WORLD HEALTH ORGANIZATION
International Agency for Research on Cancer

Exposure to Artificial UV Radiation and Skin Cancer

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EXPOSURE TO ARTIFICIAL UV RADIATION AND SKIN CANCER

This report represents the views and expert opinions of an IARC Working Group that met in Lyon, France

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LIST OF ABBREVIATIONS

ACGIH	American Conference of Governmental Industrial Hygienists
BCC	Basal cell carcinoma
CI	95% confidence interval
CIE	Commission Internationale de l'Eclairage
DF	Degrees of freedom
GVHD	Graft versus host disease
GP	General practitioner (family doctor)
IARC	International Agency for Research on Cancer
ICNIRP	International Commission of Non-Ionising Radiation Protection
IPD	Immediate pigment darkening
ISO	International Organization for Standardization
MED	Minimal erythemal dose
NRPB	National Radiation Protection Board
NTP	National Toxicology Program
OR	Odds ratio
PUVA	Psoralen photochemotherapy
RR	Relative risk
SCC	Squamous cell carcinoma
SED	Standard erythemal dose
UNEP	United Nations Environment Programme
UV	Ultraviolet
WHO	World Health Organization

PREAMBLE

The concern that there may be an association between exposure to artificial UV radiation and skin cancer was reactivated in 2003-4 when the 10th Report on Carcinogens published by the National Toxicology Program in the USA classified UVA radiation as a "Known Carcinogen to Humans".

In October 2004, the French Ministry of Health contacted the Director of the International Agency for Research on Cancer (IARC), Dr Peter Boyle, raising a particular concern about the continuous increase in incidence of melanomas in France and in the world. Since the last IARC Monograph on ultraviolet (UV) radiation in 1992, a large number of epidemiological and experimental studies have been conducted on the risks associated with exposure to UV radiation. The Ministry therefore requested IARC to investigate the possibility of reevaluating the carcinogenic risk associated with this radiation, particularly concerning artificial UV sources and the use of indoor tanning facilities.

A Working Group and a Secretariat were gathered by Dr Peter Boyle to this end. The Secretariat met in January to prepare for the meeting of the Working Group in June 2005. The Working Group met on 27–29 June 2005 to compile the present document.

EXECUTIVE SUMMARY

We have assessed the available evidence relating to possible detrimental health effects of exposure to artificial ultraviolet radiation through use of indoor tanning facilities, in particular whether their use increases the risk for skin cancer. Epidemiologic studies to date give no consistent evidence that use of indoor tanning facilities in general is associated with the development of melanoma or skin cancer. However, there was a prominent and consistent increase in risk for melanoma in people who first used indoor tanning facilities in their twenties or teen years.

Limited data suggest that the risk of squamous cell carcinoma is similarly increased after first use as a teenager. Artificial tanning confers little if any protection against solar damage to the skin, nor does use of indoor tanning facilities grant protection against vitamin D deficiency. Data also suggest detrimental effects from use of indoor tanning facilities on the skin's immune response and possibly on the eyes (ocular melanoma).

Knowledge of levels of UV exposure during indoor tanning is very imprecise. Moreover, early studies published had low power to detect long-term associations with artificial UV exposure that become evident only following a prolonged lag period. Although the available findings are therefore not conclusive, the strength of the existing evidence suggests that policymakers should consider enacting measures, such as prohibiting minors and discouraging young adults from using indoor tanning facilities, to protect the general population from possible additional risk for melanoma and squamous cell carcinoma.

Physical characteristics and sources of exposure to artificial UV radiation

For most individuals, the main source of exposure to ultraviolet (UV) radiation is the sun. Nevertheless, some individuals are exposed to high doses of UV through artificial sources. Sunbeds and sunlamps used for tanning purposes are the main source of deliberate exposure to artificial UV radiation.

Physical characteristics of UV radiation

UV radiation belongs to the non-ionizing part of the electromagnetic spectrum and ranges between 100 nm and 400 nm; 100 nm has been chosen arbitrarily as the boundary between non-ionizing and ionizing radiation. UV radiation is conventionally categorized into 3 regions: UVA (>315–400 nm), UVB (>280–315 nm) and UVC (>100–280 nm) (Figure 1).

These categories have been confirmed by the Commission Internationale de l'Eclairage (CIE, 1987), although there is variation in usage. In the medical and biological fields, for example, 320 nm is used as the limit between UVA and UVB. More recently, it was proposed to distinguish between UVA-1 (>340–400 nm) and UVA-2 (320–340 nm).

Units and measurements of UV radiation

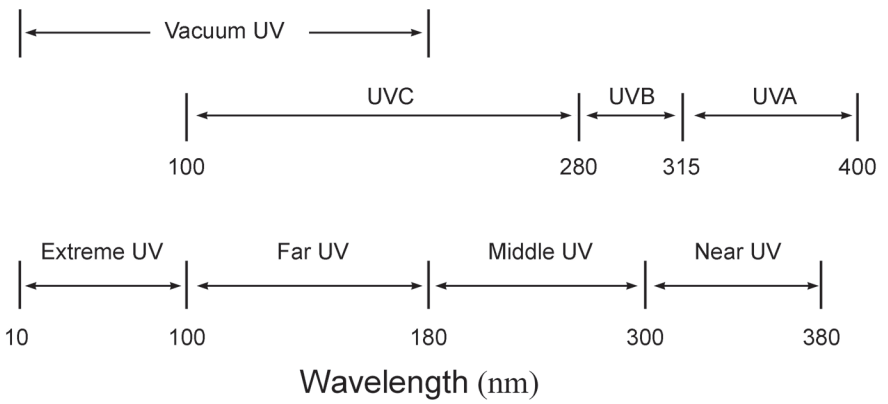
Measurement of ambient solar UV radiation

Measurement of ambient solar UV radiation has been performed worldwide for many years. However, UV radiation detectors for research or individual use have been developed only recently. There are two principal types of instruments: steady spectroradiometers, which screen the entirety of the UV spectrum (100–400 nm) within a few minutes, and broad-spectrum dosimeters, which can measure solar irradiance within a few seconds. Individual dosimeters, which can easily be placed at strategic places on individuals, are of the second type.

Broad-spectrum instruments often include a weighting factor representative of a given biological spectrum (e.g. skin erythema). In current practice, the margin of error for the measurement is relatively high, around 30%.

The biologically relevant UV radiation dose at a given wavelength corresponds to the measured UV radiation multiplied by a weighting factor specific to the biological endpoint considered (e.g. erythema, pigmentation, carcinogenesis, etc.) at that wavelength. For the overall dose (Eeff

Figure 1. Ultraviolet (UV) region of the electromagnetic spectrum



Adapted from IARC (1992)

Table 1. Specifications of relative erythemal effectiveness

Wavelength (λ; nm)	Relative erythemal effectiveness ($S\lambda$) (weighting factor)
$\lambda < 298$	1
$298 < \lambda < 328$	$10^{0.094(298-\lambda)}$
$328 < \lambda \leq 400$	$10^{0.015(139-\lambda)}$

From McKinlay & Diffey (1987); International Electrotechnical Commission (1989)

expressed in watts per square meter ($W.m^{-2}$)), the weighted components are added for all the wavelengths included in the interval considered.

The specifications of the relative erythemal effectiveness are defined by the parameters described in Table 1.

Standard erythemal dose (SED) and minimal erythemal dose (MED)

The standard erythemal dose (SED) is a measure of UV radiation equivalent to an efficient erythemal exposure of 100 joules per square meter ($J.m^{-2}$).

The clinically observed minimal erythemal dose (MED) is defined as the minimal amount of energy required to produce a qualifying erythemal response, usually after 24h. The erythemal responses that qualify can be either just-perceptible reddening or uniform redness with clearly demarcated borders, depending on the criterion adopted by the observer.

Since 1997, the Erythemal Efficacy Spectrum of human skin has become an International Organization for Standardization/International Commission on Illumination (ISO/CIE) standard that allows, by integration with the emission spectrum of any UV source, calculation of the erythemal output of this source.

UV index

The UV index is a tool designed for communication with the general public. It is the result of a common effort between the World Health Organization (WHO), the United Nations Environment Programme (UNEP), the World Meteorological Organization and the International Commission on Non-Ionising Radiation Protection (ICNIRP), and is standardized by ISO/CIE. The UV index expresses the erythemal power of the sun: UV index = 40 x E_{eff} $W.m^{-2}$ (Table 2).

