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Cyanobacteria – insidious foe of the skin?

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ABSTRACT

Cyanobacteria are ancient photosynthetic microorganisms that shaped today's atmosphere. Anthropocentric and irresponsible activities are changing the atmosphere which favor the frequent occurrence and mass development of cyanobacteria. Extensive cyanobacterial blooming causes numerous problems, including negative effects on human skin. Climate change, depletion of ozone layer, and the increased ultraviolet radiation also affect the skin and lead to more frequent occurrence of skin cancer. This research, for the first time, attempts to establish a connection between these two factors, or whether, in addition to ultraviolet radiation, cyanobacteria can influence the incidence of melanoma. With this objective in mind, an epidemiological investigation was conducted in Vojvodina, Serbia. It was observed that the incidence of melanoma was higher in municipalities where water bodies used for recreation, irrigation and fishing are blooming; however, results could be considered as inconclusive, because of the restrictions in the cancer database. Nevertheless, results gathered from the reviewed literature support the hypothesis that cyanobacteria could be a new potential risk factor for melanoma, while climate change could be a catalyst that converts these potential risk factors into cofactors, which act synergistically with the main risk factor – ultraviolet radiation – and induce an increase of melanoma incidence.

Key words | climate change, cyanobacteria, melanoma, skin, ultraviolet radiation

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HIGHLIGHTS

- Effects of cyanobacteria on melanoma investigated for the first time in Vojvodina.
- Connection between melanoma and cyanobacterial exposure could not be verified.
- Review concerning effects of cyanobacteria/cyanotoxins on skin.
- Ultraviolet radiation and cyanobacteria present potential risk factor for melanoma.

INTRODUCTION

Microorganisms can, in different ways, affect the environment, and this especially refers to cyanobacteria. These ancient Gram-negative photoautotrophic microorganisms are one of the pioneering organisms of the planet Earth that appeared about two to three billion years ago (Knoll 2008). Since they were the first organisms that produced oxygen through photosynthesis, they influenced the creation of the present atmosphere and evolution of life on Earth. This makes them one of the most powerful and successful organisms on our planet. Even today, they are present in freshwater, marine, and terrestrial ecosystems worldwide, where they play an important role in the functioning of these ecosystems. In addition, cyanobacteria possess significant potential for biotechnological application; however, there is the other side of the coin, which is the phenomenon of cyanobacterial blooming (massive proliferation – when the abundance of cyanobacterial cells is greater than 10,000 per mL of water

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(Falconer 1999)) and the subsequent production of potent cyanotoxins.

Cyanotoxins are secondary metabolites which may evoke different negative effects on other microorganisms, plants, animals, and can lead to acute or chronic health problems in humans. For instance, cyanotoxins (primarily most toxic and most studied microcystins) have carcinogenic potency but the mechanisms of action are still being discovered. Nevertheless, epidemiological studies in China have shown the correlation between the presence of cyanobacteria/cyanotoxins in drinking water sources and higher incidence of primary liver cancer and colorectal cancer (Yu 1989; Ueno *et al.* 1996; Zhou *et al.* 2002). The same has been observed in Central Serbia, where in addition to these two cancers, another eight were found to have an increased incidence in the districts that are supplied with water from the blooming reservoirs (Svirčev *et al.* 2013, 2014a). One of those cancers is melanoma of the skin.

Melanoma is the 12th most common cancer worldwide (Ferlay *et al.* 2015) and is a most deadly form of skin cancer (4% of all cutaneous malignancies, but accounts for 65% of all skin cancer mortalities (Cummins *et al.* 2006; Porter 2011)), hence it presents a global health problem. It is the most aggressive and unpredictable skin cancer. Melanoma of skin is a malignant proliferation of melanocytes – the pigment forming cells of skin. Therefore, it primarily occurs in the skin (95% of cases), but also in the mucous membranes of the nose, mouth, intestine, anus, and vagina (Lian & Mihm 2014). Skin cancer is becoming the most common worldwide malignancy and its incidence and mortality have been increasing dramatically over the past decades. The global incidence of melanoma in 2015 was 351,880 cases with 59,782 deaths (Karimkhani *et al.* 2017). The incidence of melanoma is highest in Australia and New Zealand (higher ambient ultraviolet radiation (UVR) regions), where it is the fourth most common cancer; in the USA and Canada it is the seventh, then tenth in Scandinavia, and the eighteenth most common cancer in the UK (Marks 2000). Incidence appears to be low in Africa, Asia, and Latin America, since limited data are available from these regions, while most of the studies are focused on white populations in Australia, USA, and Europe.

Melanoma mortality in Europe is the third highest in the world, after Australia/New Zealand and North America. Melanoma incidence and mortality in Europe are high but variable among regions of the continent. For example, in 2008, the incidence in Scandinavia was the highest (15 cases per 100,000 inhabitants), while in Mediterranean countries was lower (5 per 100,000 inhabitants). Also, mortality of melanoma was high in Norway (3.2) and low in Greece (0.9). When it comes to countries, the incidence of melanoma was highest in Switzerland (19.2) and lowest in Greece (2.2). These differences can be the result of different geographical locations and climates, skin pigmentation – darker skin types in south-eastern Europe – genetic susceptibility differences, ethnic or custom differences, and greater resources for recreational sun exposure in north-western Europe. This explanation is not sufficient in the case of the differences between neighboring countries with similar characteristics (e.g., Romania and Hungary, or Poland and Germany) (Forsea *et al.* 2012; Kandolf-Sekulović *et al.* 2012). This divergence is noticeable even within south-eastern Europe among countries: Slovenia (14.1 males, 15.2 females – as in northern Europe), Croatia (8.3 males, 7.3 females), Central Serbia (5.3 males, 4 females), Greece (2.5 males, 2 females), and Albania (1.9 males, 1.7 females) (Ferlay et al. 2010). This could be due to incomplete databases of cancer incidence, and different levels of prevention among countries (Kandolf-Sekulović *et al.* 2012), or some other unexplained reasons. Furthermore, the unexpectedly low incidence in outdoor workers, the anatomical, gender, and age distribution indicate a more complex association (Armstrong & Kricker 1994).

Generally, the data about the epidemiology of melanoma of skin in south-east Europe are scarce, with the majority of information obtained from the cancer registries. Based on the Cancer Registry of Central Serbia, crude incidence of melanoma (C43) in 2015 was 9.1 in males and 8.4 in females, while for other skin malignomas (C44) incidence was 66.9 in males and 57.3 in females. The number of new cases was 456 (C43) and 3,223 (C44), while the number of deaths was 195 (C43) and 140 (C44) (Miljuš *et al.* 2017). In total, around 500 new cases of melanoma are diagnosed in Serbia annually and the incidence is rising, reflecting the same trends noted in the rest of Europe and the world. In Serbia from 1999 to 2008, on average, there were 170 female and 173 male new cases of melanoma, as well as 66 and 82 deaths in females and males, respectively (Miljuš *et al.* 2010). Hence, rising trends in melanoma incidence and mortality are more than obvious, but what could be the probable cause?

