induction for an adverse health effect may be lower than those recognized for a "standard" individual. Consequently, if a worker is regarded as at particular risk an individual risk assessment is requested. Removal from exposure or the implementation of more stringent preventive or protective measures could be necessary in some cases.

Exposure to agents disrupting skin or mucosal barriers (such as skin and respiratory irritants, as well as detergents) has to be assessed. On one side these agents may facilitate the absorption of immunotoxic chemicals while on the other side the disruption of a biological barrier elicits itself an immune response, which may represent a feature making more complex the action of an immunotoxic chemical. Risks due to chemical agents has to be assessed in the workplace in any case [68] (Directive 98/24/EC) on the basis of the hazard classification (CLP Regulation) of the chemical/s used or produced in the working process and, if the case, the determination of the exposure levels.

Exposure to carcinogenic chemicals acting both at the skin level and/or involving internal organs (e.g. polycyclic aromatic hydrocarbons, crystalline silica, wood dust, carcinogenic metals) has to be assessed. This is a duty of the employer stated by regulatory provisions [69] (Directive 2004/37/EC), but it is important for an additional reason: a mild to severe degree of local or systemic immune depression may increase the risk of cancer for both skin and some internal organs. Consequently, a prolonged exposure to one or more immunotoxicants may facilitate the action of known carcinogenic agents, for instance lowering the dose of a carcinogen required to induce a given response in terms of cancer induction (e.g. the fraction of exposed individuals developing cancer).

Outdoor workers are likely to be the best example of the concerns in implementing regulatory provisions on occupational health and safety.

The work environment is not controlled as in the case of the indoor one, additional risk factors (such as SR and atmospheric agents) are present, variability of environmental conditions is high and workers may be occasionally or repeatedly exposed to severe or extreme conditions, such as natural disasters and epidemic events [70-71], outdoor and indoor extreme temperatures [72-73] and thunderstorms [74-76].

Moreover, exposure to chemicals used in or produced by the working process is flanked by exposure to the urban and other atmospheric pollutants. In these settings, the identification and protection of workers at particular risk may pose additional concerns (a profile of conditions of increased susceptibility to categories of occupational risk factors relevant for outdoor workers is given in [77]). Therefore, the case of occupational outdoor exposure to SR and immunotoxic chemicals in the framework of a changing climate is paradigmatic in this regard for the previously reported reasons.

The depicted scenario may contribute to add pieces in order to define the "exposome" of several groups of outdoor workers. Following the definition of exposome coined by Wild's in 2005 [78] that: "……. *encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards*", the term exposome acquired a more extensive significance and, for instance, was defined as: "…… *the summation and integration of external forces acting upon our genome throughout our lifespan*" [79].

The enormous complexity of the concept of exposome lead some authors to split it into subdomains, each one theoretically of less complex definition and measurement. Regarding outdoor workers may be of particular interest the concept of urban exposome, since many outdoor workers perform their activities in urban settings. The urban exposome *can be defined as the continuous spatiotemporal surveillance/monitoring of quantitative and qualitative indicators associated with the urban external and internal domains that shape up the quality of life and the health of urban populations, using small city areas, i.e. neighborhoods, quarters, or smaller administrative districts, as the point of reference* [80]. In this regard some authors stress the importance to promote different control strategies, including the engineering ones [81].

Presently, there are no approaches to assess the health effects of complex combined exposures, especially if they involve a high number of different chemicals and physical agents. The individual response to environmental agents may be explored by emerging methodologies, those collectively known as "omics" [82-86]. However, regardless concerns related to the full development of these technologies and costs, the central question remains the interpretation in terms of biological significance, individual susceptibility, disease risk and outcome severity of the big data sets obtained from omics technologies [87-90] applied to a variety of biological samples.

4. Conclusions

The protection of outdoor workers from the effects due to combined exposure to immunotoxicants, SR and variables connected to CC needs a careful assessment of all the factors involved. Moreover, co-exposure to chemical or physical agents able to modulate the effects due to a given level of exposure to an immunotoxic agent or a combination of immunotoxic agents has to be taken into account and, when possible, quantified. This topic is quite complex to address, especially when individual features, pathological conditions, medical treatments and lifestyles are to be taken into account and negative but in some cases even positive health consequences may result.