Limit values

The American Conference of Governmental Industrial Hygienists (ACGIH) and ICNIRP have determined the maximal daily dose that a worker exposed to UV would be able to receive without acute or long-term effects on the eyes. This dose has been established at 30 $J.m^{-2}$ (eff), which corresponds to a little less than 1/3 of SED. The value takes into account an average DNA repair capacity in the cells.

There are currently no recommendations for safe doses for human skin.

Sources of natural and artificial UV radiation

Solar radiation

The sun is the main source of exposure to UV for most individuals. Sunlight consists of visible light (400–700 nm), infrared radiation (>700 nm) and UV radiation. The quality (spectrum) and quantity (intensity) of sunlight are modified during its passage through the atmosphere. The stratosphere stops almost all UV radiation <290 nm (UVC) as well as a large proportion of UVB (70–90%). Therefore, at ground level, UV radiation represents about 5% of solar energy, and the radiation spectrum is between 290 and 400 nm.

An individual's level of exposure to UV varies with latitude, altitude, time of year, time of day, clouding of the sky and other atmospheric components such as air pollution.

Artificial UV radiation

Artificial sources of UV radiation emit a spectrum of wavelengths specific to each source. Sources of artificial UV radiation include various lamps used in medicine, industry, business and research, and for domestic and cosmetic purposes.

Table 2. UV index and Standard Erythemal Dose[1]

UV index	Number of SED/hour	Power of the sun	Duration of exposure equivalent to 1 SED
1	1	Weak	2h20
2	2	Weak	1h10
3	2.5	Medium	45 mn
4	3.5	Medium	35 mn
5	4.15	Strong	30 mn
6	5	Strong	25 mn
7	6	Very strong	20 mn
8	7	Very strong	18 mn
9	8.5	Extreme	16 mn
10	9.5	Extreme	14 mn
11	10.5	Extreme	12 mn

[1] Exposure to 2 SED triggers a light but visible erythema in an unacclimatised sensitive individual (phototype I).

(a) UV sources used for tanning: The device used for tanning may be referred to as sunbed, sunlamp, artificial UV, artificial light or tanning bed, among other terms. Also, a number of terms are used to define a place where indoor tanning may occur: solarium, tanning salon, tanning parlour, tanning booth, indoor tanning salon, indoor tanning facility. In addition, indoor tanning may take place in private, non-commercial premises. For the purpose of this report, the term "indoor tanning facility" has been used throughout.

From the 1940s until the 1960s, exposure to UV radiation emitted by mercury lamps was popular in Northern Europe and North America. Typically, these were portable devices equipped with a single mercury lamp, sometimes accompanied by infrared lamps to heat the skin. The UV spectrum of mercury lamps consisted of about 20% UVC and 30–50% UVB radiation (Diffey *et al.,* 1990). Sometimes, ordinary glass covered the mercury lamps, limiting emission of UVB and UVC to a certain extent depending on the thickness of the glass. Exposure of individuals to these lamps was of short duration but could lead to the development of erythema, burns and blistering. These lamps were used primarily for children, to help synthesis of vitamin D, although adults may have used them to tan. These lamps were banned in most countries around 1980.

Fluorescent tubes emitting UV radiation and designed for general public use for tanning purposes were produced commercially in the 1960s. The first-generation tubes were of small size. UV units generally comprised three to six short fluorescent lamps, and tanning of the whole body was tedious, as it required exposing one body part after another. Before regulations were enforced, UVB could represent up to 5% of the UV output of these tanning devices.

In the 1980s and 1990s, amid growing concern about the carcinogenic potential of UVB, the UV output of low-pressure fluorescent lamps was shifted towards UVA, allowing so-called "UVA tanning". The term "UVA tanning" is misleading, as the output of a tanning appliance equipped with low-pressure fluorescent lamps always contains some UVB, which is critical for the induction of a deep, persistent tan. With the advent of low-pressure fluorescent tubes of 150–180 cm length, body-size tanning units became commercially available.

More recently, high-pressure lamps producing large quantities of long-wave UVA (>335–400 nm) per unit of time were marketed; these lamps can emit up to 10 times more UVA than is present in sunlight. Some tanning appliances combine high-pressure long-wave UVA lamps with low-pressure fluorescent lamps.

In the late 1990s the trend was to equip tanning appliances with fluorescent lamps emitting UV that mimicked tropical sun (e.g. the "Cleo Natural Lamps" of Philips Cy, Eindhoven,

the Netherlands). These lamps emit a larger proportion of UVB (around 4%). The rationale for solar-like tanning appliances is that with the correct UV energy dosage, tanning sessions might resemble habitual sun exposure with a similar balance between total UV, UVB and UVA (de Winter & Pavel, 2000).

Today, lamps originally designed and intended for industrial applications (drying, polymerization) and which emit UV (UVA, UVB and UVC), visible and infrared radiations in different proportions are available on the general market or may be purchased directly through the Internet where they are advertised for building home-made solaria. Even though they emit artificial UV radiation, these lamps (small convoluted fluorescent tubes fitted to a classic bulb socket) and tubes are not considered tanning appliances and escape technical regulations in those countries where tanning appliances are regulated (for instance, upper limit of 1.5% UVB in France and Sweden).

McGinley *et al.* (1998) measured the UV irradiance of different types of tanning appliances used in Scotland. UVA irradiances ranged from 54 to 244 $W.m^{-2}$ for tanning appliances with type-1 tubes and from 113 to 295 W.m-2 with type-2 tubes, while UVB irradiances were 0.2–1.2 $W.m^{-2}$ for type-1 and 1.1–2.8 $W.m^{-2}$ for type-2 tubes. A difference of a factor of three in irradiance was found to result from variation in the age of the tube.

(b) Medical and dental applications: Phototherapy has been used for medical conditions, including a very large number of skin diseases such as acne, eczema, cutaneous T-cell lymphoma, polymorphic light eruption and, most particularly, psoriasis. The devices used to deliver phototherapy have changed considerably over the years from those emitting predominantly UVB to those emitting predominantly UVA, or narrow-band UVB in recent times.

Psoralen photochemotherapy: This form of treatment (PUVA) involves the combination of the photoactive drugs psoralens (P) with UVA radiation to produce a beneficial effect. PUVA therapy has been successful in treating many skin diseases.

Broad-band UVB phototherapy: The skin diseases most frequently treated with broad-band UVB phototherapy are psoriasis and eczema.

Narrow-band UVB phototherapy: This therapy (TL2 Philipps lamps emitting at 311 nm) has proved to be the most beneficial for psoriasis and looks promising in the treatment of some other skin conditions including atopic eczema and vitiligo, pruritus, lichen planus, polymorphous light eruption and early cutaneous T-cell lymphoma.

Broad- and narrow-band UVB in psoriasis patients: Whilst treatment of psoriasis with PUVA is more widely used and better studied in terms of risk for skin cancer, broadband UVB therapy (280–320 nm) has been used for longer, and in most centres narrow-band UVB therapy (311 nm) is now increasingly used. Indeed narrow-band UVB is viewed by many as the treatment of choice for psoriasis (Honigsmann, 2001). Narrow-band UVB is thought to be more effective than broadband UVB and almost as effective as PUVA in the treatment of psoriasis, and it may become a safer alternative to PUVA for long-term use (Honigsmann, 2001).

Neonatal phototherapy: Phototherapy is sometimes used in the treatment of neonatal jaundice or hyperbilirubinaemia. Although intended to emit only visible light, the lamps used for neonatal phototherapy may also have a UV component (Diffey & Langley, 1986).

Fluorescent lamps: Irradiation of the oral cavity with a fluorescent lamp has been used in the diagnosis of various dental disorders such as early dental caries, the incorporation of tetracycline into bone and teeth, dental plaque and calculus (Hefferren *et al.*, 1971).

Polymerization of dental resins: Pits and fissures in teeth have been treated using an adhesive resin polymerized with UVA.

Other medical conditions: In recent years bright light therapy has emerged as treatment for a number of chronic disorders such as seasonal affective disorder (SAD) (winter depression)

(Pjrek *et al.,* 2004), sleep disorders and the behavioural/activity disorders in dementia (Skjerve *et al*., 2004). The light boxes used for such treatment can emit light levels up to approximately 10,000 lux (Pjrek *et al*., 2004; Skjerve *et al*., 2004), an intensity 5 to 10 times lower than that of bright sunlight. The emission spectrum is variable, and some lamps may contain a small but non-negligible proportion of UVA and UVB (Remé *et al.,* 1996), which however is largely inferior to that of indoor tanning appliances. It is noteworthy that the UV component of the light emitted is not involved in the therapy.

