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Review

A Critical Appraisal of the Recent Reports on Sunbeds from the European Commission's Scientific Committee on Health, Environmental and Emerging Risks and from the World Health Organization

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Review

A Critical Appraisal of the Recent Reports on Sunbeds from the European Commission's Scientific Committee on Health, Environmental and Emerging Risks and from the World Health Organization

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Abstract. *The European Commission's Scientific Committee on Health, Environmental and Emerging Risks and the World Health Organization recently published reports which concluded that a large proportion of melanoma and non-melanoma skin cancer is attributable to sunbed use, and that there is no need to use sunbeds as there are no health benefits and they are not needed to achieve an optimal vitamin D level. The overall conclusion from both bodies was that there is no safe limit for UV irradiance from sunbeds. We are, however, deeply concerned that these assessments appear to be based on an incomplete, unbalanced and non-critical evaluation of the literature. Therefore, we rebut these conclusions by addressing the incomplete analysis of the adverse health effects of UV and sunbed exposure (what is 'safe'?) and the censored representation of beneficial effects, not only but especially from vitamin D production. The stance taken by both agencies is not sufficiently supported by the data and in particular, current scientific knowledge does not support the conclusion sunbed use increases melanoma risk.*

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When preparing their policies and proposals relating to consumer safety, public health and the environment, both the World Health Organization (WHO) and the European Commission rely on scientific committees/commissions, collaborating centers and non-governmental organizations that should be independent and should provide them with sound scientific advice and draw their attention to new and emerging problems. In November 2016, the European Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) adopted a "Final Opinion on Biological effects of ultraviolet radiation relevant to health with particular reference to sunbeds for cosmetic purposes" (1) and in June 2017, the World Health Organization (WHO) published a report entitled "Artificial

Tanning Devices: Public Health Interventions to Manage Sunbeds" (2). In agreement with the WHO report, the SCHEER report concluded that: (i) sunbed use is responsible for a noticeable proportion of both melanoma and non-melanoma skin cancer (NMSC) and for a large percentage of melanomas arising before the age of 30 years; (ii) sunbed exposure has little health benefit; (iii) there is no need to use sunbeds to achieve an optimal vitamin D level; and (iv) because of evidence of the carcinogenic effects of sunbed exposure and of the nature of skin cancer induction, there is no safe limit for UV irradiance from sunbeds. While these reports were purportedly based on the best available scientific evidence, we are deeply concerned about their scientific quality and obvious lack of objectivity, most likely owing to an infusion with the laudable zeal to combat alarming increases in skin cancer. Both publications show an implicit tendency toward an unbalanced view and must be criticized because of many scientific misinterpretations and shortcomings. The main conclusions are not sufficiently supported by the data presented nor by our present scientific knowledge. Notably, both reports ignore (i) meta-analyses that show no association of sunbed use with increased melanoma risk in Europe; (ii) epidemiological and animal studies that show no increase in melanoma risk following chronic and sub-erythemal UV exposure; (iii) beneficial health effects of UV radiation; and (iv) consequences of vitamin D deficiency.

