* TREMFYA® ist indiziert: 1) für erwachsene Patienten mit mittelschwerer bis schwerer **Plaque-Psoriasis**, die für eine systemische Therapie in Frage kommen; 2) allein oder in Kombination mit MTX für die Behandlung der aktiven **Psoriasis-Arthritis** bei erwachsenen Patienten, wenn das Ansprechen auf eine vorherige nicht-biologische krankheitsmodifizierende antirheumatische (DMARD-)Therapie unzureichend gewesen ist oder nicht vertragen wurde.[1]

\# PASI 90: 84% (Wo 48; n=534) Non Responder Imputation (NRI)[2]; PASI 100: 52,7% (Wo 252; n=391) Treatment Failure Rules (TFR)[3]; Signifikante Überlegenheit vs. Placebo in Bezug auf ACR20 (64% vs. 33%, p<0,0001; NRI) nach 24 Wochen in der 8-Wochen-Dosierung (n=248) in bionaiven Patient:innen mit aktiver PsA.[4]

1. Aktuelle Fachinformation TREMFYA®. **2.** Reich K et al. Lancet. 2019;394(10201):831–839. **3.** Reich K et al. Br J Dermatol. 2021 Jun 9. doi: 10.1111/bjd.20568.
4. Mease P et al. The Lancet 2020; https://doi.org/10.1016/S0140-6736(20)30263-4 (Supplementary)

▼Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Daher ist es wichtig, jeden Verdacht auf Nebenwirkungen in Verbindung mit diesem Arzneimittel zu melden.

Tremfya® 100 mg Injektionslösung in einer Fertigspritze/in einem Fertigpen. Wirkstoff: Guselkumab. **Zusammensetz.:** Fertigspritze/Fertigpen enth. 100 mg Guselkumab. Sonst. Bestandt.: Histidin, Histidinmonohydrochlorid-Monohydrat, Polysorbat 80, Saccharose, Wasser f. Injektionszw.. **Anw.geb.:** Für d. Bhdlg. erw. Pat. m. mittelschwerer bis schwerer Plaque-Psoriasis indiziert, d. für e. syst. Therapie in Frage kommen. Als Monotherapie od. in Komb. m. Methotrexat für d. Bhdlg. erw. Pat. m. Psoriasis-Arthritis indiziert, d. auf e. vorherige nicht-biolog. krankheitsmodifiz. antirheumat. (DMARD)-Therapie unzureich. angesprochen od. diese nicht vertragen haben. **Gegenanz.:** Schwerwieg. Überempf. gg. d. Wirkst. od. e. d. sonst. Bestandt., klin. relev. aktive Infekt. (einschl. aktive Tuberkulose), Schwangersch., Stillzeit (b. Entscheidg. üb. Unterbrechen d. Therapie m. TREMFYA od. Verzicht auf Einleiten d. Therapie m. TREMFYA muss Nutzen d. Stillens für d. Kind m. Nutzen d. Therapie für d. Frau abgewogen werden). **Warnhinw.:** Arzneim. f. Kdr. unzugängl. aufbew.. **Nebenwirk.:** Atemwegsinfekt., Kopfschm., Diarrhö, Arthralgie, Reakt. a. d. Injektionsst., Transamin. erhöht, Herpes-simpl-Infekt., Tinea-Infekt., Gastroenteritis, Überempf.reakt., Anaphylaxie, Urtikaria, Hautausschlag, Neutrophilenzahl erniedr.. **Verschreibungspflichtig. Pharmazeut. Unternehmer:** JANSSEN-CILAG International NV, Turnhoutseweg 30, 2340 Beerse, Belgien. **Örtl. Vertreter für Deutschland:** Janssen-Cilag GmbH, Johnson & Johnson Platz 1, 41470 Neuss. **Stand d. Inform.:** 09/21.

CP-324073

Janssen-Cilag GmbH
www.tremfya-pso.de

janssen Immunology
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Review

Submitted: 1.9.2021
Accepted: 19.4.2022

DOI: 10.1111/ddg.14818

Syncarcinogenesis of natural UV radiation and polycyclic aromatic hydrocarbons in the development of squamous cell carcinomas of the skin?

Wobbeke Weistenhöfer, Regina Lutz, Julia Hiller, Simone Schmitz-Spanke, Hans Drexler

Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Erlangen, Germany

Summary

Squamous cell carcinomas (SCC) of the skin can be induced by occupational exposures to polycyclic aromatic hydrocarbons (PAHs), as in tar and soot, or to UV radiation and can be recognized and compensated as occupational diseases. A possible syncarcinogenic effect of these exposures in the development of SCC in humans is under discussion. For the scientific validation of this question, a systematic literature search was conducted using the databases PubMed, Web of Science, and Scopus. Studies on individuals with SCC of the skin and their precursors as well as occupational, non-occupational, or therapeutic exposure to UV radiation and PAHs were selected. In addition, animal studies with exposure to UV radiation and PAHs were evaluated. After screening the abstracts of 510 identified studies, the full texts of 131 studies were reviewed. None of the epidemiological studies provided robust evidence for a syncarcinogenesis of PAHs and UV radiation in the development of SCC of the skin in humans. Nevertheless, as there are indications for a (super-)additive effect of UV radiation and PAH exposure from animal studies and mechanistic investigations, syncarcinogenesis seems possible. However, quantitative dose-response relationships are lacking which would allow comparison of the onset of an adverse effect between the different exposure levels.