(c) Occupational exposures: Artificial sources of UV are used in many different ways in the working environment: some examples include welding, industrial photoprocesses (e.g. polymerization), sterilization and disinfection (sewage effluents, drinking water, swimming pools, operating theatres and research laboratories), phototherapy, UV photography, UV lasers, quality insurance in the food industry, and discotheques. For some occupations, the UV source is well contained within an enclosure and, under normal circumstances, presents no risk of exposure. In other applications, workers are exposed to some radiations, usually by reflection or scattering from adjacent surfaces. Of relevance, indoor tanning facilities may comprise 20 or more UVA tanning appliances, thus potentially exposing operators to high levels (>20W/m^2) of UVA radiation (Diffey, 1990).

Comparison of UV spectrum from sunlight and from tanning appliances

During a sunny day on the Mediterranean coast, the solar UV spectrum at noon contains 4–5% of UVB and 95–96% of UVA.

When UV output is calculated in terms of biological activity, as estimated by the erythema-effective irradiance, the emission of many tanning appliances is equivalent to or exceeds the emission of the midday sun in the Mediterranean (Wester *et al.,* 1999; Gerber *et al.,* 2002). The UV intensity of powerful tanning units may be 10 to 15 times higher than that of the midday sun (Gerber *et al.,* 2002), leading to UVA doses per unit of time received by the skin during a typical tanning session well above those experienced during daily life or even sunbathing. As a result, the annual UVA doses received by frequent indoor tanners may be 1.2 to 4.7 times those received from the sun, in addition to those received from the sun (Miller *et al.,* 1998). This widespread repeated exposure to high doses of UVA constitutes a new phenomenon for human beings.

In the 1990s, regulations in some countries (e.g. Sweden, France) limited to 1.5% the maximum proportion of UVB in the UV output of tanning appliances. However, in practice, the UV output and spectral characteristics of tanning appliances vary considerably. Surveys in the United Kingdom on tanning appliances operated in public or commercial facilities revealed substantial differences in UV output, mainly for UVB, for which up to 60-fold differences in output have been observed (Wright *et al.,* 1996; McGinley *et al.,* 1998). The proportion of UVB in total UV output varied from 0.5 to 4%, and thus emission spectra similar to that of the sun in the UVB range were sometimes attained (Gerber *et al.,* 2002). These differences are due to tanning appliance design (e.g. type of fluorescent tubes used as sources, materials composing filters, distance from canopy to the skin), tanning appliance power and tube ageing. Tanning appliances in commercial facilities may have a greater output in the UVB range than those used in private premises (Wright *et al.,* 1997). With tube ageing, the output of fluorescent lamps decreases, and the proportion of UVB decreases more rapidly than that of UVA.

European and international positions regarding artificial sources of UV radiation

Full details are given in the Appendix and are summarized below.

Standard for appliances designed specifically for tanning purposes

Appliances designed specifically for tanning purposes are defined according to an international standard prepared by the International Electrotechnical Commission (IEC 60 335-2-27).

This standard was first established in 1985 and further modified in 1990, in 1995 and in 2002. A first amendment was added in 2004 and a second amendment is currently being voted on internationally. This standard regulates all appliances sold worldwide, except for the USA who are regulated by the Food and Drug Administration (FDA).

Appliances emitting UV radiation must belong to one of four types of such appliances, determined by their wavelength spectrum and irradiance efficiency (see Appendix for detail).

National and international scientific policies

Several national and international authorities (ICNIRP, WHO, EUROSKIN, the National Radiological Protection Board [United Kingdom] and the National Toxicology Program [USA]) have adopted explicit positions regarding the use of UV-emitting appliances for tanning purposes. These positions are almost invariably accompanied by recommendations targeting the safety of the customers.

Regulations

Regulations and recommendations by health authorities exist in a dozen countries, predominantly in Western and Northern Europe and the USA. Details of the regulations for each country are given in the Appendix.

Biological effects of exposure to UV radiation relevant to carcinogenesis

A large body of literature documents the effects of UV radiation on different living organisms, including humans, animals and bacteria. Experimental as well as epidemiological data strongly indicate that the spectrum of UV radiation reaching the Earth's surface is involved in the development of melanoma (IARC, 1992).

The biological effects of exposure to UV radiation were described in detail in an IARC Monograph on UV radiation (IARC, 1992), and the molecular effects in recent review articles (Griffiths *et al.,* 1998; Pfeifer *et al.*, 2005). In this section, we summarize the aspects most relevant to the understanding of the biological issues associated with exposure to artificial sources of UV radiation.

Biological lesions induced by UVA and UVB radiation

DNA damage

(a) Experimental systems: UVB is a complete carcinogen that is absorbed by DNA and can directly damage DNA. DNA damage induced by UVB irradiation typically includes the formation of cyclobutane pyrimidine dimers (CPD) and 6-4 photoproducts (6-4P). If repair mechanisms fail to restore genomic integrity, mutations are likely to occur and persist through subsequent cell divisions. These mutations are C $\rightarrow$ T and CC $\rightarrow$ TT transversions, commonly referred to as "UVB fingerprint" or "UVB signature" mutations. UVB can also induce the formation of singlet oxygen species (O_2^-), an oxidative compound that is highly reactive and can cause DNA damage indirectly (Griffiths *et al.,* 1998).

UVA is not readily absorbed by DNA and thus has no direct impact on DNA. Instead, UVA induces DNA damage indirectly through the absorption of UVA photons by other cellular structures (chromophores), with formation of reactive oxygen species (such as singlet oxygen and hydrogen peroxide [H_2O_2]) that can transfer the UVA energy to DNA via mutagenic oxidative intermediates such as 8-hydroxydeoxyguanosine (8-OHdG). DNA damage by UVA radiation typically consists of T$\rightarrow$G transversions, called "UVA fingerprint" or "UVA signature" lesions (Dobretsky *et al.,* 1995).

One study in hamster fibroblasts showed that UVB produces numerous immediate mutations, whereas UVA produces fewer immediate mutations and more delayed mutations than UVB (Dahle & Kvam, 2003).

(b) Effects on humans: The mutagenic properties of UVA in humans have been confirmed in several studies (Robert *et al.*, 1996; see Pfeifer *et al.,* 2005; Halliday, 2005 for reviews). The possibility that indirect DNA damage induced by UVA could play a major role in melanoma occurrence is underlined by reports of multiple cutaneous melanomas developing in patients genetically highly susceptible to oxidative agents (Pavel *et al.*, 2003).

Experiments in human volunteers conducted during the last decade have shown that commercial tanning lamps produce the types of DNA damage associated with photocarcinogenesis in human cells. Volunteers whose skin was exposed to UVA lamps used in tanning appliances show DNA damage, p53 mutations induced by oxidative damage, and alterations of the p53 protein similar to those observed after sun exposure or after UV exposure of experimental animals (Woollons *et al.,* 1997; Whitmore *et al.,* 2001; Persson *et al.,* 2002).

Studies in humans show that a pre-vacation artificially-induced tan offers little or no protection against sun-induced DNA damage (Hemminki *et al.,* 1999; Bykov *et al.,* 2001; Ruegemer *et al.,* 2002).

Cell damage

UVA and UVB radiation can cause cell damage through different mechanisms: both UVA and UVB lead to differential expression of p53 and

bcl-2 proteins, which may play an important role in regulating UV-induced apoptosis (Wang *et al.,* 1998). DNA repair and apoptosis protect the cell's integrity against UV-induced damage. One study conducted in cells from medaka fish suggested that different apoptotic pathways exist depending on the wavelength, i.e. for long- (UVA) and for short- (UVB or UVC) wavelength radiations (Nishigaki *et al.,* 1999). Irradiation of melanocytes with UVA or UVB leads to alterations of different intracellular proteins, suggesting that UVA and UVB may induce initiation of melanoma via separate intracellular pathways (Zhang & Rosdahl, 2003).

UVA, UVB and human skin

In humans UVA penetrates deeper into the skin than does UVB. Because UVA represents the majority of the UV spectrum of tanning appliances and of solar radiation reaching the Earth's surface, far more UVA than UVB reaches the basal layers of the epidermis, where skin keratinocytic stem cells and melanocytes are located. DNA analysis of human squamous cell carcinoma (SCC) and solar keratosis showed that UVA fingerprint mutations are mostly detected in the basal germinative layer of these lesions, whereas UVB fingerprint mutations are found predominantly more superficially in these lesions (Agar *et al.,* 2004).