Critical Analysis of SCHEER and WHO Reports

The overall conclusion of the SCHEER report states "There is strong evidence from meta-analyses and individual studies of an increased risk of melanoma with ever use of sunbeds." [p. 43 in (1)]. This immediately exemplifies the misleading inherent bias as this statement should at least have read "There is weak evidence…of an overall marginally increased risk of melanoma associated with ever-use of sunbeds (including one time and habitual intensive users)". Importantly, the direct causality implied is by no means proven. This statement is not in accordance with generally accepted principles of evidence-based medicine (3). None of the supporting evidence demonstrates causation [the gold standard to prove this would be a randomized, controlled trial (RCT)]. Our present scientific knowledge on this topic is based on observational studies (case–control and cohort studies) that demonstrate associations that are confounded by other known factors and that do not demonstrate causation (4-55). Several meta-analyses of poor quality consolidate the observational study data and compound the flaws of these studies (44, 47, 48). For example, Boniol *et al*. (44) report a summary relative risk (SRR) of 1.20 [95% confidence interval (CI) = 1.08-1.34] for the association of ever-exposure to UV radiation from sunbeds with melanoma risk (based on 27 studies). Overall the quality of the entire evidence is poor due to lack of interventional studies and severe limitations of case–control and cohort studies that include unobserved or unreported confounding (56). Notably, many limitations of the studies these reports rely on (3-56) do not result in an undirected bias but will inevitably cause overestimation of the association of sunbed use with melanoma risk. For example, dermatological phototherapy is often included when only sunbed use should be assessed [*e.g*. Landi *et al*. (20)], and in many studies, subgroups of individuals with presumably high UV exposure in the past (*e.g*. individuals with history of 'non-melanoma skin cancer' or 'dermatological conditions') are excluded from controls but not cases (control selection bias). Additionally, it should be noted that studies available are characterized by high heterogeneity and by difficulties in adjusting for important confounding factors, including solar UV and lifestyle: only a minority of studies report odds ratios (ORs) adjusted for the same confounding factors, 12 studies not for a single confounder (56). Moreover, because individual confounders were assessed using different interrogations, these studies are only partly comparable limiting the ability to interpret results of a combined estimate. and these results should not be considered reliable (56). It has to be emphasized that one has to distinguish between associations, as reported in these case–control/cohort studies and meta-analyses, and causation. In this context, the same results and risk estimates as given in Boniol *et al*. (44) and Colantonio *et al*. (47) could well be obtained in the following scenario, as indicated elsewere (56). Sunbed use has no effect on melanoma risk, lifestyle factors such as extensive sunbathing in the summer as a sun worshipper or an 'unhealthy lifestyle' (*e.g*. alcohol, smoking use), do increase melanoma risk with true OR=1.2 (it has been reported previously that sun worshippers and individuals with an 'unhealthy lifestyle' go more frequently to tanning salons (57)). Many of the confounding factors, including extensive sunbathing in the summer and unhealthy lifestyle, have not been adequately and systematically considered in studies performed to date. For example, the comparison of sunbed users to non-users is confounded by their lifestyle habits, with typical sunbed users found to be females who tend to smoke cigarettes and drink alcohol more frequently than non-users, as well as eating less healthy food (57).

The WHO report states "…and the first use of sunbeds before the age of 35 increases the risk of developing melanoma by 59% (6)" [p. 12 in (2)]. This is not correct. As reported elsewhere (56), the report by Boniol *et al*. (44), that this statement refers to, and the IARC report (46) have to be criticized for defining "first use in younger age" as first use before the age of 36 years, but include studies that consider first use prior to ages 25 to 30 years (7, 26, 39). Moreover, some studies (30, 31) restricted their investigation to melanoma cases diagnosed before the age of 36 years however, this could have resulted in the exclusion of older cases and controls that may have been exposed at a younger age (21).

In strong contrast to the WHO (2) and SCHEER (1) reports, we therefore postulate (due to lack of interventional studies and severe limitations including unobserved or unrecorded confounding) that for main outcomes reported (association of ever exposure, first exposure at younger age and high/low exposure to UV radiation from a solarium with melanoma risk) (44, 46, 47), and according to generally accepted principles of evidence-based medicine (*e.g.* recommendations of the Oxford Centre for Evidence-based Medicine (3)), the resulting evidence levels and grades of recommendation are not "strong", as inaccurately stated in the SCHEER report (which used a highly questionable classification of evidence levels) (1), but are very weak (*e.g.* level 3a– for systematic reviews of case–control studies with heterogeneity, and grade of recommendation D for outcome "ever" *vs.* "never" use of a solarium). In conclusion, our present scientific knowledge does not support the notion that sunbed use *per se* may increase melanoma risk.

Available Evidence Overlooked by SCHEER and WHO Reports

Criticism on inadequate epidemiological studies and analysis thereof in the "Draft summary record" of the public hearing on sunbeds held on April 12, 2016 in Luxemburg published by the European Commission gave a rather revealing explanation: "The SCENIHR representatives acknowledged that there is an insufficient number of studies on European populations, but explained that this left them with no choice but to use the best data from published peer-reviewed scientific studies available to date ……" [first paragraph on p4 (58)]. There is not an "insufficient number of studies" but insufficient evidence from a large number of EU studies. It has to be recognized that the "best data from published peer-reviewed scientific studies available to date" do not show a statistically significant association of sunbed use ("ever" *vs.* "never") with melanoma risk in Europe [*e.g.* meta-analysis by Colantonio *et al*. 2014 (47)]. The lack of association in this subgroup analysis for Europe is very unlikely to be caused by a lack of power because the number of participants in studies performed in Europe is much greater as compared with studies from America that still show an association in subgroup analyses. It is unclear to us why this very important meta-analysis finding is completely ignored in this "Draft summary record" and in the "Final Opinion".