Introduction

Non-melanoma skin cancer (NMSC) can be induced by exposure to UV radiation or polycyclic aromatic hydrocarbons (PAHs). Whereas precancerous stages triggered by tar (contains PAHs), so-called tar or pitch warts, differ from precancerous conditions induced by UV radiation (actinic keratoses), it is currently not possible to differentiate between SCCs caused by PAHs or UV radiation. Pursuant to No. 5103 of the appendix of the Ordinance on Occupational Diseases in Germany and the General Clause in Austria, SCCs or multiple actinic keratoses of the skin caused by natural UV radiation (as shown in Figure 1) can be recognized and compensated as an occupational disease (*Berufskrankheit*, BK). Skin cancer and skin lesions susceptible to cancer development caused by soot, crude paraffin, tar, anthracene, pitch, or similar substances can be recognized pursuant to No. 5102 in Germany and pursuant to No. 17 in § 177 and the appendix of the General Social Security Act (*Allgemeines Sozialversicherungsgesetz*, ASVG) in Austria [1, 2]. Both the disease (SCC and precursors) and the exposure (sunlight and processing of PAH-containing working materials) are very common. The majority of so-called *outdoor workers* (including bricklayers, civil engineers, farmers) are occupationally exposed not only to UV radiation, but also to tar, soot, and similar substances. To date, scientific studies on a potential syncarcinogenic effect in the development of squamous cell carcinomas in humans are insufficient to serve as basis for assessing its correlation with occupational diseases.

Therefore, we investigated whether epidemiological studies provide evidence for or against a syncarcinogenic effect of UV radiation and PAHs in the development of squamous cell carcinomas in humans and whether these data demonstrate an increased risk in case of simultaneous exposure.

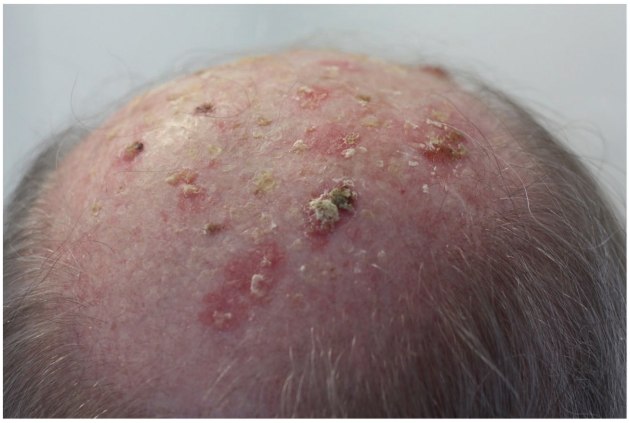

Figure 1 Multiple actinic keratoses after chronic UV exposure.

Materials and Methods

For this systematic review, the PRISMA guidelines [3] were observed and a literature search concerning the syncarcinogenic effect of UV radiation and PAHs was conducted in epidemiological original studies according to the PICO scheme ("*To assess the synergistic effects of PAH and solar UV-radiation for development of squamous skin cancer in humans*."). On this basis, inclusion and exclusion criteria were defined *a priori* [4].

Search strategy and selection process

The terms presented in Table 1 were used in the comprehensive (sensitive) search of the databases PubMed (Medline), Scopus, and Web of Science. Furthermore, additional publications were identified by cross-references or manual search in German journals. Original publications of any study type were included in this qualitative analysis; meta-analyses and reviews were only used to search for cross-references. There was no restriction on the publication period. The last update of the search was on August 19, 2021.

Screening and evaluation of the literature were performed independently by three research assistants, two of whom were physicians. Following screening of all titles, abstracts identified as relevant, and subsequently, the full text of publications considered important were reviewed. The following information was extracted from the studies included in this review: study type, collective, UV exposure, PAH exposure, disease, age of onset, and findings. The studies were evaluated descriptively. Based on the available data, meta-analytical aggregation was not possible.

Table 1 Overview of the search terms.