The immune profile of the worker is a primary step to evaluate during the health surveillance, paying attention to conditions of mild immune depression. The combination of immune markers to assess, through the execution of basal and/or second level tests (conducted on blood, urine or other body fluid by conventional or innovative techniques), is based on individual features and environmental exposures and may include cellular phenotypes, activation markers, antibody profiling, cyto- and chemokines as well as cell proliferation. Individual profile in terms of use of drugs (primarily immunosuppressive ones), pathological conditions and lifestyles has to be scrupulously assessed. Smoking habit and alcohol consumption may be important with regard to their potential influence on the immune response. The disruption of circadian rhythms may affect the immune response: consequently, shift work represents an additional concern in this regard. Moreover, though SR is not a risk factor during nighttime, all other outdoor exposures may persist an in some cases even increase.

The level of protection has ideally to be set on the basis of a balance between adverse and potential beneficial effects; workers have to be provided with adequate information and training, while the identification and implementation of preventive and protective measures must agree as much as possible to the needs and preferences expressed by the individual worker. This is particularly true for protection from SR (clothing, eyeglasses, hat and sunscreens). The use of SR protective clothing/devices by a worker has to be graded based on the level of exposure to SR, but must also be harmonized with features concerning thermal comfort and with the use of other devices eventually needed to protect the worker him/herself from dust, fumes, chemical and biological aerosols etc.

As outdoor working activities are frequently interfaced with the indoor ones and the same worker may be alternatively exposed to outdoor and indoor risk factors even within the same working day or working shift, it is important to match outdoor concerns with indoor ones. An unhealthy indoor environment represents an additional challenge for the immune system and an individual immune response previously impaired by different patterns of exposure to outdoor physical and/or chemical agents (the exposure to which, in turn, is likely to be modified by CC as stated above) may be less effective.

Moreover, CC affects not only the outdoor settings but, directly or indirectly, the indoor ones too. In summary, as stated by the NIOSH itself: "*Variation in temperature, precipitation, wind, or other type of weather have the potential to affect human health in several direct and indirect ways. The challenge is to research and characterize how these climate conditions may influence worker health and safety and to establish plans for mitigating, responding to, and adapting to current and anticipated health impacts*" (https://www.cdc.gov/niosh/topics/climate/default.html).

The acquisition of a more complete an coherent set of information on the topics discussed in this paper requires, in our opinion, the design and conduction of multicentric case-control studies on outdoor workers, accounting for all the factors potentially involved in immune modulation and for a large number of potential health outcomes. Comparisons should be mostly focused on geographical location, meteorological data, environmental pollution, job performed, time effectively spent outdoor, occupational history, leisure time, life habits, health status and immunological parameters. Moreover, it should be of great utility to recruit occupational cohorts to be followed over time.

On another side, it is essential to continue to explore omics approaches, including those able to detect the epigenetic profile at individual and group level (e.g methylation patterns and microRNAs expression) as well as the epigenetic response to environmental factors involved. An important goal is the identification and validation of suitable biomarkers of exposure, effect and individual susceptibility in the case of multiple and complex exposures to occupational and environmental agents modulating the immune response in relation to short and long term impact on the health status.

Finally, an effective link between occupational and public health should be promoted in order to plan the optimal preventive and protective measures against diseases and vulnerabilities due to CC and complex environmental exposures. In perspective, they have to include adaptation strategies involving education to healthier lifestyles.

References

[1] Bell, J. E., Brown, C. L., Conlon, K., Herring, S., Kunkel, K. E., Lawrimore, J., Luber, G., Schreck, C., Smith, A., Uejio, C. (2018). Changes in extreme events and the potential impacts on human health. Journal of Air Waste Management Association, 68,265-287. doi: 10.1080/10962247.2017.1401017.

[2] Perkison, W. B., Kearney, G. D., Saberi, P., Guidotti, T., McCarthy, R., Cook-Shimanek, M., Pensa, M. A., Nabeel, I.; ACOEM task force on climate change. (2018). Responsibilities of the occupational and environmental medicine provider in the treatment and prevention of climate change-related health problems. Journal of Occupational and Environmental Medicine, 60, e76-e81. doi: 10.1097/JOM.0000000000001251.