Differential effects of UVA and UVB on skin cancers

Experimental systems

Several studies showed that UVA could induce squamous cell cancers in nude mice, but the ability of UVA alone (without exogenous photosensitizers such as those used in PUVA therapy — see Page 41) to induce squamous cell skin cancers was about 5000 to 10000 times lower than that of UVB alone (IARC, 1992; de Laat *et al.,* 1997; Griffiths *et al.,* 1998). Both in-vitro experiments and epidemiological studies have demonstrated that long-lasting, chronic exposure to UVB is the main cause of SCC of the skin (see IARC, 1992; Brash *et al.,* 1996 for reviews). Accordingly, before 1990, only UVB, and not UVA, was considered to be carcinogenic.

In the 1990s, studies in newborn rodents and on human foreskin grafted on immunosuppressed nude mice have provided compelling evidence that high UVB doses were required in the genesis of melanoma or of melanocytic tumours considered to be precursor lesions of melanoma (Mintz & Silvers, 1993; Atillasoy *et al.,* 1998; Robinson *et al.,* 1998; Sauter *et al.,* 1998; Robinson *et al.,* 2000a; Noonan *et al.,* 2001; van Schanke *et al.,* 2005). At the same time, several in-vivo studies showed that UVA can induce melanoma in backcross hybrids of freshwater fishes of the genus *Xiphophorus* (platyfish and swordtail; Setlow *et al.,* 1993) and melanocytic tumours in the South American opossum *Monodelphis domestica* (Ley, 1997, 2001). However, UVA was less efficient than UVB for the induction of melanocytic tumours in *Monodelphis domestica* (Ley 2001), and experiments with UVA on newborn rodents and on human foreskin could not reproduce the results obtained with UVB (Robinson *et al.,* 2000b; Berking *et al.,* 2002; de Fabo *et al.,* 2004; van Schanke *et al.,* 2005).

Other studies showed that radiation emitted by lamps used in tanning appliances (mainly UVA) could significantly increase the carcinogenic effect of broad-spectrum UV radiation (Bech-Thomsen *et al.,* 1991, 1992), indicating the possibility of a complex interplay between UVA and UVB radiation in human skin.

Relevance of experimental data to human skin cancers

To date, evidence obtained from experimental studies on the involvement of high UVB doses in the causation of SCC is consistent with observations in humans. In contrast, experimental studies provide conflicting results on an implication of UVB and UVA in the induction of melanoma in humans. The same uncertainties hold true for basal cell carcinoma (BCC), a type of tumour that shares many of the epidemiological characteristics of melanoma.

The relevance of animal models for elucidating the biological mechanisms involved in the development of melanoma and BCC remains

questionable, as even engineered mice with multiple deficiencies in key genes involved in cell cycle regulation and growth factor synthesis do not represent a model equivalent to the human skin. In addition, experiments on animals cannot reproduce the complex relationship existing in individuals between highly variable natural susceptibilities to UV radiation, different sun exposure behaviours, and exposure to various sources of UV radiation. In the case of indoor tanning, such relationships may be critical, as users are more inclined than the average population to engage in outdoor tanning activities (Autier *et al.,* 1991), and indoor tanning sessions often precede or follow active sun exposure or outdoor tanning.

Changes in immune response

Several reports (IARC, 1992, 2001; Ullrich, 2005) have extensively reviewed the studies on the effects of UV on the immune system and of the underlying mechanisms. This section only refers to studies relevant to UVA and use of indoor tanning facilities.

Experimental systems

Both UVA and UVB radiation can affect the immune response that may be involved in the promotion of melanoma (Kripke, 1974; Singh *et al.,* 1995), but the two types of radiation seem to act differently. UVB can induce immune suppression at both local and systemic levels whereas UVA does not induce systemic immune suppression. However, studies have shown that a number of local responses induced by UVB radiation on the skin could be suppressed by a UVB filter, but the melanoma growth stimulation effect could not be suppressed (Donawho *et al.,* 1994; Wolf *et al.,* 1994). This result suggests that UVA may influence local immune responses different from those influenced by UVB.

Studies in humans

Observations in human volunteers have demonstrated that UV exposure suppresses the induction of immunity (Cooper *et al.,* 1992; Tie *et al.,* 1995; Kelly *et al.,* 1998). Few studies have specifically investigated the effects of exposure to tanning appliances on the systemic and local immune systems. UV lamps similar to those used in tanning appliances are used without concomitant use of photosensitizer for treating skin conditions such as dermatitis and sun allergies, illustrating the effect of that radiation spectrum on the skin immune system.

Studies in volunteers have shown that exposure to tanning appliances induces reductions in blood lymphocyte counts, changes in proportion of lymphocyte subpopulations, immune response to known carcinogens applied to the skin, and changes in the skin immune system (Hersey *et al.,* 1983, 1988; Rivers *et al.,* 1989; Clingen *et al.,* 2001). These studies also indicated that UVA and UVB would affect the immune system via interacting and overlapping mechanisms, depending on the amount of UVA and UVB emitted (Clingen *et al.,* 2001), which would then lead to the suppression of known immune reactions (Nghiem *et al.,* 2001, 2002). Hence, these studies indicate that UVA can suppress established immune reactions at the skin level, but it remains to be established how these effects relate to the induction of neoplastic processes.

Effects of natural and artificial UV radiation on human skin

Variety of skin types

There is a considerable range of susceptibility of the human skin to the carcinogenic effects of UV radiation, and in humans, there is an estimated 1000-fold variability in DNA repair capacity after UV exposure (Hemminki *et al.,* 2001). Susceptibility to sun-induced skin damage is closely related to pigmentary traits, and subjects having the following characteristics are at increased risk for developing a skin cancer (melanoma, SCC and BCC):

- Red hair, followed by blond hair, followed by light brown hair.
- Skin phototype (Fitzpatrick, 1988): subjects who always burn and never tan when going

unprotected in the sun (skin phototype I) have a much higher risk for skin cancer than subjects who never burn and always develop a deep tan (skin phototype IV). Intermediate risk categories are subjects who always burn then develop a light tan (skin phototype II), and subjects who sometimes burn and always develop a tan (skin phototype III). Subjects of skin phototypes V and VI belong to populations with natural brown or black skin, and are resistant to sunlight.

- Freckles (ephelides) on the face, arms or shoulders. The skin cancer risk increases with increasing sensitivity to freckling.

- Skin colour: pale colour, followed by increasing depth of pigmentation.

- Eye colour: blue, followed by grey/green eyes, then by brown eyes.

Subjects with red hair, many freckles and who never tan are at particularly high risk for skin cancer.

Sunburn

Sunburn is the occurrence of painful erythemal reaction after exposure to UV radiation. Sunburn during childhood or during adulthood is a risk factor for melanoma, and the risk increases with increasing number of sunburns (IARC, 1992). Skin erythema or sunburns are reported by 18–55% of users of indoor tanning facilities in Europe and North America (reviewed in Autier, 2004). Although UVB is more potent than UVA for triggering sunburn, high fluxes of UVA are capable of inducing skin erythemal reactions after 10 to 20 minutes in subjects susceptible to sunlight and having moderate tanning ability (Fitzpatrick skin phototype II).

Tan acquisition

The production of melanin (tanning) accounts for part of the protection against UV radiation, but there is mounting scientific evidence that facultative tan is triggered by UV-induced DNA damage in the skin (Pedeux *et al.,* 1998; Gilchrest & Eller 1999 for a review). Facultative tanning is now considered a better indicator of inducible DNA repair capacity than of efficient photoprotective skin reaction. Inducible DNA repair capacity rather than pigmentation itself could result in the lower incidence of skin cancer observed in darker-skinned individuals (Young *et al.,* 1998; Agar & Young, 2005; Bohm *et al.,* 2005).

In subjects who tan easily, exposure to tanning appliances will first lead to the oxidation of melanin already present in superficial keratinocytic layers of the skin (i.e. immediate pigment darkening [IPD]). IPD is essentially triggered by UVA (Young, 2004). It develops rapidly after exposure during an indoor tanning session, and fades away after a few hours. A more permanent tan is acquired with accumulation of exposure, depending on tanning ability and on the amount of UVB present in the UV spectrum of the lamps. The permanent tan conferred by "UVA-tanning" has a uniform and less deep brown appearance than the tan acquired in the sun.

IPD has no photoprotective effect against UV-induced erythema (Black *et al.,* 1985). A UVA-induced permanent tan provides practically no photoprotection either (Gange *et al.,* 1985; Rivers *et al.,* 1989), and UVA-induced moderate skin thickening would afford even less photoprotection than tanning (Seehan *et al.,* 1998).