No.	Search terms
#1	*sunlight OR "ultraviolet light" OR "ultraviolet radiation" OR "uv light" OR "uv radiation"*
#2	*"polycyclic aromatic hydrocarbons" OR "polycyclic aromatic hydrocarbon" OR "polycyclic-aromatic-hydrocarbons" OR "polycyclic-aromatic-hydrocarbon" OR "aromatic hydrocarbons" OR "aromatic hydrocarbon" OR "PAH" OR "PAHs" OR benzoapyren* OR benzopyren* OR coal OR tar OR bitumen OR "coal tar pitch" OR "CTP-I"*
#3	*skin*
#4	*#1 AND #2 AND #3*

Inclusion and exclusion criteria

Original publications (peer-reviewed) in German and English language that included individuals with NMSC and (1) occupational exposure to UV radiation and PAHs, (2) therapeutic exposure to UV radiation and tar, or (3) non-occupational exposure to UV radiation and PAHs (environmental exposure) were selected for the evaluation. Studies were excluded which focused exclusively on (1) basal cell carcinomas or (2) malignant melanomas, with exclusive assessment of (3) therapeutic efficacy of Goeckerman/PUVA therapy without evidence for potential side effects or long-term effects, on (4) the impact of food/food supplements on the development of cancer, and studies on (5) pure phototoxicity (without carcinogenicity) and (6) pure photosensitization.

Additional search and evaluation: including animal studies

Only few epidemiological studies were identified for a discussion on syncarcinogenesis of PAHs and UV radiation. Therefore, in a second step, we also assessed animal studies identified in the literature search presenting data on tumor incidence and including experimental studies on exposure to either UV radiation or PAHs, as well as combination effects.

Results

We identified 683 publications, screened 510 abstracts, and reviewed the full text of 131 studies for eligibility. Eight epidemiological studies were included in the qualitative review [5–12]. In addition, 16 suitable animal studies were identified [13–28]. The detailed search process is presented in the flow chart in Figure 2.

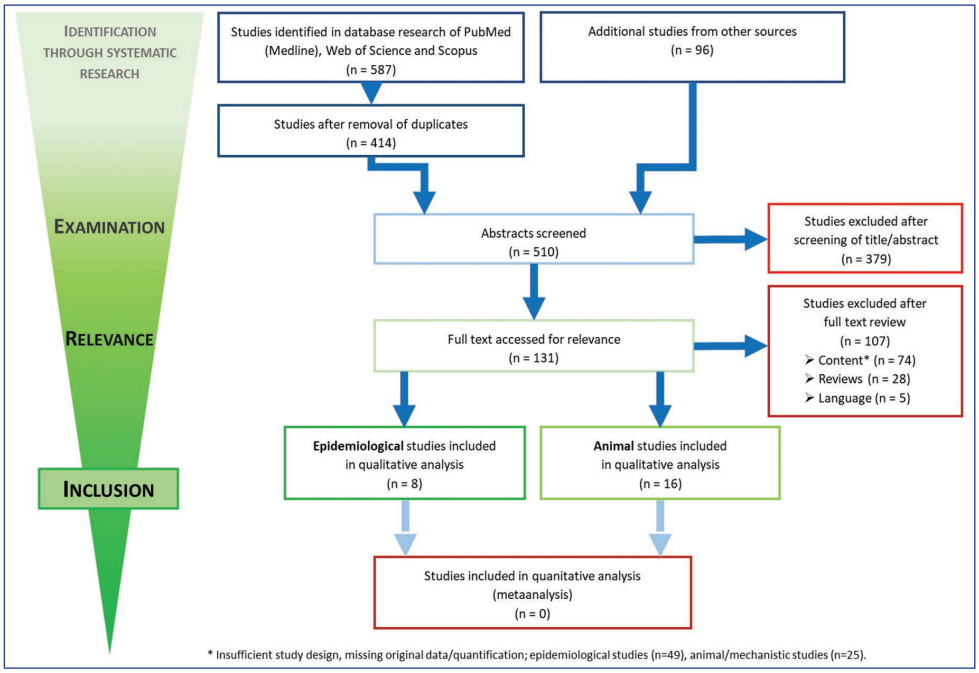

Figure 2 Flow chart: Number of studies identified, abstracts reviewed, and studies either included or excluded.

Epidemiological studies

Case reports or series of a total of 30 patients were identified that were assessed for NMSC or respective precancerous diseases due to occupational exposure to tar and UV radiation in various occupations with respect to the presence of occupational disease [5, 6, 9]. Moreover, job-time-exposure matrices for skin contact with crude oil, mineral oil, and ionizing radiation were used in a cohort study of 24,917 offshore oil workers with a follow-up period of 13.5 years in conjunction with surveys on sunbathing behavior at the start of the study [11]. In > 90%, skin tumors (112 melanomas, 70 NMSCs) were observed in locations without regular exposure to petrochemicals such as head, neck, and trunk. A significantly increased risk of developing NMSC was shown for an employment duration of more than 19 years irrespective of exposure.

Apart from collectives with occupational exposure, data are available from patient collectives exposed to PAHs and UV radiation for therapeutic reasons.

In the study of Lindelöf and Sigurgeirsson [7] on 24 patients developing squamous cell carcinoma after PUVA (psoralene + UVA) therapy and 96 control individuals also treated with PUVA therapy, a non-significant 1.3-fold increase in risk was observed after previous tar therapy. Stern et al. [12] conducted a prospective study on a collective of 1,380 psoriasis patients with PUVA treatment and identified 89 incident squamous cell carcinomas and 43 basal cell carcinomas. The risk of developing squamous cell carcinoma was significantly increased by a high dose of tar. However, additional calculations did not reveal any correlation between PUVA and tar.