[3] D'Ovidio, M. C., Grandi, C., Marchetti, E., Polichetti, A., Iavicoli, S. (2016). Preface. Climate change and occupational health. Annali dell'Istituto Superiore Sanità, 52,323-324. doi: 10.4415/ANN_16_03_03.

[4] Li, B., Selmi, C,. Tang, R., Gershwin, M. E., Ma, X. (2018). The microbiome and autoimmunity: a paradigm from the gut–liver axis. Cellular and Molecular Immunology 15,595-609. doi: 10.1038/cmi.2018.7.

[5] Kerry, R. G., Patra, J. K., Gouda, S., Park, Y., Shin, H-S., Das G. (2018). Benefaction of probiotics for human health: a review. Journal of Food and Drug Analysis, 26, 927-939. doi: 10.1016/j.jfda.2018.01.002.

[6] Sharma, A., Gilbert, J. A. (2018). Microbial exposure and human health. Current Opinion in Microbiology, 44, 79-87. doi: 10.1016/j.mib.2018.08.003.

[7] Asif, N., Iqbal R., Nazir C. F. (2017). Human immune system during sleep. American Journal of Clinical and Experimental Immunology, 6,92-96.

[8] Zhuang, X., 1 Rambhatla, S. B., Lai, A. G., McKeating, J. A. (2017). Interplay between circadian clock and viral infection. Journal of Molecular Medicine, 95, 1283-1289. doi: 10.1007/s00109-017-1592-7.

[9] Colosio, C., Birindelli, S., Corsini, E., Galli, C. L., Maroni, M. (2005). Low level exposure to chemicals and immune system. Toxicology and Applied Pharmacology, 207, S320-S328.

[10] Duramad, P., Holland, N. T. (2011). Biomarkers of immunotoxicity for environmental and public health research. International Journal of Environmental Research and Public Health, 8, 1388-1401. doi: 10.3390/ijerph8051388.

[11] Kreitinger, J. M., Beamer, C. A., Shepherd, D. M. (2016). Environmental immunology: Lessons learned from exposure to a select panel of immunotoxicants. Journal of Immunology, 196,3217-3225. doi: 10.4049/jimmunol.1502149.

[12] Corsini, E., Sokooti, M., Galli, C. L., Moretto, A., Colosio C. (2013). Pesticide induced immunotoxicity in humans: A comprehensive review of the existing evidence. Toxicology, 307,123-135. doi: 10.1016/j.tox.2012.10.009.

[13] Ngobili, T. A., Daniele, M. A. (2016). Nanoparticles and direct immunosuppression. Experimental Biology and Medicine, 241, 1064-1073. doi: 10.1177/1535370216650053.

[14] Attreed, S. E., Navas-Acien, A., Heaney, C. D. (2017). Arsenic and immune response to infection during pregnancy and early life. Current Environmental Health Reports, 4,229-243. doi: 10.1007/s40572-017-0141-4.

[15] Fenga, C., Gangemi, S., Di Salvatore, V., Falzone, L., Libra, M. (2017). Immunological effects of occupational exposure to lead (Review). Molecular Medicine Reports, 15,3355-3360. doi: 10.3892/mmr.2017.6381.

[16] Maqbool, F., Niaz, K., Hassan, F. I., Khan, F., Abdollahi, M. (2017). Immunotoxicity of mercury: pathological and toxicological effects. Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis Ecotoxicology Reviews, 5,29-46. doi: 10.1080/10590501.2016.1278299.

[17] Meldrum, K., Gant, T. W., Macchiarulo, S., Leonard, M. O. (2016). Bronchial epithelial innate and adaptive immunity signals are induced by polycyclic aromatic hydrocarbons. Toxicological Research, 5,816-827. doi: 10.1039/c5tx00389j.

[18] Abdel-Shafy, H. I., Mansour, M. S. M. (2016). A review on polycyclic aromatic hydrocarbons: source, environmental impact, effect on human health and remediation. Egyptian Journal of Petroleum, 25,107-123.

[19] Li, Z., Tighe, R. M., Feng, F., Ledford, J. C., Hollingsworth, J. W. (2013). Genes of innate immunity and the biological response to inhaled ozone. Journal of Biochemical and Molecular Toxicology, 27, 3-16. doi: 10.1002/jbt.21453.