There are several mechanisms leading to induction of melanoma, for instance: suppression of the immune system of the skin, induction of melanocyte cell division, free radical production, and damage of melanocyte DNA (Gordon 2013). The main endogenous risk factors for developing melanoma are: individual susceptibility and predisposition, phototype (light skin and eye color), tendency to freckle, presence of atypical or numerous moles, basal cell nevus syndrome, *Xeroderma pigmentosum*, other genetic factors such as family history of melanoma and prior melanoma (Cummins *et al.* 2006; Porter 2011; Gordon 2013; Lian & Mihm 2014). Some medical procedures can contribute to the appearance of skin cancer, such as psoriasis treatment, radiation treatment (for eczema and acne, breast or prostate cancer), and medically induced immunosuppression in organ transplantation recipients. Even human papilloma virus (HPV) can present a risk factor (Andersson *et al.* 2012). Additionally, occupational exposure to chemical hazards (arsenic, industrial tar, coal, paraffin, and certain types of oil) may increase the risk for skin cancer (Applebaum *et al.* 2007). Still, the main environmental risk factor is sun exposure (type/degree/period) and UVR, including history of sunburn, sun protection behavior, and indoor tanning (Gordon 2013). UVR exposure to p16-mutated cells allows uncontrolled proliferation of the damaged melanocytes. Mutations at the p16 (melanoma susceptibility gene) are accountable for many nonfamilial cases of melanoma (Gandini *et al.* 2005; Cummins *et al.* 2006).

It is believed that intermittent sun exposure during recreational activities is more conducive for melanoma development then chronic or cumulative exposure. Despite this, people are spending more and more time in the sun, which is due to a popular lifestyle and the desire for an attractive tanned skin, but it can also be associated with climate change and global warming. Increased summer temperatures could influence behavioral changes and encourage people to seek more sun-driven holidays, and thereby contribute to the increase of melanoma incidence in the future, probably more than ozone depletion (Diffey 2004). This could also contribute to the exposure to another potential risk factor – cyanobacteria, since these microorganisms also prefer and flourish in warm water and weather (Paerl & Huisman 2008). Climate change in combination with anthropogenic influence can be a catalyst for the further expansion and blooming of cyanobacteria, thus creating a way of human exposure. Exposure to cyanobacteria and cyanotoxins can occur via contaminated water during recreational activities (dermal contact, inhalation, and accidental ingestion), by ingestion of contaminated drinking water, intravenously during hemodialysis, and through consumption of contaminated food products (aquatic organisms, vegetables, fruits, and cyanobacterial dietary supplements) (Drobac *et al.* 2013). When it comes to the effects on the skin, the most common is recreational or occupational exposure (Stewart *et al.* 2006a), although some skin rashes were also reported after bathing or showering with water containing cyanobacterial products (Falconer 1998). Some of the consequential major health problems are skin irritation, rashes, desquamation, swelling, sores, allergic reactions most likely due to direct contact with contaminated water and cyanobacteria (e.g., Stewart *et al.* 2006a). There are even indications that cyanotoxins are skin tumor promoters (Falconer 1991). The aim of this paper was to examine the hypothetical connection between the occurrence of melanoma in Vojvodina, Serbia with the appearance of cyanobacteria and cyanotoxins in local water bodies used for recreation, irrigation, and fishing. Therefore, the increase in the occurrences of blooming waterbodies in certain municipalities should result in the increase of the occurrence of melanoma in the same municipalities. This kind of research has never been performed before. In addition, a review of the literature on the current state of knowledge on the effects of cyanobacteria and their metabolites on the skin (case studies, epidemiological research, and skin tests) has also been made, with an emphasis on skin cancer, as well as a potential link with climate change. Finally, some beneficial influences that cyanobacteria can have on the skin are also presented.

MATERIALS AND METHODS

Vojvodina region

Research has been performed in Vojvodina region, an autonomous province of Serbia, located in the northern part of the country. Vojvodina is in the southeast part of the Pannonian Plain and it is divided by two major rivers: Danube and Tisa. There are two mountains in Vojvodina: Vršačke planine in the southwest with the highest peak in Vojvodina at an altitude of 641 m, and Fruška Gora (the only national park in Vojvodina), with the highest peak of 548 m. Vojvodina has a population of almost two million, and the region is divided into 45 municipalities. There are more than 25 Caucasian ethnic groups.

Melanoma databases

Data on melanoma of the skin in Vojvodina, Serbia were obtained from the Cancer Registry of Vojvodina. Patients with malignant melanoma were identified using the International Classification of Diseases for Oncology, 10th edition (C43.0–C43.9) in the five-year period from 2013 to 2017. This study encompasses 621 patients diagnosed in the period 01.01.2013–01.01.2018, most of whom were operated on at the Clinic for Plastic and Reconstructive Surgery, the Clinical Center of Vojvodina in Novi Sad, as well as in other health institutions throughout Vojvodina, and who were sent to the Oncology Institute of Vojvodina after surgery. In patients who were operated on outside the Clinical Center of Vojvodina, the histological finding was checked and, if necessary, supplemented with the data that were needed for our study. The entire processing was carried out in accordance with the recommendations of the World Health Organization and the International Union for the Fight against Cancer, as well as the rules of the GCP (Good Clinical Practice). Crude incidence rates of melanoma in 45 Vojvodina municipalities were calculated by dividing the number of new cases during a five-year period by the corresponding number of citizens in each municipality according to the 2011 census. The results are expressed as a rate per 100,000 persons at risk. Crude incidence rates, and not standardized, have been presented since data from only one doctor have been used.

Serbian cyanobacterial database

Data concerning cyanobacterial blooming events were taken from the 25-year monitoring program done by the Republic Hydrometeorological Institute in Serbia, Serbian Cyanobacterial Database (https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN) containing publications on the presence and blooming of cyanobacteria, including cyanotoxin production, in various aquatic ecosystems throughout Serbia from 1882, as well as PhD thesis (Simeunović 2009; Tokodi 2016) and a series of published papers on this subject (e.g., Svirčev *et al.* 2007, 2014b, 2017a).

RESULTS

In the period from 2013 to 2017 in Vojvodina, there were 621 new cases of melanoma. Reported cases included 276 (44%) females and 345 (54%) males from the ages of 17 to 95, with the average age of patients being 60. Patients were divided into three age groups: 12% of patients were 39 and younger, 44% were between 40 and 64, and 44% older than 65 years when diagnosed. Different types of melanoma, depending on their localizations on the body, have been recorded (Figure 1).

The highest occurrence has been noted for C43.5 (47%), which is Melanoma malignum trunci, then C43.7 (18%) and C43.6 (11%), indicating that the most common places of melanoma occurrence were trunk then lower and upper extremities. Diagnosis from C43.0 to C43.4 refers to localization of melanoma on the head, and this was found in about 17% of all the patients. Furthermore, crude incidence rates of melanoma in municipalities are presented in Table 1 and Figure 2, together with the known blooming ecosystems in the vicinity of each municipality.

Based on the crude incidence rate of melanoma, municipalities were divided into four groups: (a) no recorded cases/crude incidence rate; (b) low crude incidence rate (<20 cases per 100,000 people); (c) medium crude incidence rate (20–50 cases per 100,000 people); and (d) high crude incidence rate (>50 cases per 100,000 people). There were eight municipalities with high, 17 with medium, 12 with low crude incidence rates of melanoma, while for eight, mostly southern municipalities, in Vojvodina, there were no new cases recorded in the five-year period examined.