Experimental animal models, including genetically engineered mice, the *Xiphophorus* hybrid fish, the South American opossum, and human skin xenografts, constitute important vehicles for elucidating the relevance of UV in melanomagenesis. Both the SCHEER and WHO reports underappreciate the large body of evidence from epidemiological and animal studies that demonstrates no increase in melanoma risk following chronic (moderate) UV exposure (59-66). As an example, important information was obtained analyzing UV-inducible melanomagenesis in the hepatocyte growth factor/scatter factor (HGF/SF) transgenic mouse (59-61). Using this model, it was demonstrated that dermal melanomas arise in untreated mice with a mean age of onset of approximately 21 months, a latency that was not overtly altered in response to chronic sub-erythemal, or skin non-reddening UV irradiation (59-61). In contrast, erythemal doses to 3.5-day-old-neonatal HGF/SF mice induced cutaneous melanoma with significantly reduced latency (59-61). It should be noted that UV-induced murine melanomas frequently resemble their human counterparts with respect to histopathological appearance and graded progression. Many other studies also support the concept that sub-erythemal exposure to UV doses not only does not increase melanoma risk, but may even be protective (61-66). Occupational exposure to UV radiation was associated with a reduced risk of melanoma in a European population with lightly pigmented skin (66). It also should be noted that neither the SCHEER (1) nor the WHO (2) report discusses the fact that relevant UV signature mutations have not been reported in the B-rapidly accelerated fibrosarcoma (B-RAF) gene nor in other important drivers of melanomagenesis.

It further underlines the unbalanced view of the SCHEER and WHO reports, that they conceal the large body of evidence demonstrating beneficial health effects of UV radiation (*e.g.* 67-127). As an example, a large cohort study reported a longer life expectancy amongst participants with active sun exposure habits, which was related to a decrease in cardiovascular disease (CVD) and non-cancer-related mortality (67). The SCHEER report also misinterprets important findings of that study, stating that the investigation showed an increased risk of death due to cancer amongst participants with active sun exposure habits. This is not true. In this large cohort study, the risk of cancer death was non-significantly decreased (67). However, due to greater survival in those with CVD and those with non-CVD/non-cancer disease, the percentage of cancer death was increased. Furthermore, low sun exposure as a risk factor for all-cause death was comparable in magnitude to smoking, and women with active sun exposure habits were found to live 1 to 2 years longer as compared to those with the lowest sun exposure habits.

Two cohort studies have reported on a relation between personal sunbed use and all-cause mortality (67, 70). Both studies found 30-40% lower all-cause mortality associated with sunbathing vacations (67, 70). In contrast, Yang *et al*. report all-cause mortality risk practically doubled [hazard ratio (HR)=1.9, 95% confidence interval (CI)=1.3-2.7] amongst those in the upper extreme, *i.e.* >12 times per year of sunbed use (70). In the study of Lindqvist *et al*., all users of sunbeds (namely mostly those using a sunbed <12-times per year, *i.e.* sensible users) were at 13% lower risk of all-

cause mortality (HR=0.87, 95% CI=0.8-0.98) (67). Furthermore, the SCHEER report (1) states erroneously that the study population was not a representative sample of the Swedish population, yet the sample was drawn by computerized randomization from the population registry and is a representative sample comprising 20% of the south Swedish female population of the selected age groups.