Maughan et al. [8] analyzed data from 305 patients treated for atopic dermatitis according to the Goeckerman regimen. During the study, only few tumors were observed and patients with tumors did not have more or longer contact with tar than patients without tumors. In the study of Pittelkow et al. [10], data from 260 patients with psoriasis and Goeckerman therapy were analyzed for a mean follow-up period of 20 years. While 19 patients developed 32 NMSCs, no increased incidence for NMSC was found when comparing the collective treated by Goeckerman therapy with the general population [10].

The findings and results of all studies relevant for the evaluation are presented in Table S1 (*online supplement information*).

Given the low number of identified epidemiological studies and the heterogeneity with respect to study design as well as to documentation and quantification of exposure, it was only possible to conduct a qualitative discussion of the syncarcinogenic effects.

Results of animal studies

Eleven of the 16 animal studies investigating the development of skin tumors with and without exposure to UV radiation and PAHs, individually and in combination, and reporting on tumor incidence, provided evidence for a syncarcinogenic

effect. In seven studies [13–16, 18, 23, 28], exposures to PAHs and UV were tested both individually and in combination, revealing an increased effect when both exposures were combined. In one study on female BALB/c mice, the animals were treated with benzo[a]pyrene (B[a]P), ventrally applied by brush, and irradiated dorsally with UVB light [17]. A syncarcinogenic effect was again demonstrated, as the tumor incidence was significantly higher with additional UVB radiation. In three studies [24–26], the tumor incidence increased after exposure to dimethylbenzanthracene (DMBA) in combination with low or subcarcinogenic UV doses. The combination with higher UV doses decreased the tumor incidence. The authors interpreted this finding as inhibition. The publication of Santamaria et al. [23] reported on various experiments with exposures to 3,4-benzo[a]pyrene and UV radiation. Since the tumor incidence was highest in the animal group with combined exposure (although not at the highest exposure level) and the tumors developed significantly earlier compared to exposure to 3,4-benzo[a]pyrene alone, these experiments also provide evidence for syncarcinogenesis. In the further course of the study, however, UV radiation inhibited the development of tumors compared to the group without exposure.

Results from four animal studies argue against a syncarcinogenic effect [19–21, 27]. Kohn-Speyer [19] replicated the experiments of Findlay [16], but failed to demonstrate any syncarcinogenesis. In their series of experiments with exposure to 1,2,5,6-dibenzanthracene, methylcholanthrene, 9,10-dimethyl-1,2-benzanthracene, and UV radiation, Rusch et al. [20, 21] observed no syncarcinogenetic effects. In the experiments of Teutschländer [27] with exposure to tar and UV radiation, the tumor incidence increased in darkroom animals treated only with tar.

Detailed study designs and results of the animal studies included in this review are presented in Table S2 (*online supplement information*).

Discussion

On the question of syncarcinogenesis of PAHs and UV radiation, only a few epidemiological studies were identified in the systematic literature search. Moreover, these did not allow for any conclusions in terms of quantifiable risks or dose-response relationships.

Epidemiological studies

The authors of the studies on individuals with notified BK 5102 and 5103 [5, 6, 9] assumed syncarcinogenesis of PAHs and UV radiation on the skin, but also pointed out the absence of the dose-response relationship required by the Ordinance on Occupational Diseases. Although exposures to PAHs and UV radiation were confirmed for all individuals, no reliable evidence for syncarcinogenesis could be derived. Occupational exposure to UV radiation of well over 40% at the site of tumor development had already been reported in the majority of these individuals, hence recognition of a UV-related occupational disease would have been possible. While an early onset of disease was discussed, this is insufficient evidence for a syncarcinogenic effect, but at best an indication of a carcinogenic effect of one of the two exposures.

In the cohort study on offshore oil workers with occupational contact to PAHs and information on non-occupational UV exposure [11], an elaborate but only semi-quantitative determination of exposure was performed by means of job-time-exposure matrices. With respect to UV exposure, only data on self-reported sunbathing behavior (sunbaths and visits to tanning studios before and after the age of 20, frequency of sunburns) and indications for high non-occupational UV exposure were available [11, 29]. After adjustment (age, sunburn, education), the risk of developing NMSC on the hands/forearms due to contact to PAHs from crude oil was not significantly increased. A significant interaction between the dichotomous variables (never/ever exposed) on the frequency of sunburns and contact to crude oil or benzene was observed for the risk of developing skin cancer on the upper extremities. However, the eight NMSCs and 16 cutaneous melanomas were considered as one disease group. According to the authors, only limited conclusions can be drawn on a possible syncarcinogenesis, given that all affected patients were exposed to PAHs and UV radiation. In another study on this collective, the frequency of sunburns was identified as a predictor for the development of skin cancer. In addition, the use of tanning studios increased the risk of developing NMSCs [29].