DISCUSSION

Cases of skin irritation and epidemiological research

For decades, freshwater cyanobacterial blooms, including *Anabaena, Aphanizomenon, Gloeotrichia, Microcystis,*

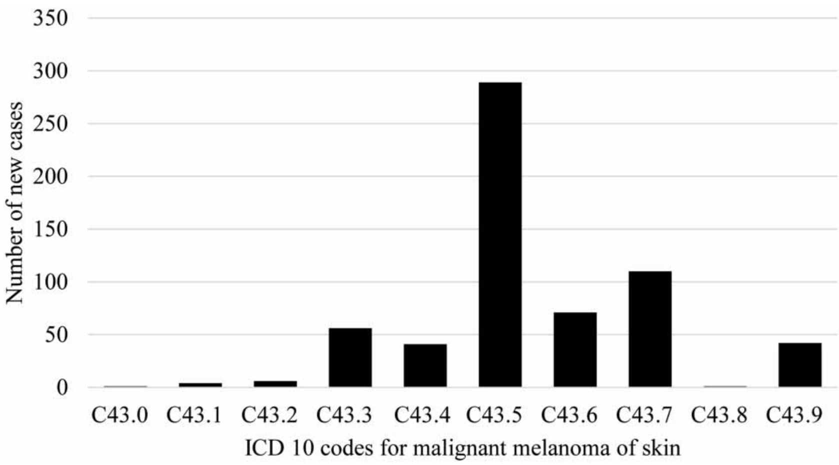

Figure 1 | Occurrence of different melanoma types in patients in Vojvodina (2013–2017). C43.0: Melanoma malignum labii oris; C43.1: Melanoma malignum cutis palpebrae, canthum includens; C43.2: Melanoma malignum auris et meatus acustici externi; C43.3: Melanoma malignum partium faciei aliarum et non specificatarum; C43.4: Melanoma malignum capillitii et colii; C43.5: Melanoma malignum trunci; C43.6: Melanoma malignum extremitatis superioris, refionem omae includens; C43.7: Melanoma malignum extremitatis inferioris, regionem coxae includens; C43.8: Melanoma malignum cutis, limites transiens; C43.9: Melanoma malignum, non specificatum.

Nodularia, and *Oscillatoria* have been associated with skin irritations, conjunctival and allergic reactions after water-based recreational activities (Codd *et al.* 1999). Worldwide, allergic or irritative dermal reactions of diverse severity have been linked with cyanobacteria. These reactions can be especially pronounced under the bathing suits of bathers, where cyanobacterial cells accumulate and are decomposed during swimming (Chorus *et al.* 2000). Even though somewhat rare, there are several case studies and epidemiological investigations into the effects of cyanobacteria/cyanotoxins on the skin. For instance, Turner *et al.* (1990) reported blistering around the mouth of army recruits after recreational contact with water containing toxic *Microcystis aeruginosa* at a freshwater reservoir in England. El Saadi *et al.* (1995), in a case-control study, found elevated risks of dermatological symptoms associated with domestic use of water from the Murray River, Australia during a period of raised cyanobacterial cell counts. Also in Australia, Pilotto *et al.* (1997) carried out a comprehensive survey of health effects in people after recreational pursuits in waters containing cyanobacteria. After 7 days of exposure there was a significant trend of increasing symptom occurrence (including skin rashes, mouth ulcers, eye or ear irritations, flu-like symptoms, and fever) with duration of exposure and an increase in cyanobacterial cell density. Stewart *et al.* (2006b) conducted a prospective cohort study to investigate the incidence of acute symptoms in people exposed to cyanobacteria through recreational activities in Australia and Florida. A significant increase of symptoms, including skin rash, redness of the skin not related to sunburn, and unusual itchiness, was associated with exposure to higher levels of cyanobacteria. Recently in Serbia, cyanobacterial bloom occurred in the Vrutci reservoir used for water supply of the city Užice, also for recreation and fishing. Consequently, the epidemiological data showed that the number of people suffering from diseases of the digestive system, skin, and subcutaneous tissue was higher during the likely period of blooming due to potential exposure to cyanobacteria and their toxins (Svirčev *et al.* 2017b).

Therefore, in several cases, skin and mucous membranes' irritations, hypersensitivity immune responses such as allergic contact dermatitis and severe systemic manifestations (generalized urticarial rash, conjunctivitis, asthma, and hay fever) were diagnosed after recreation in water contaminated with cyanobacteria. These signs and symptoms are usually variable (due to different cyanobacteria/cyanotoxins' composition, molecular mechanisms, individual susceptibility, and additional phototoxic effects), mild, self-limited, not distinctive and can be caused by other pathogens as well. For these reasons they are often not recognized, under-reported, under-diagnosed, or misdiagnosed, hence are rarely published in scientific papers and educational literature (Vranješ & Jovanović 2011). For this reason, little is known about the relationship between

Table 1 | Crude incidence rates of melanoma per municipalities in Vojvodina in the period from 2013 to 2017 and nearby blooming freshwater ecosystems

No.	Municipality in Vojvodina	Crude incidence rate (2013–2017)	Groups based on crude incidence rate	Freshwater ecosystem where potential exposure to cyanotoxins could occur
1	Alibunar	0	No recorded cases/crude incidence rate	–
2	Bela Crkva	0		River Danube[c,d]
3	Kovin	0		Slatina pond[d], River Danube[d]
4	Opovo	0		River Tamiš[d]
5	Pančevo	0		Rivers Ponjavica[d] and Danube[c,d]
6	Pećinci	0		River Sava[d]
7	Plandište	0		–
8	Sremski Karlovci	0		River Danube[c,d]
9	Stara Pazova	1.52	Low crude incidence rate (<20 cases per 100,000 people)	River Danube[c,d]
10	Vršac	1.92		–
11	Kovačica	7.91		River Tamiš[d]
12	Novi Bečej	8.36		River Tisa[d], Mrtva Tisa[a,c]
13	Nova Crnja	9.74		–
14	Žitište	11.91		River Begej[d]
15	Subotica	12.72		Tavankut[a], lakes Palić[c,d] and Ludoš[d], River Krivaja[d]
16	Sečanj	15.07		River Tamiš[d]
17	Ruma	16.56		Pavlovci[a,c], Rriver Sava[d]
18	Zrenjanin	17.02		Rivers Danube[c,d], Tamiš[d], Tisa[d] and Begej[d], Ečka[b] and Mužlja fishpond[b], Carska bara pond[d]
19	Apatin	17.28		Kupusinovački Dunavac pond[d], River Danube[c,d], Opovački dunavac[a,d]
20	Novi Kneževac	17.75		River Tisa[d]
21	Kikinda	21.87	Medium crude incidence rate (20–50 cases per 100,000 people)	Kikinda canal[a,d] (part of the Danube-Tisa-Danube canal system)
22	Žabalj	23.28		Jegrička[d] and Mrtva Tisa[a], River Tisa[d]
23	Vrbas	23.76		Canal Danube-Tisa-Danube[a,d], Canal Kralja Petra[a,d], Jegrička[a,c]
24	Bačka Topola	24.01		Zobnatica[a,c], River Krivaja[d]
25	Inđija	25.30		River Danube[c,d]
26	Šid	26.33		Rivers Bosut[d], Studva[d] and Sava[d]
27	Sombor	33.02		Kolut fishpond[b], Canal Kralja Petra[a,d], Franjina skela pond[d], River Danube[c,d]
28	Ada	35.31		Rriver Tisa[d]
29	Kanjiža	35.51		Kapetanski rit fishpond[b], Rivers Tisa[d] and Kereš[d]
30	Sremska Mitrovica	41.28		Manđelos (Vranješ)[a,c], River Sava[d]
31	Bač	41.65		Provala[a,c], Rriver Danube[c,d], Canal Danube-Tisa-Danube[a,d]
32	Senta	42.89		Rriver Tisa[d]
33	Odžaci	43.05		Canal Danube-isa- Danube[a,d], River Danube[c,d]
34	Čoka	43.87		River Zlatica[d], River Tisa[d]
35	Titel	44.48		Rivers Tisa[d] and Danube[c,d], Koviljski rit[a,c]
36	Kula	48.72		Canal Danube-Tisa-Danube[a,d], Canal Kralja Petra[a,d]
37	Srbobran	49.03		Canal Kralja Petra[a,d] and Danube-Tisa-Danube[a,d]