[20] Veraldi, A., Costantini, A.S., Bolejack, V., Miligi, L., Vineis, P., van Loveren, H. (2006). Immunotoxic effects of chemicals: a matrix for occupational and environmental epidemiological studies. American Journal of Industrial Medicine, 49,1046-1055.

[21] Chighizola, C., Meroni, P. L. The role of environmental estrogens and autoimmunity. (2012). Autoimmunity Reviews, 11, A493-A501. doi:10.1016/j.autrev.2011.11.027.

[22] Chen, L., Liu, J., Zhang, Y., Zhang, G., Kang, Y., Chen, A., Feng, X., Shao, L. (2018). The toxicity of silica nanoparticles to the immune system. Nanomedicine 13, 1939-1962. doi: 10.2217/nnm-2018-0076.

[23] Smith, M. J., Brown, J. M., Zamboni, W. C., Walker, N. J. (2014). From immunotoxicity to nanotherapy: the effects of nanomaterials on the immune system. Toxicolology Sciences, 138,249-255. doi: 10.1093/toxsci/kfu005.

[24] Pallardy, M. J., Turbica, I., Biola-Vidamment, A. (2017). Why the immune system should be concerned by nanomaterials? Frontiers in Immunology, 8,544. doi: 10.3389/fimmu.2017.00544.

[25] Boverhof, D. R., Ladics, G., Luebke, B., Botham, J., Corsini, E., Evans, E., Germolec, D., Holsapple, M., Loveless, S. E., Lu, H., van der Laan, J. W., White, K. L. Jr., Yang, Y. (2014). Approaches and considerations for the assessment of immunotoxicity for environmental chemicals: a workshop summary. Regulatory Toxicology and Pharmacology, 68,96-107. doi: 10.1016/j.yrtph.2013.11.012.

[26] DeWitt, J. C., Germolec, D. R., Luebke, R. W., Johnson, VJ. (2017). associating changes in the immune system with clinical diseases for interpretation in risk assessment. Current Protocols in Toxicology, 67,18.1.1-18.1.22.

[27] Svobodova, A., Vostalova, J. (2010). Solar radiation induced skin damage: review of protective and preventive options. International Journal of Radiation Biology, 86, 999-1030. doi: 10.3109/09553002.2010.501842.

[28] International Agency for Research on Cancer (IARC). A review of human carcinogens. IARC monographs on the evaluation of carcinogenic risks to humans. Vol. 100 D-radiation. Lyon: IARC; 2012.

[29] Sowa, P., Rutkowska-Talipska, J., Rutkowski, K., Kosztyła-Hojna, B., Rutkowski, R. (2013). Optical radiation in modern medicine. Postepy Dermatology and Allergology, 4,246-51. doi: 10.5114/pdia.2013.37035.

[30] Zastrow, L., Lademann, J. (2016). Light - instead of UV protection: new requirements for skin cancer prevention. Anticancer Research, 36,1389-1394.

[31] Grandi, C., Militello, A., Borra, M. (2018). The role of near infrared with regard to potential long-term adverse effects in outdoor workers exposed to solar radiation. Occupational and Environmental Medicine, 75, A419-A4200. 10.1136/oemed-2018-ICOHabstracts.1198

[32] Grandi, C., Borra, M., Militello, A., Polichetti, A. (2016). Impact of climate change on occupational exposure to solar radiation. Annali dell'Istituto Superiore Sanità, 52, 3,343-356. doi: 10.4415/ANN_16_03_06.

[33] Prasad, R., Katiyar, S. K. (2017). Crosstalk among UV-induced inflammatory mediators, DNA damage and epigenetic regulators facilitates suppression of the immune system. Photochemistry and Photobiology, 93,930-936. doi: 10.1111/php.12687.

[34] COLIPA. (2006). International Sun Protection Factor (SPF). Test Method. Brussels, COLIPA.

[35] Matthews, Y. J., Halliday, G. M., Phan, T. A. (2010). A UVB wavelength dependency for local suppression of recall immunity in humans demonstrates a peak at 300 nm. Journal of Investigative Dermatology, 130,1680-1684. doi: 10.1038/jid.2010.27.