Another cohort of tar-refinery workers with occupational skin tumors was examined and monitored in three studies [30–32]. Given that verified exposures were only available for PAHs, these studies were not included in the results of this review. The UV exposures were not recorded, although there was occupational UV exposure (outdoor workplace) in addition to private exposure. While non-melanoma skin lesions were mainly localized on sun-exposed areas, such as the face, forearms, and hands, they were different from the typically predominant localizations of sun-exposed tumors (upper lip > lower lip, forearm > wrist, nostril > nasal bridge).

Apart from collectives with occupational exposure, data on patient collectives with PAH/UV co-exposure for therapeutic reasons are also available. In the last century, for example, the photosensitizing effect of tar substances was utilized predominantly for the treatment of psoriasis according to the Goeckerman regimen that involved treatment of the skin with tar and subsequent radiation with UV light [33]. Two retrospective cohort studies with 25 years of follow-up

in patients with psoriasis [10] and atopic dermatitis [8], respectively, treated with the Goeckerman regimen, did not reveal any evidence for increased occurrence of squamous cell carcinomas and thus no evidence for syncarcinogenesis.

Moreover, the combination of UVA radiation with orally administered psoralene (PUVA, psoralene + UVA) has been used for the therapy of severe dermatoses for many decades. While numerous studies on this treatment are available, there are hardly any long-term observations with respect to an elevated risk of developing NMSC that consider also potential additional therapies with tar products. In the study by Lindelöf and Sigurgeirsson [7], a non-significant elevated risk of developing squamous cell carcinoma was observed in PUVA-treated patients with previous therapies with tar. While the UV exposure is reported in detail, precise information on tar treatments is lacking. Overall, there are no robust data for syncarcinogenesis of PAHs and UV radiation. In the study by Stern et al. [12] on PUVA-treated psoriasis patients which had a statistically significantly increased risk of developing squamous cell carcinoma and a history of high tar doses, additional calculations revealed no association between PUVA and tar. Due to the relatively short follow-up period of 5.7 years, there was no robust evidence for syncarcinogenesis. In a pilot study of the authors [34] with a total of 1,373 psoriasis patients, exposure to tar and UV radiation were dichotomized into "*high*" and "*not high*" (*no/low/moderate exposure*). For 59 patients with unspecified skin tumors and 924 unmatched controls, a relative risk (RR) of 2.4 (95% confidence intervall (CI): 1.4–4.2) was determined for the development of skin cancer in individuals with "high" compared to "not high" exposure to tar and/or UV radiation. In 58 patients with skin tumors and 126 matched controls, the RR of developing skin cancer was 4.7 (95% CI: 2.2–10.0). There was no robust evidence with respect to syncarcinogenesis. Given the imprecise documentation of exposure in both exposure scenarios to be assessed (and/or) and the unspecified skin tumors, this study was not included in the list of identified studies.

Altogether, there are a few epidemiological studies on collectives with occupational and therapeutic co-exposure to PAHs and UV radiation and NMSC, but these do not allow scientifically robust conclusions for syncarcinogenesis to be drawn.

Animal studies

The 16 identified animal studies showed heterogeneous results with respect to potential syncarcinogenesis.

Seven studies found clear evidence for a syncarcinogenic effect of PAHs and UV radiation [13–16, 18, 23, 28]. Additional evidence for syncarcinogenesis was provided by the increased tumor incidence after DMBA exposure together with low or subcarcinogenic UV doses [24–26]. Higher exposure to UV radiation one hour after DMBA resulted in lower tumor incidence. This finding was discussed by the authors as inhibition due to photochemical deactivation of the carcinogen by UV radiation after exposure. In some of these studies, croton oil was used additionally as a promotor. Santamaria et al. [22] used the extent of cell damage to explain the observed syncarcinogenesis in terms of light-induced acceleration of tumor formation upon exposure to 3,4-benzo[a]pyrene and the subsequent inhibition of tumor formation after continued light exposure. Longer exposure to light would result in more severe cell damage, thus preventing the formation of carcinogenic cell clones. Gensler et al. [17] exposed mice dorsally to UV radiation and/or ventrally to PAHs. The authors interpreted the statistically significantly higher tumor incidence and the significantly shorter tumor-free survival of the animals treated with tar and UV radiation at different regions of the body as a systemic effect.

The results of four animal studies argue against a syncarcinogenic effect [19–21, 27]. Neither the replication [19] of the experiments performed by Findlay [16] nor the series of experiments performed by Rusch et al. [20, 21] detected syncarcinogenic effects. In the study by Teutschländer [27], the animals treated only with tar actually developed more tumors.