Prevalence of exposure to artificial UV radiation for tanning purposes

The indoor tanning industry developed in Europe and the USA in the early 1980s, a time when UVA radiation was thought to be harmless, with the introduction of tanning applances emitting UVA at levels similar to or even exceeding those from natural sunlight. In the USA, indoor tanning is now a more than $5 billion industry that employs 160,000 persons (Indoor Tanning Association, 2004), and in the United Kingdom the turnover in the indoor tanning industry exceeds an estimated £100 million per annum (source: www.raywatch.co.uk; accessed on 15/06/2005).

Prevalence of exposure by region/country

Indoor tanning is a widespread practice in most developed countries, particularly in Northern Europe and the USA, and is gaining popularity even in sunny countries like Australia.

Few surveys have estimated specifically the prevalence of indoor tanning among adult populations. In 1996, a telephone survey was carried out among white adults (18 to 60 years old) from the two most densely populated regions (Montreal and Quebec) of the Province of Quebec, Canada (Rhainds *et al.,* 1999). Of the 1003 respondents, 20% reported having used a tanning appliance in a commercial tanning facility at least once during the last 5 years before the survey. The prevalence of use during the last 12 months before the study was 11%.

Recently, a brief report describing prevalence of indoor tanning in Minnesota, USA, derived from a telephone interview (45% response rate) concerning quality of life, employment and health of 802 randomly selected adults, showed that in 2002, 38% of adults had ever used indoor tanning facilities (Lazovich *et al*., 2005).

The prevalence of use of indoor tanning facilities can be estimated from the proportion of exposed controls in population-based case–control studies on risk factors for melanoma and basal and squamous cell skin cancers (Table 3).

The prevalence varies greatly with country, gender and age. Prevalence of ever having used indoor tanning facilities ranges from 5% in Northern Italy to 87% in Swedish women, and is currently very high in Northern European countries, particularly in Sweden and the Netherlands. Prevalence of exposure to tanning appliances may still be low in some European countries or populations. In a survey conducted among 33,021 adults older than 30 years attending health check-up centres in France, only 2% of subjects reported use of indoor tanning facilities (Stoebner-Delbarre *et al.*, 2001).

Time trends

The prevalence of indoor tanning is currently increasing in many countries, and current available estimates may therefore be rapidly outdated. In studies conducted approximately 20 years ago, the practice of indoor tanning was generally low: 7% in Germany, 18% in Denmark. Prevalence of exposure to tanning appliances by the controls included in case–control studies is higher in the most recent studies than in studies conducted before 1990 (Table 3).

A survey in Minnesota (Lazovich *et al*., 2005) indicated that prevalence of use has increased over the last decades. Few men and women had used a tanning appliance before 1980. Women were almost twice as likely as men to report tanning indoors during the 1980s (19% versus 10%), but in the following decade, the proportion of men using indoor tanning facilities approached that of women (15% versus 17% in the 1990s).

The fact that the prevalence of indoor tanning has increased during the 1990s can be demonstrated by comparing prevalence of use as reported in studies conducted by the same investigators in the same countries at intervals of several years.

A case–control study conducted in 1991 in five centres in Belgium, France and Germany

Table 3. Prevalence of use of indoor tanning facilities by population controls from epidemiological studies

Reference	Location	Inclusive years of recruitment		Disease[1]	Type of Study	No. of controls	Source of controls	Age range (years)	Prevalence of ever use	
									Number	%
Holman *et al.* (1986)	Western Australia	1980	1981	M	Case-control	511	Population, electoral roll, matched on age, sex	NR	NR	NR
Osterlind *et al.* (1988)	East Denmark	Oct. 1982	Mar. 1985	M	Case-control	926	Population, National Population Register	20–79	168	18
Zanetti *et al.* (1988)	Torino, Italy	May 1984	Oct. 1986	M	Case-control	416	Population, from the National Health Service	NR	21	5
Walter *et al.* (1990 and 1999)	Southern Ontario, Canada	Oct. 1984	Sep. 1986	M	Case-control	608	Population, Property tax assessment rolls	20–69	109	18
Autier *et al.* (1994)	Germany, France, Belgium	Jan. 1991	onwards	M	Case-control	447	Population, door to door	≥ 20	120	27
Westerdahl *et al.* (1994)	Sweden	July 1988	June 1990	M	Case-control	640	Population, National Population Registry	15–75	159	25
Holly *et al.* (1995)	San Francisco, USA	Jan. 1981	Dec. 1986	M	Case-control	452	Population, random digit telephone dialling	25–59	NR	NR
Bajdik *et al.* (1996)	Alberta, Canada	1983	1984	BCC / SCC	Case-control	406	Population, health insurance plan subscriber list	25–79	33	8.1
Chen *et al.* (1998)	Connecticut, USA	Jan. 1987	May 1989	M	Case-control	512	Population, telephone random digit dialling	NR	95	19
Westerdahl *et al.* (2000)	South Health Care region, Sweden	Jan. 1995	June 1997	M	Case-control	913	Population, National Population Registry	NR	372	41
Karagas *et al.* (2002)	New Hampshire, USA	July 1993	June 1995	BCC / SCC	Case-control	539	Population, Dept. of Transportation, medicare medicaid	25–74	75	14
Veierød *et al.* (2003)	Norway and Sweden	1991	1992	M	Cohort	79616	Population, prospective cohort	10–39	14 377[2]	18
Bataille *et al.* (2004)	North East Thames, UK	Aug. 1989	July 1993	M	Case-control	416	Hospital and general practice, excluding skin disease	16–75	110	26
Bataille *et al.* (2005)	Belgium, France, Netherlands, Sweden & UK	Dec. 1998	July 2001	M	Case-control	622	Sweden, population-based; France & Belgium, door to door; UK & Netherlands, GP	18–50	354	57

NR, not reported; GP, general practitioner

[1] BCC, basal cell carcinoma; M, melanoma; SCC, squamous cell carcinoma

[2] ≥ 1 time/month

(Autier *et al.*, 1994) showed that 19% of controls had ever exposed themselves to a sunlamp or a sunbed, this proportion being higher in Germany (25%) than in Belgium (20%) or in France (6%). Of the recorded exposures, 84% had started after 1979. In a more recent case–control study conducted by the same investigators between 1998 and 2000 in Belgium, France, Sweden, the Netherlands and the United Kingdom among persons younger than 50 years (mean age of controls, 37 years), 57% of controls had ever exposed themselves to artificial UV tanning, with the highest prevalence of use being found in Sweden (87%) (Bataille *et al.,* 2005).

According to two studies conducted within the same population in the south of Sweden in 1988–1990 and in 1995–1997, the prevalence of exposure doubled in 7 years. In 1988–1990, 46% of individuals younger than 30 years had ever exposed themselves to sun lamps or solaria (56% of women and 12% of men, these figures being higher in the group aged 15–24 years) while this proportion was only 24% among individuals older than 30 years (31% of women and 16% of men)(Westerdahl *et al.,* 1994). After 1995, the prevalence of solarium use in the population aged 16–80 years was 41%, but 70% of women and 50% of men aged 18–50 years reported having ever used a solarium (Westerdahl *et al.,* 2000).

Personal characteristics of adult users

Sex

Use of indoor tanning facilities is more prevalent among women, particularly among younger age groups and in Northern countries.

A survey of tanning appliances in commercial use in Scotland was conducted in 1997 to measure the spectal irradiance of the different models and compare this irradiance with UV doses received during sunbathing (McGinley *et al.,* 1998). As part of the study, a questionnaire was distributed to sunbed users, seeking information about their age, sex, skin type, frequency of use, attitudes and reasons for use. A total of 205 questionnaires were collected. The majority of users were women (170 versus 35 men).

A significantly higher proportion of women and young people (18–34 years old) was found among tanning bed users in the Montreal–Quebec survey (Rhainds *et al.,* 1999). In the Minnesota survey (Lazovich *et al.,* 2005), indoor tanning was also more prevalent among women than among men: 45% versus 30%. Among users, the median number of times used was 10 for men and 20 for women (range, 1–600), and 21% of women reported frequent use (defined as more than 30 times).