[36] Elmets, C. A., Calla, C., Xu, H. (2014). Photoimmunology. Dermatologic Clinics, 32,277-290.

[37] Norval, M., Halliday, G. M. (2011). The consequences of UV induced immunosuppression for human health. Photochemistry and Photobiology, 87,965-977. doi: 10.1111/j.1751-1097.2011.00969.x.

[38] Guo, B., Naish, S., Hu, W., Tong, S. (2015). The potential impact of climate change and ultraviolet radiation on vaccine preventable infectious diseases and immunization service delivery system. Expert Review of Vaccines, 14,561-567. doi: 10.1586/14760584.2014.990387.

[39] Godar, DE. UV doses worldwide. (2005). Photochemistry and Photobiology, 81,736-749.

[40] Milon, A., Sottas, P. E., Bulliard, J. L., Vernez, D. (2007). Effective exposure to solar UV in building workers: influence of local and individual factors. Journal of Exposure Science and Environmental Epidemiology, 17,58-68.

[41] Modenese, A., Bisegna, F., Borra, M, Grandi, C., Gugliermetti, F., Militello, A., Gobba, F. (2016). Outdoor work and solar radiation exposure: evaluation method for epidemiological studies. Medycyna Pracy, 67,577-587.

[42] Borra, M., Bisegna, F., Burattini C., Gobba F., Grandi C., Gugliermetti, F., Militello, A., Modenese, A. (2018). A simple method to determine the cumulative dose in outdoor workers exposed to solar radiation. Occupational and Environmental Medicine, 75, A1-A650.

[43] Intergovernmental Panel on Climate Change (IPCC). Climate Change 2014. Synthesis Report. Geneva: IPCC; 2014.

[44] Chiabai, A., Quiroga, S., Martinez-Juarez, P., Higgins, S., Taylor, T. (2018). The nexus between climate change, ecosystem services and human health: Towards a conceptual framework. Science of the Total Environment, 635,1191-1204. doi: 10.1016/j.scitotenv.2018.03.323.

[45] McGushin, A., Tcholakov, Y., Hajat S. (2018). Climate change and human health: Health impacts of warming of 1.5°C and 2°C. International Journal of Environmental Research and Public Health, 15, E1123. doi: 10.3390/ijerph15061123.

[46] Patz, J. A., Thomson, M. C. (2018). Climate change and health: Moving from theory to practice. PLoS Medicine, 15, e1002628. doi: 10.1371/journal.pmed.1002628.

[47] Zinsstag, J., Crump, L., Schelling, E., Hattendorf, J., Maidane, Y. O., Ali, K. O., Muhummed, A., Umer, A. A., Aliyi, F., Nooh, F., Abdikadir, M. I., Ali, S. M., Hartinger, S., Mäusezahl, D., de White, M. B. G., Cordon-Rosales, C., Castillo, D. A., McCracken, J., Abakar, F., Cercamondi, C., Emmenegger, S., Maier, E., Karanja, S., Bolon, I., de Castañeda, R. R., Bonfoh, B., Tschopp, R., Probst-Hensch, N., Cissé G. (2018). Climate change and one health. FEMS Microbiology Letters, 365, doi: 10.1093/femsle/fny085.

[48] Schulte, P. A., Chun, H. K. (2009). Climate change and occupational safety and health: establishing a preliminary framework. Journal of Occupational and Environmental Health, 6,542-554. doi:10.1080/15459620903066008

[49] Schulte, P. A., Bhattacharya, A., Butler, C. R., Chun, H. K., Jacklitsch, B., Jacobs, T., Kiefer, M., Lincoln, J., Pendergrass, S., Shire, J., Watson, J., Wagner, G. R. (2016). Advancing the framework for considering the effects of climate change on worker safety and health. Journal of Occupational and Environmental Hygiene, 13,847-865. doi: 10.1080/15459624.2016.1179388.

[50] Bais, A. F,. McKenzie, R. L., Bernhard, G., Aucamp, P. J., Ilyas, M., Madronich, S., Tourpali, K. (2015). Ozone depletion and climate change: impacts on UV radiation. Photochemistry and Photobiology Sciences, 14, 19-52. doi: 10.1039/c4pp90032d.