(*continued*)

Table 1 | continued

No.	Municipality in Vojvodina	Crude incidence rate (2013–2017)	Groups based on crude incidence rate	Freshwater ecosystem where potential exposure to cyanotoxins could occur
38	Bečej	56.22	High crude incidence rate (>50 cases per 100,000 people)	Mrtva Tisa[a,c], Bečej fishpond[b], Biserno ostrvo fishpond[b], River Tisa[d], Canal Danube-Tisa-Danube[a,d]
39	Mali Iđoš	58.18		River Krivaja[d]
40	Beočin	63.59		River Danube[c,d]
41	Irig	64.42		Borkovac[a,c]
42	Novi Sad	65.28		Koviljski rit[a,c], Futog I fishpond[b], River Danube[c,d], Canal Danube-Tisa-Danube[a,d]
43	Bačka Palanka	70.23		River Danube[c,d]
44	Temerin	91.92		Jegrička[a,c]
45	Bački Petrovac	127.80		Canal Danube-Tisa-Danube[a,d], River Danube[c,d]

[a]Reservoirs used for irrigation.
[b]Production of fish for consumption.
[c]Recreation in and around water body (water sports, fishing, etc.).
[d]Tourist visits/nearby populated areas.

cyanobacteria and the negative effects on the skin, even among experts such as dermatologists, thereby a vicious circle of obscurity is formed. In order to break this circle, it is necessary to continue with epidemiological and experimental research in order to elucidate this relationship.

Nonetheless, the World Health Organization recommended guideline levels for recreational exposure to cyanobacteria suggesting: high probability of adverse effects (acute e.g., skin irritations and long-term illness) from contact with cyanobacterial scum formations, moderate probability of adverse effects for waters containing 100,000 cells/mL or 50 μg chlorophyll-a/L, and low probability of adverse health effects for waters with 20,000 cyanobacterial cells/mL or 10 μg chlorophyll-a/L. It is challenging to determine safe values for cyanobacteria in recreational water in relation to skin and allergenic reactions, since individual sensitivities vary greatly (Chorus *et al.* 2000).

Individual sensitivity and skin tests

It seems that only certain individuals show an allergenic response to cyanobacterial antigens. For instance, Heise (1949) documented allergenic reactions in ten people, after applying intradermal injections of glycerosaline extracts of dried *Microcystis* and Oscillatoriaceae species, while another 50 people exhibited no reaction. Mittal *et al.* (1979) complemented these findings with the observations from research in which after intradermal skin tests response rates ranged from 1.7% for *Oscillatoria* to 25.7% for *Lyngbya* in allergic volunteers (nasal-bronchial allergies), but in non-allergic volunteers no positive skin reactions were displayed. Contrary to that, Pilotto *et al.* (2004) demonstrated that people who were diagnosed as atopic, or suffered from eczema, hay fever, and asthma, did not show a statistically significant increase in response rate compared with non-atopic healthy volunteers subjected to skin-patch testing with a range of non-toxic and toxic cyanobacterial strains. Therefore, around 20% of healthy individuals may develop a mild skin reaction to cyanobacteria during water recreation. Two similar studies were done using skin-patch testing containing cyanobacterial extracts where, in both cases, only one subject (from 26 to 39 volunteers, respectively) showed positive reactions, indicating the rare occurrence of hypersensitivity reactions to cyanobacteria (Cohen & Reif 1953; Stewart *et al.* 2006c). Another method, a skin-prick testing with detoxified cyanobacteria species, was applied for the purpose of testing skin sensitization. In this manner, Bernstein *et al.* (2011) obtained 86% positive reactions to *M. aeruginosa* and 12% to *Aphanizomenon flos-aquae*; also, there was a strong connection between number of positive reactions and having allergic rhinitis. Furthermore, this research has demonstrated that cyanobacterial allergenicity lies within nontoxin-containing components of this microorganism.