The most known and well-documented beneficial health effects of UV radiation are mediated *via* vitamin D (see following paragraph). However, other factors might be involved, indicating that preventing and treating vitamin D deficiency may not account for all beneficial effects of solar or artificial UV exposure. Melatonin is involved in the circadian system, with there being a higher level during the night than in the daytime. Light information from the retina influences the production of melatonin *via* the suprachiasmatic nuclei of the hypothalamus. A mutation of the melatonin receptor affecting the melatonin system (*MTNR1B*) is known to be related to increased risk of type 2 diabetes, through the inhibition of insulin release. Thus, the increased susceptibility to type 2 diabetes mellitus noted among women with low sun exposure habits might at least partly be due to interference with the melatonin system (127). Hypertension is a major determinant of CVD. Experimental and observational data support the notion that lack of UVB radiation may be involved in the pathogenesis of hypertension (79, 80) and CVD (75) by (i) suppression of the renin–angiotensin–aldosterone system, (ii) a direct effect on endothelial cells, and effects on (iii) calcium metabolism and (iv) blood pressure, all of which might explain the lower all-cause death risk with increasing sun exposure. Solar UVA radiation induces the release and increases the cutaneous production of NO, resulting in a sustained reduction in blood pressure and has been suggested to act in a cardioprotective manner. Both high acute and chronic stress levels have a role in the activation of coagulation factors and may increase the risk of CVD, high blood pressure and thromboembolism. The finding that UV radiation induces β-endorphin synthesis, which may attenuate stress levels and have a cardioprotective and thromboprophylactic effect, is of note (77, 132). Moreover, epidemiological evidence provides support for solar UVB protection against a number of cancer types, including breast, colorectal, lung, ovarian, pancreatic and prostate cancer (72).

The SCHEER and WHO reports do not adequately consider the large body of evidence demonstrating the negative health consequences of vitamin D deficiency (*e.g.* 72, 78, 86-126). In fact, one of the leading theories of the evolution of skin pigmentation is that it is a compensatory mechanism for vitamin D production in low UVB environments (71). Populations with lighter skin tones (maximally depigmented skin) are those inhabiting environments with the lowest annual and summer peak levels of UVB. During hominin evolution, depigmented and tannable skin evolved numerous times. Facultative pigmentation, or tanning, developed in populations where levels of UVB varied strongly by season (71). It has been estimated that at present, although oral vitamin D supplements are easily available, approximately one billion people worldwide are vitamin D-deficient or insufficient (88). This epidemic causes serious health problems that are still widely under-recognized (*e.g.* 88-91) Apart from well-documented problems in bone and muscle function, there are associations between vitamin D deficiency and increased incidence of or unfavourable outcome for a broad variety of independent acute and chronic diseases, including type 2 diabetes and various types of malignancies (*e.g.* colon, skin, and breast cancer), autoimmune, infectious, neurocognitive and cardiovascular diseases (*e.g.* 72, 78, 86-126). Caini and co-workers provided evidence through meta-analysis that higher levels of vitamin D are associated with reduced risk of non-melanoma skin cancer [summary relative risk of 1.64 (95% CI=1.02-2.65] for highest *vs.* lowest level] (125). Mechanistically, vitamin D acts as an antiproliferative agent and modulates cell growth and development in many tissues (124). Furthermore, vitamin D has profound effects on immune system activity and has been found to have a protective effect against many autoimmune and inflammatory diseases, particularly those of the central nervous system (123).

A recent meta-analyses demonstrated the benefit of vitamin D supplementation in preventing respiratory tract infections (118). In pregnancy, a reduced risk of preterm delivery was found to be associated with vitamin D supplementation (110, 121), as well as of asthma and wheezing in children born to mother's taking adequate vitamin D during pregnancy (119).

A large meta-analysis assessed the beneficial and harmful effects of vitamin D supplementation in the prevention of mortality in healthy adults and adults in a stable phase of disease (114). In that study, 56 randomized trials with 95,286 participants provided usable data on mortality. The age of participants ranged from 18 to 107 years. Most trials included women older than 70 years. The mean proportion of women was 77%. Forty-eight of the trials randomly assigned 94,491 healthy participants. Of these, four trials included healthy volunteers, nine included postmenopausal women and 35 included older people living on their own or in institutional care. The remaining eight trials randomly assigned 795 participants with neurological, cardiovascular, respiratory or rheumatoid diseases. Vitamin D was administered for a weighted mean of 4.4 years. More than half of the trials had a low risk of bias. All trials were conducted in high-income countries. Forty-five trials (80%) reported the baseline vitamin D status of participants based on serum 25-hydroxyvitamin D level. Participants in 19 trials had vitamin D adequacy (at or above 20 ng/ml). Participants in the remaining 26 trials had vitamin D insufficiency (less

than 20 ng/ml). Vitamin D reduced mortality in all 56 trials when analyzed together [5,920/47,472 (12.5%) *vs.* 6,077/47,814 (12.7%); RR=0.97, 95% CI=0.94 to 0.99, p=0.02; I^2=0%). 'Worst-best case' and 'best-worst case' scenario analyses demonstrated that vitamin D was associated with a dramatic increase or decrease in mortality, respectively Trial sequential analysis supported the findings regarding vitamin D_3, with the cumulative Z-score breaking the trial sequential monitoring boundary for benefit, corresponding to 150 people treated over 5 years to prevent one additional death. Vitamin D_3 statistically significantly reduced cancer mortality (RR=0.88, 95% CI=0.78 to 0.98), p=0.02; I^2=0%; 44,492 participants; four trials) (114).