In Europe, a recent case–control study found use of indoor tanning facilities to be more prevalent among women (61%) than among men (43%) (Bataille *et al.,* 2005). Another recent survey explored exposure to tanning appliances and sun exposure behaviour in a cohort of adult volunteers. In 2001, a self-administered questionnaire was specifically developed and addressed to 12 741 adult volunteers in France enrolled in the SU.VI.MAX cohort (a cohort recruited in 1994 and followed for 8 years, which included men aged 45–60 years and women aged 35–60 years). Over 60% of the questionnaires were returned, of which 97% were useable. Among the 7 359 individuals who answered the questionnaire, 1 179 (16%) – 953 women (22%) and 226 men (8%) – reported having ever experienced indoor tanning. Men and women reported similar prevalences for regular use (6% and 7%, respectively) and for a duration of at least five years (10% for men and women). Among women, 44% of users belonged to the youngest age group at recruitment (35–44 years), versus 33% in non-users (in men, data were not available for this age group); 48% of female users lived in the North or in Ile-de-France, versus 39% of non-users (45% and 36% for men, respectively) (Ezzedine *et al.,* 2005) (Table 4).

Bataille *et al.* (2005) recently observed that indoor tanning is becoming more frequent in men and in younger age groups, with important variations by country: exposure of men is highest in Sweden (78%) and Netherlands (60%), while 39% of men in the United Kingdom and 13% in France reported ever having used indoor tanning facilities.

Table 4. Lifetime use of indoor tanning facilities and sun exposure behaviour among 7 359 healthy adults (SU.VI.MAX cohort)

Use of indoor tanning facilities	Women		Men	
	Users N = 953 (22%)	Non-users	Users N = 226 (8%)	Non-users
Regular use	7%	-	6%	-
Use ≥ 5 years	10%	-	10%	-
Residence North of France or Ile-de-France	48%	39%	45%	36%
Sunbathing between 11 a.m. and 4 p.m.	56%	37%	53%	38%
Regular sunscreen use during sunbathing	39%	24%	17%	7%
Progressive sun exposure	54%	43%	53%	38%
Nudism	13%	6%	19%	8%
Sunburns in adulthood	93%	88%	93%	89%
Important or extreme tan seeking behaviour	37%	20%	26%	11%

From Ezzedine *et al.* (2005)

Age

Younger age (<35 years) is significantly associated with higher likelihood of using indoor tanning facilities among both men and women.

In an early case–control study conducted in several countries in Europe (Autier *et al.,* 1994), indoor tanning was more prevalent in younger age groups (31% among controls < 40 years). In a more recent case–control study in Europe (Bataille *et al.,* 2005), exposure before the age of 15 years was reported in 3% of all controls, but reached 20% in Sweden. The mean age at first exposure was 20 years in Sweden, 23 years in the United Kingdom and 27 years in France.

In the survey conducted in Scotland (McGinley *et al.,* 1998), 73% of users were under 35 years old, with 32% of users being under 25 years old.

In the Minnesota survey (Lazovich *et al.,* 2005), 13% of men and 22% of women reported first tanning indoors as adolescents.

Skin type

Few studies have analysed specifically the use of indoor tanning facilities as a function of skin type. Since most studies have been conducted primarily in relation to skin cancer risk factors, use by skin type cannot be derived from the reported results.

In the survey conducted in Scotland (McGinley *et al.,* 1998), 38% of users described their skin phototype as type I or II, and 38% also indicated that they had experienced an adverse reaction when using indoor tanning facilities; 31% of users had more than 10 courses of over 5 sessions in a year, and for 16% this amounted to over 100 sessions per year.

In several case–control studies, use of indoor tanning facilities was more frequent among controls with a poor ability to tan: for example, 27% and 31% among controls with blond or red hair, respectively, in a European study (Autier *et al.,* 1994).

In the SU.VI.MAX cohort, individuals with a pale complexion were more likely to use indoor tanning facilities (Ezzedine *et al.,* 2005). This was not the case among controls from a recent case–control study conducted in Europe, where approximately one third of controls using indoor tanning facilities were of phototype I or II (Bataille *et al.,* 2005) (Table 5). However, it must be stressed that in this study, phototype was declared by participants and it is likely that few of them perceived themselves as sun-sensitive, as exemplified by the very low proportion of persons with self-reported phototype I in the Swedish population.

Other factors

Higher education levels or income are significantly associated with a higher likelihood of using indoor tanning facilities among men.

Table 5. Prevalence of indoor tanning according to skin type among controls in a European case–control study (Bataille *et al.,* 2005)

Country	Phototype (%)			
	I	II	III	IV
Belgium	13.3	23.3	43.3	20.0
France	6.4	38.7	25.8	29.0
Sweden	1.2	24.7	64.2	9.8
The Netherlands	6.0	17.9	53.0	23.1
United Kingdom	12.7	32.1	39.0	6.9

Data courtesy of V. Bataille.

The most common reasons given for use of indoor tanning facilities is to develop a "base tan" before a holiday and to feel more relaxed (McGinley *et al.,* 1998).

In the SU.VI.MAX survey, the most frequently reported motivations for using artificial tanning were aesthetic (35%) and skin preparation before sun exposure (34%) (Ezzedine *et al.,* 2005). In this cohort, there was a clear link between use of indoor tanning facilities and sun-seeking behaviour (Table 4).

Personal characteristics of adolescent and children users

Since 1989, a total of 16 studies (18 reports) have examined indoor tanning among children and adolescents aged 8–19 years. These studies are summarised in Table 6 (see Lazovich & Forster, 2005 for review). Studies were conducted in Europe (Norway, Sweden and the United Kingdom), in various locations throughout the USA (including two nationally representative samples) and in Australia. Adolescents were identified through paediatric clinics, schools, as offspring of adult cohort study participants, or through random selection of defined populations. Sample size ranged from 96 to over 15,000. Use of indoor tanning facilities was defined either as ever use, or use in the past 6 or 12 months. Given the differences in the study populations and in the definition of indoor tanning between studies, it is not surprising that prevalence estimates vary greatly. However, all these studies show frequent use by adolescents and children, sometimes at a very young age. According to the most recent studies, 30% of adolescents in Sweden and 24% of adolescents in the USA aged 13–19 years reported ever use of indoor tanning facilities, and 8% and 12% respectively were frequent users (10 times per year or more). In a recent survey in the United Kingdom, while 7% of children aged 8–11 years reported exposure to a sunbed in the last 6 months, as many as 48% expressed a desire to use a sunbed (Hamlet & Kennedy, 2004).

The earliest studies in Sweden and in the USA tended to find indoor tanning to be more prevalent among adolescents with fair skin types who are more prone to sunburn (Mermelstein & Riesenberg, 1992; Boldeman *et al.,* 1996; Robinson *et al.,* 1997). More recent studies in the USA found either the opposite (Cokkinides *et al.,* 2002; Geller *et al.,* 2002; Demko *et al.,* 2003) or no association (Lazovich *et al.,* 2004).

Studies of compliance to regulations and recommendations

Few studies have assessed the compliance of indoor tanning facility operators or consumers with recommendations and regulations. In this section, studies are first summarised and then data are presented according to each regulation.

Compliance of operators

(a) Study descriptions – overall compliance rates:
In 1991, Oliphant *et al.* (1994) surveyed over 1000 high school students aged 13 to 19 years in suburban Minnesota (USA) via a self-administered questionnaire regarding use of indoor tanning facilities and knowledge about risks of indoor tanning. The survey assessed compliance of staff with regulations and recommendations as reported by the users.

In 1998, Culley *et al.* (2001) quantified the level of compliance by indoor tanning facility operators with selected federal and state regulations and recommendations. A person posing as a potential customer visited 54 tanning facilities in

Table 6. Studies of adolescent use of indoor tanning facilities

Reference	Year of survey	Location	Population source	*N*	Age range (years)	Prevalence (%)[1]			Characteristics assessed in relation to use of indoor tanning facilities
						Boys	Girls	All	
Banks *et al.* (1992)	1989	Vienna, VA, USA	Adolescents seen at nine pediatrics clinics	96	16–19	16	33	23	Gender, age, frequency
Mermelstein & Riesenberg (1992)	1990	Chicago, IL, USA	10 schools participating in skin cancer intervention study	1 703	9th and 10th graders	7	19	NR	Gender, age, skin type
Oliphant *et al.* (1994)	1991	St. Paul, MN, USA	One high school	1 008	13–19	15	51	34	Gender, age, frequency, knowledge of risks, practice, symptoms
Wichstrom (1994)	1992	Norway	56 randomly selected high schools	15 169	17.3 (mean)	35	75[2]	NR	Gender, age, frequency
Boldeman *et al.* (1996, 1997)	1993	Stockholm, Sweden	60 randomly selected classes	1 252	14–19	32	68	57	Gender, age, knowledge of risks, smoking, frequency, skin type, symptoms, sunbathing, skin disease, perceived attractiveness, attitudes
Robinson *et al.* (1997)	1994	Chicago, IL, USA	Population-based random sample	658	11–19	1	16	8	Gender, age, skin type, socio-economic status
Brandberg *et al.* (1998)	1996	Sweden	Population-based random sample	2 615	13, 15, 17	4	16	10	Gender, age, satisfaction with self
Boldeman *et al.* (2001)	1999	Stockholm, Sweden	Population-based random sample	4 060	13–19	19	40	30	Gender, age, frequency, symptoms
Lucci *et al.* (2001)	1999	Dallas & Houston, Texas, USA	Junior and senior high students	210	14–19	NR	NR	18[3]	None
Cokkinides *et al.* (2002)	1998	USA	Population-based random sample	1 192	11–18	5	16	10[2]	Gender, age, race, parent education and income, residence, sun sensitivity, skin type, sunbathing, sun protection, health-provider advice, attitudes, parent tans