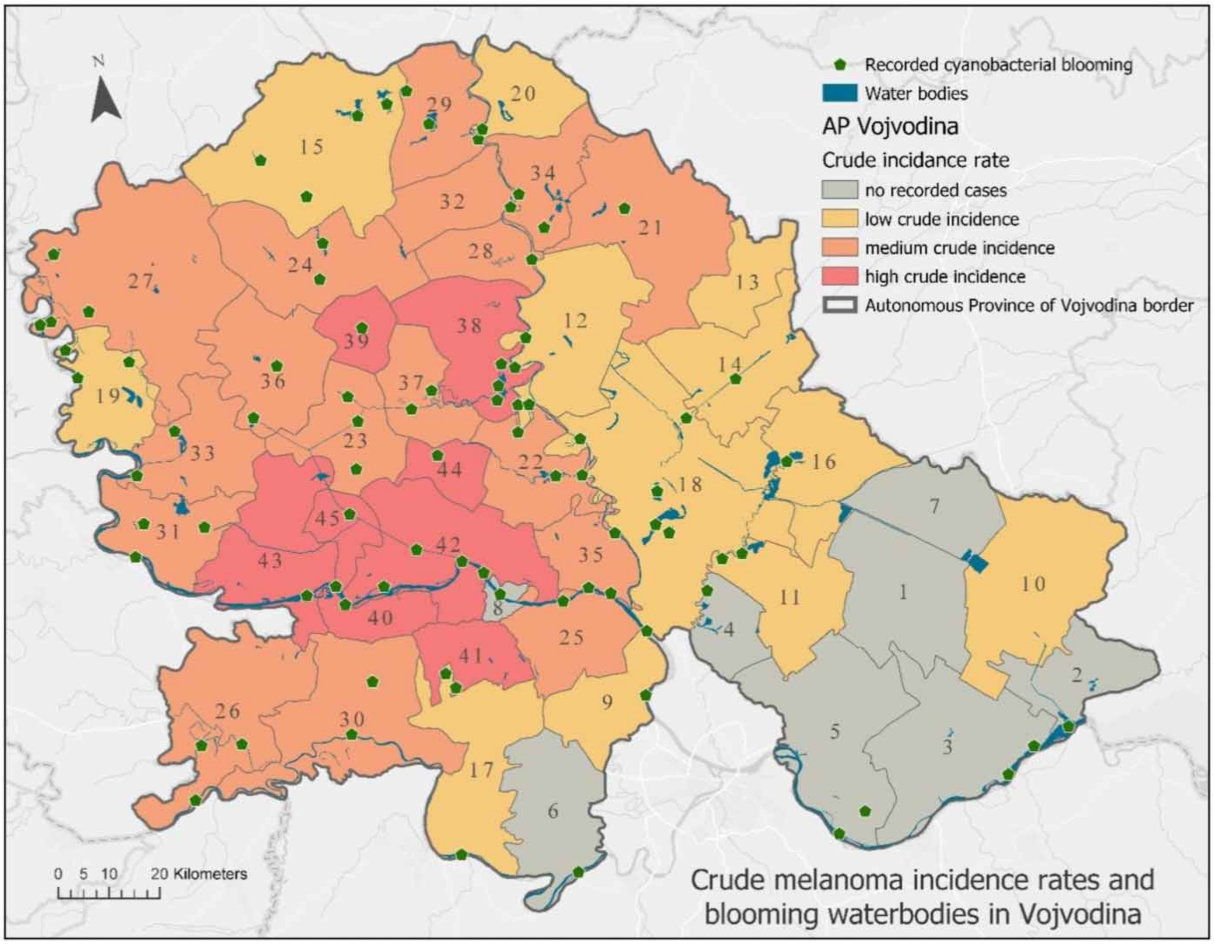

Figure 2 | Crude melanoma incidence rates (2013–2017) and blooming freshwater ecocystems in Vojvodina. Municipalities in Vojvodina: 1: Alibunar; 2: Bela Crkva; 3: Kovin; 4: Opovo; 5: Pančevo; 6: Pećinci; 7: Plandište; 8: Sremski Karlovci; 9: Stara Pazova; 10: Vršac; 11: Kovačica; 12: Novi Bečej; 13: Nova Crnja; 14: Žitište; 15: Subotica; 16: Sečanj; 17: Ruma; 18: Zrenjanin; 19: Apatin; 20: Novi Kneževac; 21: Kikinda; 22: Žabalj; 23: Vrbas; 24: Bačka Topola; 25: Inđija; 26: Šid; 27: Sombor; 28: Ada; 29: Kanjiža; 30: Sremska Mitrovica; 31: Bač; 32: Senta; 33: Odžaci; 34: Čoka; 35: Titel; 36: Kula; 37: Srbobran; 38: Bečej; 39: Mali Iđoš; 40: Beočin; 41: Irig; 42: Novi Sad; 43: Bačka Palanka; 44: Temerin; 45: Bački Petrovac.

Causative agents and mechanisms of toxicity

There is another uncertainty about what exactly causes the negative effects on the skin. Some of the aforementioned research attributed the sensitivity of individuals to cyanobacterial cells rather than to individual cyanotoxins or toxin content. Sensitization and irritation tests were done on guinea pigs since their sensitivity is similar to that of humans, and no correlation was found between the toxin content and the allergenic reaction. The most toxic strain *M. aeruginosa* was not the most allergenic, while the non-toxic *Aphanizomenon* was the most allergenic, and pure microcystin-LR (MC-LR) even in high concentration (1.5 mg/mL) was only slightly allergenic (Törökné *et al.* 2001). This clearly suggests a possible role for other cyanobacterial constituents, and since the cyanobacteria are Gram-negative microorganisms it is possible that lipopolysaccharide endotoxins (constituents within the plasma membranes like in classic Gram-negative heterotrophs, e.g., *Escherichia coli*) may play that role. Lipopolysaccharides could stimulate the immune system, leading to or enhancing adaptive IgE specific immune responses and histamine release (Bernstein *et al.* 2011). One of the first studies on cutaneous sensitization found that at least one of the cyanobacterial constituents responsible for contact dermatitis in a six-year-old girl was phycocyanin – a blue pigment predominant and identifiable for the blue-green algae (Cohen & Reif 1953). In addition, in the course of cyanobacterial blooming, some other compounds (e.g., aldehydes, terpenoids, and ketons), with irritating and sensitizing properties, are dissolved in water and may also be involved (Funari & Testai 2008).

Furthermore, cyanobacteria produce known dermatotoxins such as lyngbyatoxin, aplysiatoxin, and debromoaplysiatoxin. The main producers of lyngbyatoxins are marine cyanobacteria *Lyngbya majuscule*, and in freshwater *Lyngbya wollei.* Isoform lyngbyatoxin-a has a skin tumor promoting activity through activation of protein kinase C by replacing activator (1,2 diacylglycerol) of this enzyme (Chorus & Batram 1999; Rzymski & Poniedziałek 2012). Aplysiatoxin and debromoaplysiatoxin are also activators of protein kinase C and are, therefore, considered to have tumorigenic properties (Fujiki *et al.* 1990). Both cyanotoxins can cause inhibition of epidermal growth factor, activation of ornithine decarboxylase in human skin cells, differentiation of HL-60 cells into macrophages, severe ear irritation in mice, and after direct contact acute skin irritation, rashes, and blisters (see Rzymski & Poniedziałek 2012). Generally, little is known about the mechanisms of toxicity, and even less about the potential tumor-promoting activity of cyanobacterial toxins. One of the scarce studies showed that skin tumor growth initiated by the carcinogen dimethylbenzanthracene was accelerated in mice that drank water containing *Microcystis*. Mice given dilute *Microcystis* for one year expressed more spontaneous tumors at the highest concentration of cyanobacterial extract. Mice stimulated to grow skin tumors by topical application of dimethylbenzanthracene showed a significantly greater weight of tumors in a group that had been drinking water with *Microcystis* extract, while another group that drank water with *Anabaena* extract did not show stimulation of tumor growth (Falconer 1991). Even though oral exposure was applied, microcystin still promoted tumor growth in the skin cells, although the mechanism is still unclear.

During the last few decades, there has been an attempt to clarify complex interactions at the molecular level leading to carcinogenesis. MC-LR tumor-promoting activity is attributed to its ability to inhibit activity of protein phosphatases (PP1, PP2A) and affect dephosphorylation of proteins (e.g., protein kinase) that are involved in cell proliferation, survival, and invasion. More recent research is dealing with MC-LR ability to enhance carcinoma cells' invasion, and Zhang *et al.* (2012) found that exposure to MC-LR enhanced the invasion ability of the melanoma cells (MDA-MB-435). MC-LR, by acting as an activator of nuclear factor kappaB (NF-κB transcription factor that controls inflammation, apoptosis, survival, and invasion), promotes overexpression of metalloproteinases genes (matrix metalloproteinases (MMPs) proteolytic enzymes responsible for the extracellular matrix destruction and colonization of tumor cells) involved in tumor metastasis, carcinoma progression, and poor prognosis in patients. Further investigation by Xu *et al.* (2013) revealed that MC-LR promotes invasion and metastasis of MDA-MB-435 cells via activation of phosphatidylinositol 3-kinase (PI3-K/AKT) pathway and increases expression of MMP-2/-9.