[51] Lucas, R. M., Norval, M., Neale, R. E., Young, A. R., de Gruijl, F. R., Takizawa, Y., van Der Leun, JC. (2015). The consequences for human health of stratospheric ozone depletion in association with other environmental factors. Photochemistry and Photobiology Sciences, 14, 53-87. doi: 10.1039/c4pp90033b.

[52] Madronich, S., Shao, M., Wilson, S. R., Solomon, K. R., Longstreth, J. D., Tang, X. Y. (2015). Changes in air quality and tropospheric composition due to depletion of stratospheric ozone and interactions with changing climate: implications for human and environmental health. Photochemistry and Photobiology Sciences, 14,149-169. doi: 10.1039/c4pp90037e.

[53] Applebaum, K. M., Graham, J., Gray, G. M., LaPuma, P., McCormick, S. A., Northcross A., Perry M. J. (2016) An overview of occupational risks from climate change. Current Environmental Health Reports, 3, 13-22. doi: 10.1007/s40572-016-0081-4.

[54] D'Ovidio, M. C., Annesi-Maesano, I., D'Amato, G., Cecchi, L. (2016). Climate change and occupational allergies: an overview on biological pollution, exposure and prevention. Annali dell'Istituto Superiore Sanità, 52,406-414. doi: 10.4415/ANN_16_03_12.

[55] Gatto, M. P., Cabella, R., Gherardi, M. (2016). Climate change: the potential impact on occupational exposure to pesticides. Annali dell'Istituto Superiore Sanità, 52,374-385. doi: 10.4415/ANN_16_03_09.

[56] Vonesch, N., D'Ovidio, M. C., Melis, P., Remoli, M. E., Ciufolini, M. G., Tomao, P. (2016). Climate change, vector-borne diseases and working population. Annali dell'Istituto Superiore Sanità, 52,397-405. doi: 10.4415/ANN_16_03_11.

[57] Grandi, C., D'Ovidio, M. C. Occupational exposure to immunotoxicants and solar radiation in the framework of the ongoing climate change: another step in exposome profiling. 32nd ICOH Congress 2018 The Convention Centre Dublin Sun 29th April - Fri 4th May 2018. 136. A54 Occupational and Environmental Medicine 2018; 75(Suppl 2): A1-A650. 10.1136/oemed-2018-ICOHabstracts.154

[58] Menzel, A., Matiu, M., Michaelis, R., Jochner, S. (2017). Indoor birch pollen concentrations differ with ventilation scheme, room location, and meteorological factors. Indoor Air, 27,539-550. doi: 10.1111/ina.12351.

[59] Singh, M., Hays, A. Indoor and outdoor allergies. (2016). Primary Care, 43,451-463. doi: 10.1016/j.pop.2016.04.013.

[60] Yamamoto, N., Matsuki, Y., Yokoyama, H., Matsuki, H. Relationships among indoor, outdoor, and personal airborne Japanese cedar pollen counts. PLoS One. 2015, 10:e0131710. doi: 10.1371/journal.pone.0131710.

[61] Oeder, S., Jörres, R. A., Weichenmeier, I., Pusch, G., Schober, W., Pfab, F., Behrendt, H., Schierl, R., Kronseder, A., Nowak, D., Dietrich, S., Fernández-Caldas, E., Lintelmann, J., Zimmermann, R., Lang, R., Mages, J., Fromme, H., Buters, J. T. (2012). Airborne indoor particles from schools are more toxic than outdoor particles. American Journal of Respiratory Cell and Molecular Biology, 47,575-582. doi: 10.1165/rcmb.2012-0139OC.

[62] Pongracic, J. A., O'Connor, G. T., Muilenberg, M. L., Vaughn, B., Gold, D. R., Kattan, M., Morgan, W. J., Gruchalla, R. S., Smartt, E., Mitchell, H. E. Differential effects of outdoor versus indoor fungal spores on asthma morbidity in inner-city children. (2010). Journal of Allergy and Clinical Immunology, 125,593-599. doi: 10.1016/j.jaci.2009.10.036.

[63] Jantunen, J., Saarinen, K. (2009). Intrusion of airborne pollen through open windows and doors. Aerobiologia, 25,193-201.

[64] Bielory, L., Deener, A. (1998). Seasonal variation in the effects of major indoor and outdoor environmental variables on asthma. Journal of Asthma, 35,7-48.