Furthermore, animal experiments not included in this evaluation are available in which specific approaches were chosen to make the results transferable to humans [35, 36]. Græm [35] grafted human skin onto the backs of nude mice and subsequently exposed them to 7,12-dimethylbenz[a]anthracene, 12-O-tetradecanoylphorbol-13-acetate, and UV radiation. No tumors developed over an average period of 18 weeks. In the study by Lerche et al. [36], mice were tattooed with a dye containing high amounts of B[a]P, irradiated, and monitored for one year. In the tattooed mice, the development of squamous cell carcinomas was significantly delayed compared to mice that were only irradiated. The authors hypothesized that the protective effect might be attributed to UV absorption by the black pigment resulting in reduced back-scattered radiation.

In summary, the majority of available animal studies demonstrated the syncarcinogenesis of PAHs and UV radiation in the development of NMSC, even in case of subcarcinogenic exposures.

Mechanistic studies

Mechanistic studies on syncarcinogenesis are available for human cells, cell lines, and animals. The change in toxicity and carcinogenicity of PAHs in the skin has been investigated in several mechanistic studies [37]. Polycyclic aromatic hydrocarbons only exert their toxic and/or carcinogenic effect

after metabolization. UV radiation is absorbed by PAHs, resulting in the increased formation of reactive oxygen species (ROS) and reactive intermediates. Both processes induce oxidative stress and DNA damage, for example, by DNA adducts [38–40]. Furthermore, the combined exposure to B[a]P and UVA radiation increases the formation of diol epoxide, which is considered the ultimate carcinogen [41]. Metabolization of PAHs may be mediated by activation of the arylhydrocarbon receptor (AhR) followed by increased induction of, for example, CYP450. Contradictory studies are available on the increased activation of AhR by UVB radiation [37, 42]. Newer studies performed on cell lines, reconstructed human skin, and *ex vivo* human skin models examined the hypothesis of oxidative stress in detail, including changes to glutathione metabolism, the most potent cellular defense system against oxidative stress [38, 43–45].

Limitations

The fact that the used databases Pubmed, Web of Science, and Scopus predominantly include journals in the English language and that only articles in English and German were considered for the literature search may present a potential risk of bias concerning the identification of relevant studies. However, only five abstracts were excluded based on language. Given that the primary focus of this study was on epidemiological studies concerning the question of syncarcinogenesis of exposures to PAHs and UV radiation and not on animal studies, the presence of other, as yet overlooked animal studies cannot be excluded despite our careful database search, which included cross-references. It is, however, not anticipated that these potential additional studies would have provided completely different indications with regard to syncarcinogenesis. A general problem of bias concerning the older animal studies is caused by the different sources of UV radiation, which may have provided unreliable UV exposure data, thus impeding the comparability of the studies. Furthermore, particularly sensitive hairless or albino mice were often used, which makes transferability of the results difficult. In the animal studies, different concentrations of various PAHs were usually applied by brush onto the backs or ears of the rodents, which had previously or subsequently been exposed to UV radiation. In some studies, additional promotors were used, which also complicates the comparability of the findings. Most available animal studies described a syncarcinogenic effect. It cannot be ruled out that studies with syncarcinogenic effects were published more easily and thus more frequently than studies without such results. Similarly, these studies may have been cited more often than studies without observed syncarcinogenic effects. Mechanistic studies, however, support syncarcinogenesis.

Conclusions

At present, data from epidemiological studies is insufficiently robust, partly due to inadequate study designs for the purpose, to assume syncarcinogenesis with the probability required by the Ordinance of Occupational Diseases, such as in the procedure for combined exposure to PAHs and asbestos [1]. Although an experimental epidemiological study is ethically impossible due to the carcinogenic exposures, robust results might be derived from data evaluation of large collectives, for example all individuals with therapeutic exposure to tar and UV radiation or the National Cohort. Both animal and mechanistic studies provide evidence for an amplified effect with respect to carcinogenic outcomes. Additional studies should derive dose-response relationships that quantify the transition to an adverse state between the different sources of exposure, thereby facilitating comparability.

Conflict of interest

This review was prepared as part of a project sponsored by the German Social Accident Insurance (*Deutsche Gesetzliche Unfallversicherung*, DGUV) (FB 276). The DGUV was not involved in study design, collection, analysis, or data interpretation, or in the publication of the results. All authors declare no conflicts of interest.

Correspondence to

Priv.-Doz. Dr. med. Wobbeke Weistenhöfer
Friedrich-Alexander-Universität Erlangen-Nürnberg
Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine

Henkestraße 9–11
91054 Erlangen, Germany

E-mail: wobbeke.weistenhoefer@fau.de

References

1 Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA). Dokumente zu den einzelnen Berufskrankheiten. Available from: https://www.baua.de/DE/Angebote/Rechtstexte-und-Technische-Regeln/Berufskrankheiten/Merkblaetter.html [Last accessed January 21, 2022].

2 Allgemeine Unfallversicherungsanstalt (AUVA). Meldung einer Berufskrankheit. Available from: https://www.auva.at/cdscontent/?contentid=10007.671004&portal=auvaportal&viewmode=content&pk_campaign=bk-meldung [Last accessed January 21, 2022].

3 Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 6(7): e1000097.