Human skin cancer and climate change

The world's climate is inevitably changing. The climate change phenomenon represents a global shift in weather patterns (temperature, cloud cover, rainfall, etc.) occurring over long periods of time. It affects many things, but how does it affect people's health and even more precisely the appearance of skin cancer, especially in association with ozone depletion (feeble absorption of UVR) and consequential enhanced exposure to UVR? An old mouse experiment showed that increased room temperature enhanced UVR-induced carcinogenesis, and it appears that there is a similar effect in human populations – temperature rises associated with climate change can amplify the induction of non-melanoma skin cancers by UVR (van der Leun *et al.* 2008). With the climate change and accompanying rising temperatures the total time spent outdoors (sports, recreational activities, and beach holidays) will increase, leading to prolonged UVR exposure and a higher incidence of skin cancer (Bharath & Turner 2009). This was confirmed by research conducted in Australia, where it was reasoned that on days with higher temperatures, people are spending more time outdoors wearing less covering clothes, resulting in increased sun exposure, sunburn, and higher skin cancer risk (Dobbinson *et al.* 2008).

Furthermore, climate change and global warming may augment another potential and new risk factor for a more frequent occurrence of melanoma, via spreading and blooming of cyanobacteria. Climate change entails rising temperatures (affects water viscosity, density, and vertical stratification), CO_2, salinity, and alterations in weather patterns (droughts, storms, floods), changes which are favorable for cyanobacterial blooms. Higher temperatures are beneficial for cyanobacteria because their optimal growth rates are at higher temperatures (25 °C), and are more competitive in these conditions, and they have gas vesicles for regulation of vertical position, also pigments and antioxidants for survival under high irradiance conditions. Higher atmospheric CO_2 levels are also positive for cyanobacteria, given that they demand it for photosynthesis. Rising salinity is yet another factor to which cyanobacteria are tolerant and advantageous. In addition, increased precipitations will lead to higher nutrient loading of aquatic ecosystems enabling cyanobacteria to flourish. These changes could affect aquatic food webs and grazer interactions, by eliminating the predators the space opens for cyanobacteria (Paerl & Paul 2012). Cyanobacteria possess even more unique and highly adaptable eco-physiological traits, such as nitrogen-fixation; luxury phosphorus uptake and storage; light capture at low intensities; akinete production and toxin production, which may enable them to dominate in future climate scenarios (Carey *et al.* 2012).

Several species of cyanobacteria display progressive colonization and expansion of distribution throughout the world, such as *Cylindrospermopsis raciborskii* and *Lyngbya* – producers of many bioactive compounds linked with the onset of contact dermatitis, blistering, and peeling of the skin. It is considered that several factors have contributed to this expansion, including higher water temperatures, nutrient enrichment, low-light conditions in eutrophic waters, climatic and hydrological perturbations (e.g., hurricanes), all indicating a connection to climate change (Paerl & Paul 2012). Therefore, it is realistic to anticipate that these adaptable microorganisms will use these changes to their advantage, and thrive by increasing their frequency, biomass, duration as well as distribution, and along the way provoke health problems, including skin problems.

Cyanobacteria and melanoma in Vojvodina

Epidemiological studies indicated that microcystins originating from cyanobacteria in eutrophic waters may influence an increase in incidence of primary human cancers, first and foremost, liver and colorectum (Yu 1989; Ueno *et al.* 1996; Zhou *et al.* 2002), but also other cancers such as brain, testis, ovary, stomach, retroperitoneum and peritoneum, heart, mediastinum and pleura, leukemia, including melanoma of the skin (Svirčev *et al.* 2013, 2014a). In Central Serbia, significantly higher incidence of these ten cancers were observed in three critical districts (Nišavski, Šumadijski, and Toplički) supplied with water from frequently blooming reservoirs, compared to the remaining districts of Central Serbia and especially Vojvodina, a control region that uses underground water sources for drinking water supply. Still, Vojvodina is not spared from this blooming phenomenon, because although groundwater is used for drinking, surface water bodies are an essential part for work and life in Vojvodina.

Rivers (Begej, Bosut, Danube, Kereš, Krivaja, Ponjavica, Sava, Studva, Tamiš, Tisa, and Zlatica), canals (Danube-Tisa-Danube, Kralja Aleksandra and Kralja Petra), reservoirs for irrigation (Borkovac, Jegrička, Koviljski rit, Manđelos (Vranješ), Mrtva Tisa, Pavlovci, Provala, Tavankut and Zobnatica), lakes (Ludoš and Palić), fishponds (Bečej, Biserno ostrvo, Mužlja, Ečka, Futog I, Kolut, Živača, and Kapetanski rit), and ponds (Carska bara, Slatina, Rokaš, Franjina skela, Kupusinovački Dunavac, and Opovački Dunavac) in Vojvodina proved to be sites of cyanobacterial and cyanotoxin occurrence during the historical overview of available publications in Serbia (https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN). More than 80% of the mentioned aquatic ecosystems were found blooming at least once since the beginning of systematic research in 1930. Twelve genera and 19 species of cyanobacteria were recorded during the mass development of cyanobacterial populations in aquatic ecosystems throughout Vojvodina. The most dominant bloom forming cyanobacteria belonged to *Microcystis, Aphanizomenon, Oscillatoria* (*Planktothrix*), and *Anabaena* genera. *M. aeruginosa* (53 blooms recorded) is the species most frequently blooming in aquatic ecosystems on the territory of Vojvodina, followed by the species *Aph. flos-aquae*, *Oscillatoria agardhii* and *Microcystis flos-aquae* (63 observed blooms of the aforementioned three species). From the analyzed literature it can be concluded that *M. aeruginosa* is the most frequent species that blooms in rivers, canals, lakes, and fishponds, while *Aph. flos-aquae* is the most common inhabitant of irrigation reservoirs in Vojvodina (https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN; Svirčev *et al.* 2014b, 2017a; Tokodi 2016).

The stated representatives of cyanobacteria are all well-known toxin producers, thus microcystin was the most sought and found cyanotoxin (https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN). The highest values of microcystins were detected in the Lake Ludoš water (603.61 μg/L MC-LR equivalents obtained in colorimetric protein phosphatase inhibition assay (PPI assay)), but were also recorded in sludge, as well as tissues of aquatic plants and fish (e.g., Lake Ludoš, Vojvodina fishponds, Ponjavica River). Furthermore, fish grown in blooming fishponds and Lake Ludoš, that accumulated microcystins in their tissues (including muscle intended for human consumption), also displayed histopathological changes in their liver, kidneys, gills, heart, spleen, and intestines (Drobac *et al.* 2016; Tokodi *et al.* 2018). Fish kills associated with blooming of cyanobacteria were documented in Lake Palić and Krivaja River, while livestock mortality was recorded in the Ponjavica River (Svirčev *et al.* 2014b, 2017a). Analyzed data from the Serbian Cyanobacterial Database testifies to numerous examples of microcystin accumulation and certain biological effects on various organisms in the ecosystems of Vojvodina. Additionally, it is known that species of the *Lyngbya* genus can produce potentially carcinogenic toxins that affect the skin, and representatives of this genus have been found in the waters of Vojvodina, including Lakes Palić and Ludoš, Rivers Krivaja, Tisa, and Begej, Canal Danube-Tisa-Danube, and the irrigation reservoirs Provala, Tavankut, and Koviljski rit (Simeunović 2009; https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN). The gathered results emphasize the seriousness of the occurrence and the blooming of cyanobacteria, especially in the case of the cyanotoxin production and their negative effects on the ecosystems in their entirety.