Table 6 (contd)

Reference	Year of survey	Location	Population source	*N*	Age range (years)	Prevalence (%)[1]			Characteristics assessed in relation to use of indoor tanning facilities
						Boys	Girls	All	
Geller *et al.* (2002)	1999	USA	Prospective cohort of off-springs of Nurses Health Study	10 079	12–18	2	14	10[2]	Gender, age, skin type, social factors, sun protection, attitudes
Knight *et al.* (2002)	1999	Bloomington, Indiana, USA	College students attending student health centre	489 402	≥ 17 17–22	38 NR	70 NR	62 52[2]	Gender, age, frequency, skin type, geographical region, reason for using tanning bed, believes about tanning, knowledge of risks
Demko *et al.* (2003)	1996	USA	132 schools in 80 communities	6 903	13–19	11	37	24	Gender, age, frequency, sun sensitivity, geographical region, school location, student income, maternal education, sunbathing, substance use, diet, obesity, body image, physical activity, body piercing, psychosocial factors
Hamlet & Kennedy (2004)	NR	Wishow Local Health Care, UK	23 primary schools	1 405	8–11	NR	NR	7	Age, frequency, attitudes, exposure at home or on commercial premises.
Lazovich *et al.* (2004); Stryker *et al.* (2004)	2000	Minneapolis/ St. Paul, MN and Boston, MA, USA	Random sample of households likely to have adolescents	1 273	14–17	12	42	30	Gender, age, smoking, satisfaction with looks, depression, sun protection, skin cancer risks, parent and teen knowledge of risks, parent and teen attitudes, social factors, parent tans, parent education, parent concern, parental influence score
Paul *et al.* (2004)	2000	New South Wales, Australia	Population-based random sample	1 509 78	≥ 15 15–17 18–29 30–39	5	14	10 4 11 19	Gender, age, attitudes, use of sunscreen

Adapted from Lazovich & Forster (2004)
NR, not reported.

[1]Prevalence of ever use, unless otherwise noted.

[2]Past 12 months

[3]Past 6 months

the San Diego, USA metropolitan area. Compliance with 13 regulations/recommendations was assessed by either direct query or observation of the presence/absence of signs and warning labels. No facility was in compliance with all 13 selected regulations. The mean number of regulations complied with was 8.33.

In another study conducted in the San Diego area, in 2000, Kwon *et al.* (2002) assessed the compliance of 60 tanning facilities with recommended exposure schedules by means of a telephone enquiry made by a supposedly prospective customer.

One study, conducted in Australia in 2005, explored compliance with international recommendations on solarium use in an unregulated setting: simulated customers visited 176 solaria in two face-to-face visits for each establishment and one telephone contact. Few (16%) establishments were compliant with more than 10 of the 13 recommendations. Compliance was particularly poor for those recommendations with the greatest potential for minimising harm: i.e. to discourage or exclude persons at high risk from UV exposure (Paul *et al.,* 2005).

(b) Duration/frequency of exposure: In the survey assessing compliance of staff as reported by the users (Oliphant *et al.,* 1994), 26% said they were never told to limit their time per session.

In a later study from the USA (Culley *et al.,* 2001), compliance was found to be relatively high for maximum duration allowed to tan (98%) but was relatively low for presence of and compliance with an appropriate shut-off switch (57%). Frequency allowed to tan had the lowest compliance at 6%; one facility even allowed two consecutive tanning sessions.

In the most recent study from the USA (Kwon *et al.,* 2002), only 4 out of 58 tanning salons (7%) recommended less than 3 sessions in the first week, and therefore were compliant with the regulations. All responded with a duration of exposure of less than 30 minutes, but all reported offering unlimited tanning packages, and less than 30% limited the exposure to once a day.

(c) Wearing of goggles: In the high school student survey cited above (Oliphant *et al.,* 1994), less than half of the customers interviewed (42%) had always been told to wear goggles, and 28% had never been.

In a more recent study from the USA (Culley *et al.,* 2001), compliance was found to be high for provision and sanitation of protective eyewear (100%) and for requirement to use it (89%).

(d) Age restriction: Very few studies have looked at compliance with age restriction. One study observed a low compliance (43%) with the requirement for parental permission for adolescent users aged 14–18 years (Culley *et al.,* 2001). Low levels of compliance with recommendations relating to age restriction were also found in a more recent study (Paul *et al.,* 2005).

(e) Warning of health risks: In the survey assessing compliance of staff as reported by users (Oliphant *et al.,* 1994), 50% reported that they had never received a warning about the health risks of indoor tanning, and less than half (48%) had ever noticed a warning sign at the facility. In another study in the USA (Culley *et al.,* 2001), compliance was found to be relatively high for presence of labels on warning of UV danger and of exposure (85%) and legibility, accessibility and correctness of these labels (74%); lower compliance (15–20%) was observed for warning signs in the tanning area.

(f) Other regulations: In the Australian study (Paul *et al.,* 2005), 1% of operators refused access to a pretending customer with skin phototype I, and 10% recommended against solarium use. In the same study, low levels of compliance were also found for using a sunbed while taking medications, for provision of consent forms and for discussing safety procedures.

Compliance of customers

(a) Study descriptions: The 1991 high school student survey in the USA (Oliphant *et al.* 1994) has been described above.

McGinley *et al.* (1998) conducted a survey of the output of tanning appliances in use in 1997 in Scotland. At the same time, questionnaires were distributed by the indoor tanning facilities to

users, seeking information on patterns of exposure and reasons for using sunbeds.

In 1996, a telephone survey was carried out among adults from the two most densely populated regions of Quebec, Canada, as described above (Rhainds *et al.,* 1999). The final sample included 1003 white persons 18-60 years old. Interviewers used a standardised questionnaire to document exposure habits to artificial UV radiation sources.

One study was conducted in North Carolina (USA) to assess adherence of indoor tanning clients to FDA-recommended exposure limits. A community-based survey was administered during routine state inspections of 50 indoor tanning facilities. At each facility, users' records were randomly selected (n = 483) for a survey of exposure (Hornung *et al.,* 2003).

To gain anecdotal evidence that primary school children were using sunbeds in Lanarkshire (United Kingdom), school nurses conducted a short questionnaire in 23 primary schools in 2003. Children 8-11 years old took part in the classroom surveys. Positive responses were counted by a show of hands by the children (Hamlet & Kennedy, 2004). [This small study was based on a "hands up" survey, which may have biased answers through copying of friends' actions.]

(b) Duration/frequency of use: In the high school student survey, 11% of users reported tanning indoors for more than 30 minutes. Those who reported longer usual tanning sessions were more likely to tan frequently (Oliphant *et al.,* 1994).

A user survey demonstrated that 31% of 205 responders had more than 10 courses of over five tanning sessions in a year and, for 16% of them, this amounted to over 100 sessions per year (McGinley *et al.,* 1998).

In the study by Hornung *et al.* (2003), out of 483 users, 95% were exceeding the recommended exposure times. Also, 33% of users started their first tanning session at or above exposure times recommended for users in the maintenance phase of tanning (>4.0 MED). The average duration of exposure on the first visit was 14.3 minutes (range, 3–30 minutes). Compilation of 15 common exposure schedules listed a suggested range of 2- to 15-minute sessions (average, 5.76 minutes) for the first week of tanning, with gradual increases over a 4-week or longer period to a range of 8- to 30-minute maintenance sessions (average, 20.5 minutes). The average period of tanning for each user was 6.3 weeks. Users spent approximately 43 minutes per week (range, 5–135 minutes) during an average of 2.4 sessions per week (0.25–7 sessions) (Hornung *et al.,* 2003).