[65] Sterling, D. A., Lewis, R. D. (1998). Pollen and fungal spores indoor and outdoor of mobile homes. Annals of Allergy Asthma and Immunology, 80: 279-285.

[66] Beachy, S. H., Repasky, E. A. (2011). Toward establishment of temperature thresholds for immunological impact of heat exposure in humans. International Journal of Hyperthermia, 27,344-352. doi: 10.3109/02656736.2011.562873.

[67] Directive 89/391/EEC of the Council of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work. Official Journal of the European Communities L183/1. 29.6.89.

[68] Directive 98/24/EC of the Council of 7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC). Official Journal of the European Communities L 131/11. 5.5.98.

[69] Directive 2004/37/EC of the European Parliament and of the Council of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC. Official Journal of the European Union. L 229/23. 29.6.2004.

[70] Dunin-Bell, O. What do they know? Guidelines and knowledge translation for foreign health sector workers following natural disasters. (2018). Prehospital and Disaster Medicine, 33,139-146. doi: 10.1017/S1049023X18000146.

[71] Murphy, G. T., Birch, S., Mackenzie, A., Rigby, J., Langley J. (2017). An integrated needs-based approach to health service and health workforce planning: applications for pandemic influenza. Healthcare Policy, 13,28-42.

[72] Uejio, C. K., Morano, L. H., Jung, J., Kintziger, K., Jagger, M., Chalmers, J., Holmes, T. (2018). Occupational heat exposure among municipal workers. International Archives of Occupational and Environmental Health, 9,705-715. doi: 10.1007/s00420-018-1318-3.

[73] Piedrahita, H., Oksa, J., Malm, C., Rintamäki, H. (2008). Health problems related to working in extreme cold conditions indoors. International Journal of Circumpolar Health, 67,279-287.

[74] D'Amato, G., Annesi-Maesano, I., Cecchi, L., D'Amato, M. (2018). Latest news on relationship between thunderstorms and respiratory allergy, severe asthma, and deaths for asthma. Allergy, Sep 22. doi: 10.1111/all.13616.

[75] Thien, F., Beggs, P. J., Csutoros, D., Darvall, J., Hew, M., Davies, J. M., Bardin, P. G., Bannister, T., Barnes, S, Bellomo, R., Byrne, T., Casamento, A., Conron, M., Cross, A., Crosswell, A., Douglass, J. A., Durie, M., Dyett, J., Ebert, E., Erbas, B., French, C., Gelbart, B., Gillman, A., Harun, N. S., Huete, A., Irving, L., Karalapillai, D., Ku, D., Lachapelle, P., Langton, D., Lee, J., Looker, C., MacIsaac, C., McCaffrey, J., McDonald, C. F., McGain, F., Newbigin, E., O'Hehir, R., Pilcher, D., Prasad, S., Rangamuwa, K., Ruane, L., Sarode V., Silver J. D., Southcott A. M., Subramaniam, A., Suphioglu, C., Susanto, N. H., Sutherland, M. F., Taori, G., Taylor, P., Torre, P., Vetro, J., Wigmore, G., Young, A. C., Guest, C. The Melbourne epidemic thunderstorm asthma event 2016: an investigation of environmental triggers, effect on health services, and patient risk factors. (2018). Lancet Planet Health, 2, e255-e263. doi: 10.1016/S2542-5196(18)30120-7.

[76] Clayton-Chubb, D., Con, D., Rangamuwa, K., Taylor, D., Thien, F., Wadhwa, V. Thunderstorm asthma - revealing a hidden at-risk population. (2018). Internal Medicine Journal, Mar 23. doi: 10.1111/imj.13800.

[77] Grandi, C., D'Ovidio, M. C. Climate change and occupational health and safety: characterization and protection of outdoor workers belonging to particularly sensitive risk groups. XXXIV Giornata dell'Ambiente. Strategie di adattamento al cambiamento climatico (Roma, 8 novembre 2016). Atti dei Convegni Lincei 320. Roma 2018. Pagine: 199-205. Bardi Edizioni - Editore Commerciale - ISSN: 0391-805X - ISBN: 978-88-218-1167-8.

[78] Wild, C. P. (2005). Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiology, Biomarkers & Prevention, 14,1847-1850.