Throughout numerous municipalities of Vojvodina region there are water bodies (lakes, rivers, canals, and ponds) which are used for fishing, sports, recreation, relaxation, and socializing during the warm summer months (enhanced UV radiation), when at the same time there is a massive development of cyanobacteria in these water bodies. In this way, people are exposed to cyanobacteria and their toxins by direct skin contact with water, inhalation, accidental ingestion (mainly during recreational activities), and consumption of contaminated fish that is grown in blooming waters. Furthermore, several reservoirs used for crop irrigation disperse the water and potentially aerosolize the cyanotoxins, and plants could accumulate cyanotoxins via leaves or roots and consequently have deleterious effects on human health.

As was previously explained, exposure to these organisms and their metabolites can have numerous adverse effects in the form of acute but also chronic disorders. From the crude incidence rate of melanoma, eight municipalities in Vojvodina have crude incidence rates higher than 50 cases per 100,000 people. These municipalities are concentrated in the center of Vojvodina region, near mountain Fruška gora and Rivers Danube and Tisa, but also near several aquatic ecosystems that have been previously noted for cyanobacterial and cyanotoxin presence (listed in Table 1). Since we do not know which cyanobacteria and/or their products can have an impact on the incidence of melanoma, and how long the exposure should last, we have reviewed the prior scientific publications on the history of the occurrence of cyanobacteria and their blooms (https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN; Svirčev *et al.* 2014b), as well as the presence of the most detected cyanotoxin microcystin recorded in the territory of Vojvodina (Simeunović 2009). For example, cyanobacteria (as *Aphanizomenon* sp., *Microcystis* sp.) have been detected in the River Danube since 1947, and this river passes through numerous municipalities of Vojvodina, among them four with a high incidence of melanoma (Novi Sad, Beočin, Bačka Palanka), including the highest (127.8) Bački Petrovac. Through this municipality also passes the Danube-Tisa-Danube canal, a unique hydro system covering a total area of about 12,700 km^2 with the length of the main channel being about 700 km. Detection of cyanobacteria and microcystins was conducted on several locations along this canal network, whereby the highest concentration (142.60 μg/L MC-LR equivalents in PPI assay) was found in the autumn of 2006 in Bečej Municipality, with a high crude incidence rate (56.22). Additionally, in the same municipality there is Mrtva Tisa, a former meander of the Tisa River that was transformed into a lake used for irrigation. Cyanobacteria were found in 1974 (*Microcystis* sp., *Aph.*

flos-aquae, *Oscillatoria bornetii*), and many years later in the summer of 2007 the highest microcystin concentration was recorded in Mrtva Tisa (279.87 μg/L MC-LR equivalents in PPI assay). In the immediate vicinity, fishponds Bečej and Biserno ostrvo are located, where microcystins were found in water, sludge, aquatic plants, as well as in the fish tissues. The municipality with the second highest incidence of melanoma (91.92) is Temerin, where the River Jegrička flows, which is used for irrigation. In this slow-flow river, cyanobacteria (*Anabaena spiroides*, *Cylindrospermum stagnale*, *Oscillatoria* spp.) were first observed in 1959 and microcystins were detected in 2005–2007 (the highest concentration detected in summer 38.47 μg/L MC-LR equivalents in PPI assay). A high incidence (65.28) of melanoma has also been reported in the provincial capital Novi Sad. In this municipality, cyanobacteria (*Anabaena* sp., *Anabaena spiroides*, *Anabaenopsis* sp.) were recorded in Futog fishpond back in 1977. In the same municipality, there is Koviljski rit – a marsh area in the form of a unique labyrinth of old canals and meanders of the Danube River and with a special nature reserve. Here, during a three-year study (2005–2007), Simeunović (2009) recorded cyanobacterial blooms and 11 species including *Lyngbya* sp., and also detected microcystins with maximum recorded value in summer 2005 (96.32 μg/L MC-LR equivalents in PPI assay). During the same investigation, high concentrations were recorded during the summer of 2005 in Borkovac (165.48 μg/L MC-LR equivalents in PPI assay), a reservoir for irrigation, where cyanobacterial blooming (of *M. aeruginosa* and *Aph. flos-aquae*) was detected as early as in the 1980s. Borkovac is located in Irig, a municipality with high crude incidence rate (64.42). Another municipality with over 50 cases per 100,000 people is Mali Iđoš. In the nearby River Krivaja, *Aph. flos-aquae* was first detected in 2001, and in 2003 *M. aeruginosa* bloomed, at which point, mortality of fish was also documented. Microcystins were detected from 2005 to 2007 (highest in autumn 2005, 79.56 μg/L MC-LR equivalents in PPI assay) when several cyanobacterial species bloomed and *Lyngbya* sp. was present as well (https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN; Svirčev *et al.* 2014b).

Most municipalities (17) have between 20 and 50 new cases in the investigated five-year period (Table 1 and Figure 2), with various aquatic ecosystems in the vicinity (including rivers, ponds, fishponds, canals, and accumulations for irrigation) that previously bloomed and, in some cases, microcystin production occurred (https://cloud.pmf.uns.ac.rs/index.php/s/v6tErVCVcAuaXQN). There are 12 municipalities with several aquatic ecosystems that have less than 20 cases per 100,000 people. The remaining eight municipalities that have had no new cases of melanoma recorded are located in the south of Vojvodina situated near the Danube, but with only few rivers and ponds nearby, indicate a limited exposure to cyanobacteria and cyanotoxins (Table 1 and Figure 2). Notwithstanding, a possible explanation for no recorded cases of melanoma could also be that potential patients rather go to the nearby capital city of Belgrade, even though all citizens are required to report to the region capital, Novi Sad. It is difficult to accurately determine and evaluate the impact of this anomaly on the overall research data. Although it seems that municipalities in Vojvodina with less blooming waterbodies and occurrences of cyanotoxins have lower crude incidences of melanoma (Table 1 and Figure 2), definitive conclusions based on the data from Vojvodina are not completely reliable and hence could be argued as inconclusive. Surely, more thorough investigation is warranted in the future.

Although in most municipalities some aquatic ecosystems containing potentially toxic cyanobacteria and cyanotoxins were noted, potential exposure could vary depending on the size, use, and type of the aquatic ecosystem, as well as the time or season when the occurrence of cyanobacteria took place, and the composition of present species, including their ability to produce toxic substances. Vojvodina province has many waterbodies and canals connecting them. This is the result of previous historical efforts for improvement of agricultural development. Furthermore, Vojvodina is also heavily populated (94 inhabitants per km^2), which means that nearby most of the settlements there is at least one waterbody that can be used for fish farming, recreation (including water sports, fishing), or during the summer for relaxation. Historical review of these waterbodies in our previous research has shown that almost 80% of waterbodies in Serbia have bloomed, and climate changes as well as human activities have exacerbated the water quality status and contributed to the increase of the blooms not just in Serbia, but also worldwide. Additionally, it is necessary to emphasize that only the most common cyanotoxins were measured in some water ecosystems in Vojvodina, not all the other potentially harmful metabolic products. Cyanotoxins are not systematically measured in Vojvodina, and there is no authority which monitors this issue in waterbodies throughout Serbia, which could mean that the real state regarding cyanotoxin presence could be dramatically underestimated.