The SCHEER and WHO reports purport that using a sunbed is not an efficient way to generate vitamin D and that there are no health benefits associated with sunbed use beyond cosmetic outcomes, yet numerous publications support both. Sunbeds using UVB radiation lead to sufficient vitamin D production to significantly increase serum 25(OH)D concentration within 8-12 weeks (81-84) independent of ethnicity (85). Furthermore, Tangpricha *et al*. (86) reported 90% higher concentrations of 25(OH)D in those who used sunbeds regularly in comparison with controls. The sunbed users had significantly higher bone mass density and Z scores at the total hip than did non-users (86).

Conclusion

The generally accepted principles and ethics of medical research require that all available results are systematically collected and presented in an objective and impartial manner. This does not appear to be the case in the SCHEER (1) and WHO (2) reports, as the authors/contributors seem to have decided *a priori* on their position with respect to sunbed use and selectively emphasized the results they believed to support their position.

SCHEER should provide the European Commission with the scientific advice it needs when preparing policy for the European population. However, one should keep in mind that the conclusions of the SCHEER report (1) are based on data that do not reflect the present situation in Europe, while the conclusions of both reports are based on historical data that do not reflect the present situation in Europe or in other countries. Many studies included individuals with skin type I, who in Europe are at present not allowed to use a sunbed. Moreover, many studies included data obtained on technical devices that are no longer allowed to be used in Europe. It is well known that regional differences, including impact of confounding factors (*e.g.* solar UV exposure), technical differences of UV-emitting devices and differences in their operation, strongly influence the association of ever-exposure to UV radiation from sunbeds with melanoma risk (4-56). As mentioned above, it is alarming that this SCHEER report (1) conceals the important finding, namely that meta-analyses of studies performed in Europe do not show an association of ever-exposure to UV radiation from sunbeds with increased melanoma risk (47). Because of the high number of participants in European studies, this result is most likely not due to a lack of power, but reflects regional differences concerning impact of confounding factors, including solar UV exposure, technical differences of UV-emitting devices, and differences in their use (47).

Moreover, reductions of melanoma mortality rates during the past decades do not support the hypothesis that UV radiation from sunbeds may have increased melanoma risk. While melanoma death rates had more than doubled in light-skinned populations between 1955 and 1985, reduction in melanoma mortality rates have been observed from 1985-1990 in Australia, the United States and in many European countries. Furthermore, the authors of an article analyzing the imminent inexorable decline in light-skinned populations concluded that independently from screening or treatment, death from malignant melanoma is likely to become an increasingly rare event (128). It has been suggested that better detection methods have been in use to detect melanoma earlier, which is also a possible reason for the increased risk that has been observed (129).

In conclusion, both the SCHEER (1) and WHO (2) reports claim to assess health effects of sunbed use. Unfortunately, however, as such they are partially unbalanced and inaccurate. Both documents mainly assess negative health effects of UV exposure, conceal the large body of evidence demonstrating beneficial health effects of UV radiation, and major conclusions drawn are not sufficiently supported by current scientific knowledge. It should be emphasized that the main conclusions drawn by the SCHEER (1) and WHO (2) reports are not in accordance with generally accepted principles of evidence-based medicine, they not only are not in line with recommendations of the Oxford Centre for Evidence-based Medicine (3), but, as outlined in this critical appraisal, also do not fulfil the criteria proposed by Bradford Hill for examining causality in a biological system (strength of association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy) (130). Other researchers added the ruling out of confounding factors and bias (131). With this unscientific approach, both the SCHEER (1) and WHO (2) reports are not adequate and do not properly summarize current knowledge on comparing beneficial and adverse effects of UV exposure from sunbeds.

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