[79] Miller, G. W. The Exposome: A Primer. Academic Press, Elsevier, Inc. Waltham, MA, 2014.

[80] Andrianou, X. D., Makris, K. C. (2018). The framework of urban exposome: Application of the exposome concept in urban health studies. Science of Total Environment, 636,963-967. doi: 10.1016/j.scitotenv.2018.04.329.

[81] Dai, D., Prussin A. J. 2nd., Marr, L. C., Vikesland, P. J., Edwards, M. A., Pruden, A. (2017). Factors shaping the human exposome in the built environment: opportunities for engineering control. Environmental Science and Technology, 51,7759-7774. doi: 10.1021/acs.est.7b01097.

[82] Maitre, L., de Bont, J., Casas, M., Robinson, O., Aasvang, G. M., Agier, L., Andrušaitytė, S., Ballester, F., Basagaña, X., Borràs, E., Brochot, C., Bustamante, M., Carracedo, A., de Castro, M., Dedele, A., Donaire-Gonzalez, D., Estivill, X., Evandt, J., Fossati, S., Giorgis-Allemand, L., R Gonzalez, J., Granum, B., Grazuleviciene, R., Bjerve Gützkow, K., Småstuen Haug, L., Hernandez-Ferrer C., Heude B., Ibarluzea J., Julvez. J., Karachaliou, M., Keun, H. C., Hjertager Krog, N., Lau, C. E., Leventakou, V., Lyon-Caen, S., Manzano, C., Mason, D., McEachan, R., Meltzer, H. M., Petraviciene, I., Quentin, J., Roumeliotaki, T., Sabido, E., Saulnier, P. J., Siskos, A. P., Siroux, V., Sunyer, J., Tamayo, I., Urquiza, J., Vafeiadi, M., van Gent, D., Vives-Usano, M., Waiblinger, D., Warembourg, C., Chatzi, L., Coen, M., van den Hazel, P., Nieuwenhuijsen, M. J., Slama, R., Thomsen, C., Wright, J., Vrijheid, M. (2018). Human Early Life Exposome (HELIX) study: a European population-based exposome cohort. British Medical Journal Open, 8,9:e021311. doi: 10.1136/bmjopen-2017-021311.

[83] Rappaport, S. M. Redefining environmental exposure for disease etiology. (2018). NPJ Systems Biology and Applications, 4,30. doi: 10.1038/s41540-018-0065-0.

[84] Niedzwiecki, M. M., Walker, D. I., Vermeulen, R., Chadeau-Hyam, M., Jones, D. P., Miller, G. W. (2018). The exposome: molecules to populations. Annual Review of Pharmacology and Toxicology, Aug 10. doi: 10.1146/annurev-pharmtox-010818-021315.

[85] Coughlin, S. S. (2014). Toward a road map for global -omics: a primer on -omic technologies. American Journal of Epidemiology, 180, 1188-1195. doi: 10.1093/aje/kwu262.

[86] Martyniuk, C. J., Simmons, D. B. (2016). Spotlight on environmental omics and toxicology: a long way in a short time. Comparative Biochemistry and Physiology, Part D Genomics Proteomics, 19, 97-101. doi: 10.1016/j.cbd.2016.06.010.

[87] Liu, Y., Hoppe, B. O., Convertino, M. (2018). Threshold evaluation of emergency risk communication for health risks related to hazardous ambient temperature. Risk Analysis, 38,2208-2221. doi: 10.1111/risa.12998.

[88] Ristevski, B., Chen, M. Big data analytics in medicine and healthcare. (2018). Journal of Integrative Bioinformatics, 15, doi: 10.1515/jib-2017-0030.

[89] Lee, E. C., Arab, A., Goldlust, S. M., Viboud, C., Grenfell, B. T, Bansal, S. (2018). Deploying digital health data to optimize influenza surveillance at national and local scales. PLoS Computational Biology, 14, e1006020. doi: 10.1371/journal.pcbi.1006020.

[90] Xie, J., M. a,. A, Fennell, A., Ma, Q., Zhao, J. (2018). It is time to apply biclustering: a comprehensive review of biclustering applications in biological and biomedical data. Briefings in Bioinformatics. Feb 27. doi: 10.1093/bib/bby014.