In respect of the overall epidemiological data on melanoma from Vojvodina region, they are mostly in accordance with worldwide data. A slightly higher number of male than female patients, diagnosed with melanoma, were recorded in Vojvodina, and most (88%) were older than 40 with the average age of 60. Furthermore, most diagnosed melanomas were located on the trunk and extremities (76%), while 17% of melanoma cases were located on the head and neck. Based on the summarized findings from Mathews *et al.* (2017), in countries worldwide, the age-standardized rate of melanoma incidence climbs steadily and peaks at the seventh and eighth decades of life. Melanomas that develop on the trunk occur more often in the fifth to sixth decades of life, whereas melanomas that develop in high UVR-exposed body regions, like the head and neck, occur more commonly in the eighth decade. Also, it was noted, that men are more susceptible to melanomas (Mathews *et al.* 2017).

Interestingly, throughout the world the highest incidence of melanoma is recorded (Mathews *et al.* 2017) in Australia and New Zealand (crude rate over 50), which are the epicenters of cyanobacterial blooming, where various cyanotoxins are commonly found in over a hundred aquatic ecosystems. Next comes Northern Europe (Switzerland, Sweden, Norway, Netherlands, Denmark, United Kingdom, and Finland; crude rate 32.2) where the occurrence of cyanobacteria and cyanotoxins is also frequent, and connected to fish, birds, dogs, cats, cattle, and even human intoxications including skin rashes. Further, annual incidence has risen rapidly in the fair-skinned population of North America (crude rate 21.9). On the other hand, a significant number of research and papers on cases of human and animal poisonings associated with cyanotoxins notably come from the USA. Western Europe (Czech Republic, Belgium, Germany, Italy, France, Austria, and Hungary) is not immune to both high incidence of melanoma (crude rate 20.11) and the appearance of cyanobacteria and their toxins. For instance, in our neighboring country Hungary, massive bloom of *M. aeruginosa* has led to widespread and diverse skin and eye diseases forcing the authorities to order bathing restrictions in the infected waters (Habermehl *et al.* 1997). Higher incidences of melanoma (crude rate over 10) have also been recorded in southern Europe, in particular Spain and Portugal, where in both countries cyanobacteria and cyanotoxins have been found in water sources even required for human use. Hence, epidemiological investigation in Portugal showed that the exposed population had higher activities of liver enzymes in their sera, and a higher incidence of liver, colon, and rectum cancers, compared to the non-exposed populations (Bellem 2014). This group of countries also includes Serbia, whose problems with cyanobacterial blooming and the resulting consequences have already been clarified in detail. Finally, other parts of the world, such as Eastern Europe, South America, Asia, and Africa have a significantly lower incidence of melanoma (crude rate 7–0), but also a scarce amount of data on the occurrence and effects of cyanobacteria and cyanotoxins.

Although the results obtained from the research in Vojvodina were not sufficient to make any definitive conclusions, general information from the existing literature and the data cited throughout this paper still strongly presuppose that cyanobacteria may be a legitimate new and additional risk factor, which together with solar radiation could lead to frequent incidence of melanoma. If we can make an observation that there could be a link between increased incidences of certain cancers such as melanoma, colorectal cancer, and primary liver cancer, what about other cancers, since it has been noticed that cyanotoxins can affect other organs (e.g., heart, brain, testis, ovary, kidney, stomach, blood, etc.)? This opens up the possibility for further research, in particular epidemiological studies that can shine some light on consequences that may arise from the presence and expansion of cyanobacteria, boosted by climate change.

Cyanobacteria – friends or foes of the skin

Finally, we also consider the other side of the coin. Due to the trend of malignant disease over the past years, emphasis is placed on the search for various drugs for the treatment of cancers. Interestingly, some cyanobacterial products are also undergoing clinical evaluation as anticancer drugs. As an example, bioactive compounds from *Leptolyngbya* sp. coibamide A are considered for the treatment of melanoma LOX IMVI, as well as dragonamide, and pseudodysidenin for the treatment of MEL-28 melanoma (Vijayakumar & Menakha 2015). Calothrixin A isolated from the cyanobacteria *Calothrix* is associated with a significant decrease in the cell viability of melanoma cells (A375 and Hs294t) in a time- and dose-dependent manner, thus it has the capability to block the growth of melanoma cells (Singh *et al.* 2015). Cyanobacteria can also produce natural sunscreen pigments to protect themselves from the harmful effects of UVR. Compounds such as mycosporine and scytonemin could potentially be applied for protection of the human skin from the sun. Analysis on the human melanoma A375 showed that mycosporine-2-glycine protected cells against oxidative stress-induced DNA damage (possibly via NF-κB blocking) in human cell lines (Cheewinthamrongrod *et al.* 2016). Scytonemin also appeared to have an anti-proliferating effect on melanoma cells, some even inhibited growth of melanoma cells up to 98% compared to untreated cells (Jones 2017).

In addition, there are numerous cyanobacteria-based products on the world market, which allegedly have various positive effects, even on the skin. For instance, *Spirulina* products according to numerous websites detoxify your skin, help the skin retain moisture, tone your skin, aid acne treatment, have anti-aging benefits, increase skin healing, soothe atopic dermatitis, treat allergies, prevent cancer, and much more. But is it really all so nice, clean, and simple? After the first consumption of a *Spirulina* tablet, a 17-year-old boy developed anaphylaxis. Skin-prick test with diluted *Spirulina* tablet was positive, while other separated ingredients were negative, confirming that the allergy was caused by cyanobacteria *Spirulina platensis* (Le *et al.* 2014). Based on the foregoing, it can only be concluded that we still have a great deal to learn about the complicated relationship between cyanobacteria and the skin.

CONCLUSION

Cyanabacteria and their toxins can be considered to be risk factors for some malignant diseases, while climate change could be a catalyst that converts these potential risk factors into cofactors. In the case of melanoma, cyanobacteria and their toxic metabolites combined with enhanced UVR can contribute to an increase of melanoma incidence in people exposed during recreational and occupational activities alongside blooming waters. Even though this could not be clearly validated in the Vojvodina research due to unreliable data for the southern municipalities of the province, the information gathered from the reviewed literature together with our preliminary epidemiological data support the possibility that cyanobacteria may be a new and additional risk (co)factor that could adversely affect the skin and hence lead to higher incidence of melanoma. Epidemiological studies develop and test hypotheses in order to establish relationships, but little is known about the exact mechanisms of toxicity and cancerogenesis, especially when it comes to cyanobacteria and melanoma. Therefore, further research is needed to broaden our knowledge on this important subject, and perhaps in this way we would help in the prevention of this threatening disease.

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