4 Higgins J, Thomas J, Chandler J et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021), Cochrane 2021.

5 Dickel H, Blome O, Dickel B et al. Occupational syncarcinogenesis in the skin – combined effects of two carcinogens from the German occupational disease list. J Dtsch Dermatol Ges 2016; 14(12): 1284–96.
6 Dickel H, Altmeyer P. Syncancerogenesis in occupational dermatology: Clinical Letters. J Dtsch Dermatol Ges 2013; 11(6): 553–5.
7 Lindelöf B, Sigurgeirsson B. PUVA and cancer: a case-control study. Br J Dermatol 1993; 129(1): 39–41.
8 Maughan WZ, Muller SA, Perry HO et al. Incidence of skin cancers in patients with atopic dermatitis treated with ocal tar. A 25-year follow-up study. J Am Acad Dermatol 1980; 3(6): 612–5.
9 Peckruhn M, Elsner P. Missed occupational disease due to tar (BK 5102) in a roofer – syncancerogenesis with UV-light: Clinical Letter. J Dtsch Dermatol Ges 2014; 12(7): 619–20.
10 Pittelkow MR, Perry HO, Muller SA et al. Skin cancer in patients with psoriasis treated with coal tar. A 25-year follow-up study. Arch Dermatol 1981; 117(8): 465–8.
11 Stenehjem JS, Robsahm TE, Bråtveit M et al. Aromatic hydrocarbons and risk of skin cancer by anatomical site in 25 000 male offshore petroleum workers. Am J Ind Med 2017; 60(8): 679–88.
12 Stern RS, Laird N, Melski J et al. Cutaneous squamous-cell carcinoma in patients treated with PUVA. N Engl J Med 1984; 310(18): 1156–61.
13 Cavalieri E, Calvin M. Photochemical coupling of benzo(a) pyrene with 1-methylcytosine; photoenhancement of carcinogenicity. Photochem Photobiol 1971; 14(5): 641–53.
14 Epstein JH. Comparison of the carcinogenic and cocarcinogenic effects of ultraviolet light on hairless mice. J Natl Cancer Inst 1965; 34(6): 741–5.
15 Epstein JH, Epstein WL. Cocarcinogenic effect of ultraviolet light on DMBA tumor initiation in albino mice. J Invest Dermatol 1962; 39(5): 455–60.
16 Findlay GM. Ultra-violet light and skin cancer. CA Cancer J Clin 1979; 29(3): 169–71.
17 Gensler HL. Enhancement of chemical carcinogenesis in mice by systemic effects of ultraviolet irradiation. Cancer Res 1988; 48(3): 620–3.
18 Heller W. Experimentelle Untersuchungen über den Lichtkrebs; Lichtkrebserzeugung durch Photosensibilisierung. Strahlentherapie 1950; 81(4): 529–48.
19 Kohn-Speyer A. Effect of ultraviolet radiation on the incidence of tar cancer in mice. Lancet 1929; 217: 1305–6.
20 Rusch HP, Kline BE, Baumann CA. The nonadditive effect of ultraviolet light and other carcinogenic procedures. Cancer Res 1942; 2: 183–8.
21 Rusch HP, Baumann CA, Kline BE. Effect of local applications on development of ultraviolet tumors. Proc Soc Exper Biol Med 1939; 42(2): 508–12.
22 Santamaria L, Giordano GG, Alfisi M et al. Effects of light on 3,4-benzpyrene carcinogenesis. Nature 1966; 210(5038): 824–5.
23 Santamaria L, Bianchi A, Arnaboldi A et al. Dietary carotenoids block photocarcinogenic enhancement by benzo (a) pyrene and inhibit its carcinogenesis in the dark. Experientia 1983; 39(9): 1043–5.
24 Stenbäck F, Garcia H, Shubik P. Studies on the influence of ultraviolet light on initiation in skin tumorigenesis. J Invest Dermatol 1973; 61(2): 101–4.
25 Stenbäck F. Studies on the modifying effect of ultraviolet radiation on chemical skin carcinogenesis. J Invest Dermatol 1975; 64(4): 253–7.
26 Stenbäck F, Shubik P. Carcinogen-induced skin tumorigenesis in mice: enhancement and inhibition by ultraviolet light. Z Krebsforsch Klin Onkol Cancer Res Clin Oncol 1973; 79(4): 234–40.
27 Teutschlaender O. Bedarf der Teer zur Hautkrebserzeugung ultravioletter Strahlen? Klin Wochenschr 1937; 16(37): 1284–5.
28 Wang Y, Gao D, Atencio DP et al. Combined subcarcinogenic benzo[a]pyrene and UVA synergistically caused high tumor incidence and mutations in H-ras gene, but not p53, in SKH-1 hairless mouse skin. Int J Cancer 2005; 116(2): 193–9.
29 Stenehjem JS, Robsahm TE, Bråtveit M et al. Ultraviolet radiation and skin cancer risk in offshore workers. Occup Med (Lond) 2017; 67(7): 569–73.
30 Letzel S, Drexler H. Occupationally related tumors in tar refinery workers. J Am Acad Dermatol 1998; 39(5 Pt 1): 712–20.
31 Letzel S, Drexler H, Lehnert G. Teer-induzierte Präkanzerosen und Malignome der Haut bei Beschäftigten einer Teer-Raffinerie. Dermatosen 1992; 40(3): 94–101.
32 Voelter-Mahlknecht S, Scheriau R, Zwahr G et al. Skin tumors among employees of a tar refinery: the current data and their implications. Int Arch Occup Environ Health 2007; 80(6): 485–95.
33 Goerz G, Merk H, Hölzle E. Teerbehandlung der Psoriasis. Hautarzt 1985; 36(1): 50–3.
34 Stern RS, Zierler S, Parrish JA. Skin carcinoma in patients with psoriasis treated with topical tar and artificial ultraviolet radiation. Lancet 1980; 1(8171): 732–5.
35 Graem N. Epidermal changes following application of 7,12-dimethylbenz(a)anthracene and 12-O-tetradecanoylphorbol-13-acetate to human skin transplanted to nude mice studied with histological species markers. Cancer Res 1986; 46(1): 278–84.
36 Lerche CM, Sepehri M, Serup J et al. Black tattoos protect against UVR-induced skin cancer in mice. Photodermatol Photoimmunol Photomed 2015; 31(5): 261–8.
37 von Koschembahr A, Youssef A, Béal D et al. Metabolism and genotoxicity of polycyclic aromatic hydrocarbons in human skin explants: mixture effects and modulation by sunlight. Arch Toxicol 2020; 94(2): 495–507.
38 Soeur J, Belaïdi J-P, Chollet C et al. Photo-pollution stress in skin: Traces of pollutants (PAH and particulate matter) impair redox homeostasis in keratinocytes exposed to UVA1. J Dermatol Sci 2017; 86(2): 162–9.
39 Xia Q, Chiang H-M, Yin J-J et al. UVA photoirradiation of benzo[a]pyrene metabolites: induction of cytotoxicity, reactive oxygen species, and lipid peroxidation. Toxicol Ind Health 2015; 31(10): 898–910.
40 Yu H, Xia Q, Yan J et al. Photoirradiation of polycyclic aromatic hydrocarbons with UVA light–a pathway leading to the

generation of reactive oxygen species, lipid peroxidation, and dna damage. Int J Environ Res Public Health 2006; 3(4): 348–54.

41 Saladi R, Austin L, Gao D et al. The combination of benzo[a]pyrene and ultraviolet A causes an in vivo time-related accumulation of DNA damage in mouse skin. Photochem Photobiol 2003; 77(4): 413–9.

42 Fritsche E, Schäfer C, Calles C et al. Lightening up the UV response by identification of the arylhydrocarbon receptor as a cytoplasmatic target for ultraviolet B radiation. Proc Natl Acad Sci U S A 2007; 104(21): 8851–6.

43 Pink M, Verma N, Zerries A et al. Dose-dependent response to 3-nitrobenzanthrone exposure in human urothelial cancer cells. Chem Res Toxicol 2017; 30(10): 1855–64.

44 Schittenhelm D, Neuss-Radu M, Verma N et al. ROS and pentose phosphate pathway: mathematical modelling of the metabolic regulation in response to xenobiotic-induced oxidative stress and the proposed Impact of the gluconate shunt. Free Radic Res 2019; 53(9–10): 979–92.

45 Verma N, Pink M, Boland S et al. Benzo[a]pyrene-induced metabolic shift from glycolysis to pentose phosphate pathway in the human bladder cancer cell line RT4. Sci Rep 2017; 7(1): 9773.

JA, ICH HABE MEINE VITILIGO AKZEPTIERT. SCHLIESSLICH HABE ICH KEINE WAHL.

65 % aller Menschen mit Vitiligo wird gesagt, ihre Erkrankung sei nicht behandelbar.[1] Noch gravierender ist, dass nahezu die Hälfte aller Betroffenen eine Behandlung überhaupt nicht mehr in Betracht zieht.[1] Wie Sie wissen, tritt Vitiligo meist im Teenageralter auf – und ohne zugelassene Therapie fühlen sich viele Betroffene in einem Zustand der Ungewissheit gefangen. Deshalb forschen wir an neuen wissenschaftlichen Ansätzen. Denn wenn wir uns alle mehr mit der Erkrankung Vitiligo befassen, haben Ihre Patientinnen und Patienten eines Tages vielleicht wieder eine Wahl.

entdeckevitiligo.de

Incyte Dermatology

Incyte | SOLVE ON.

ENTDECKE VITILIGO →

Date of preparation: May 2022 DE/OTHR/M/22/0002

1. Bibeau K, et al. Diagnosis and Management of Vitiligo From the Perspectives of Patients and Healthcare Professionals: Findings From the Global VALIANT Study. Maui Derm for Dermatologists. Maui, HI. January 24th–28th 2022.