(c) Wearing of goggles: In the 1991 study of high school students (Oliphant *et al.,* 1994), 59% reported always wearing goggles and 17% reported never wearing them. Those who reported longer usual tanning sessions were less likely to use goggles.

In the Scottish survey (McGinley *et al.,* 1998) 35% of users stated that they never or hardly ever wore protective goggles.

In the Canadian study (Rhainds *et al.,* 1999), 70% of 203 tanning bed users wore protective goggles during tanning sessions.

(d) Age restriction: In the US high school survey, almost 20% of those aged 14 years or younger reported using indoor tanning facilities, and half of the users had had their first session before age 15 years (Oliphant *et al.,* 1994).

Among 1405 adolescents under 16 years surveyed in the United Kingdom (Hamlet & Kennedy, 2004), 7% had used a sunbed in the last 6 months, of whom sixteen (17%) agreed that they used a sunbed regularly, i.e. twice a month or more. Of these 96 adolescent recent users, 61 (64%) reported using a sunbed in someone's house, and 23 (24%) had used a sunbed in a shop or salon.

Epidemiological data on exposure to artificial UV radiation for cosmetic purposes and skin cancers

As no valid animal model of human melanoma or other skin cancers exists, evidence of an association between indoor tanning facility exposure and skin cancer must be sought predominantly from epidemiological studies. Few studies have addressed this topic specifically, but most skin cancer studies have included one or more items about use of indoor tanning facilities. We systematically analysed the summary statistics compiled from the relevant studies in a meta-analysis. The results have also been discussed qualitatively, to allow for the large differences in study populations and study quality.

Since melanoma and other skin cancers differ somewhat in their aetiology, studies of melanoma were analysed separately from those of basal and squamous cell cancers. Epidemiological evidence from studies investigating other sources of exposure to artificial UV radiation has also been presented.

Methodology for literature search

The literature to April 2005 was searched using the following databases: Pubmed, ISI Web of Science (Science Citation Index Expanded), Embase, Pascal, Cochrane library, Lilacs and Medcarib. The following keywords and their corresponding French translations were used for search in the PASCAL database: "skin cancer", "squamous cell carcinoma", "SCC", "basal cell carcinoma", "BCC", "melanoma" for diseases. To define exposure, the following keywords were used: "sunbed", "sunlamp", "artificial UV", "artificial light", "solaria", "solarium", "indoor tanning", "tanning bed", "tanning parlour", "tanning salon" and "tanning booth".

We searched for keywords in the title and in the abstract, when available. We also performed a manual search of references cited in the selected articles, and in selected reviews or books on melanoma and skin cancer. All participants of the working group and some IARC staff were asked to report any additional published or submitted study. No language restriction was applied.

Primary inclusion criteria were developed for the selection of relevant articles, which were: case–control, cohort or cross–sectional studies published as an original article. Ecological studies, case reports, reviews and editorials were not considered eligible.

For the meta-analysis, we selected the articles fulfilling both of the following two criteria:

1. The article contained sufficient information to estimate the relative risk and 95% confidence intervals (odds ratios [OR], relative risks or crude data and corresponding standard errors, variance, confidence intervals or P-values of the significance of the estimates); and
2. The article reported an independent study (in order to avoid giving additional weight to some studies).

The selected articles were reviewed and data abstracted by means of a standardized data-collection protocol. When another article on the same study was published simultaneously, additional relevant or missing information was retrieved from the companion paper. For each study the following information was retrieved:

- General information: year of publication, recruitment years, study design, study location and latitude of the region;
- Exposure information: definition of type of exposure, age at first exposure, duration of exposure, year of exposure, place of exposure;
- Case–control information: inclusion or exclusion of specific histological types of melanoma, number and source of cases and controls, matching design, blinding of interviewers;
- Statistical information: statistical methods used, adjustment for confounding variables (demographic factors such as age and sex,

baseline host characteristics such as hair, eye and skin colour, inherent tendency to burn or tan easily, naevi, sunburns or sun exposure) and type of effect estimates (odds ratio, relative risk, standardized incidence ratio) with corresponding measures of precision, according to specific exposure category.

The minimal common information about exposure to indoor tanning devices for all studies was "ever exposed". For those studies where the definition of exposure "ever versus never exposed to indoor tanning facilities" was not present, we used the information closest to this category.

Since it has been suggested that age at exposure may influence the relative risk for skin cancer associated with UV exposure (Whiteman *et al.,* 2001), we extracted relative risks associated with use of indoor tanning facilities before the age of 35 years where available. Studies used different age categories for classifying age at first exposure, so odds ratios for the "young exposure" category were pooled without correction.

Melanoma

We identified 23 studies of use of indoor tanning facilities and melanoma (Klepp & Magnus, 1979; Adam *et al.,* 1981; Gallagher *et al.,* 1986; Holman *et al.,* 1986; Holly *et al.,* 1987; Swerdlow *et al.,* 1988; Osterlind *et al.,* 1988; Zanetti *et al.,* 1988; MacKie *et al.,* 1989; Beitner *et al.,* 1990; Walter *et al.,* 1990 (and 1999); Dunn-Lane *et al.,* 1993; Garbe *et al.,* 1993; Westerdahl *et al.,* 1994; Autier *et al.,* 1994; Holly *et al.,* 1995; Chen *et al.,* 1998; Westerdahl *et al.,* 2000; Naldi *et al.,* 2000; Kaskel *et al.,* 2001; Veierød *et al.,* 2003; Bataille *et al.,* 2004; Bataille *et al.,* 2005). All studies were case–control studies, except for one cohort study (Veierød *et al.,* 2003). No cross–sectional studies were identified. A case–control study was considered population-based when cases were derived from a population-based cancer registry and controls selected from the general population.

Description of studies

(a) Cohort study – Veierød et al. (2003): The only published prospective cohort study was conducted in Norway and Sweden, where 106 379 women aged 30–50 years at inclusion were recruited between 1991 and 1992. This population was selected from the National Population Register and followed for an average of 8.1 years. Among these, 187 cases of invasive melanoma were diagnosed during follow-up. The analysis was stratified by age at the time of exposure to sunbeds. Thirty-four cases occurred among the 14 377 women who were exposed at least once a month during one of three age periods (10–19, 20–29 or 30–39 years). The corresponding risk for melanoma for the entire cohort was 1.55 (confidence interval (CI), 1.04–2.32) when adjusting for age, region, hair colour, age-specific sunburns and annual number of weeks of summer vacations. For the age group 20–29 years, the risk for melanoma associated with solarium use more than once a month compared with rarely or never was 2.58 (CI, 1.48–4.50).

(b) Population-based case–control studies – Adam et al. (1981): A case–control study was conducted in Oxford and the south-western region of the United Kingdom between 1971 and 1976, recruiting 111 incident cases and 342 controls to study the association between the oral contraceptive and melanoma in women. Cases were selected from two cancer registries and when identified, were contacted through their General Practitioner (GP); controls were selected from the GP practice lists and matched to cases for age, marital status and GP practice. Nine cases and 10 controls had ever used sunlamps. The crude odds ratio calculated [by the Working Group] was 2.93 (CI, 1.16–7.40). [No estimate was reported for the exposure to sunlamps. The working group noted that 169 cases and 507 controls were selected from the registry, but only 111 cases and 342 controls completed questionnaires.]

Holman et al. (1986): A case–control study was conducted in Western Australia between 1980 and 1981 to evaluate constitutional traits, sunlight exposure, hormones, diet and other possible risk factors for cutaneous melanoma. This study recruited 511 incident cases and 511 controls, selected from the electoral roll and matched to cases for age and sex. Past use of sunlamps was

recorded, but only 9% of subjects had used them. The crude odds ratio for "ever use" compared to "never use" of sunlamps was 1.1 (CI, 0.6–1.8).

Osterlind et al. (1988): A case–control study conducted in East Denmark between October 1982 and March 1985 recruited 474 incident cases and 926 controls aged 20–79 years selected from the National Population Register to study risk factors for melanoma. Sixty-six cases and 168 controls had ever used sunbeds, and 50% of controls had used sunbeds less than 10 times. The crude odds ratio for ever versus never use [calculated by the Working Group] was 0.73 (CI, 0.53–1.01), and no trend was observed with number of sessions. Regarding exposure to sunlamps, 45% of cases and 42% of controls had used sunlamps, with 40% of both cases and controls having used sunlamps less than 10 times. [No estimate was reported for the use of a sunlamp.]

Zanetti et al. (1988): A case–control study investigating melanoma risk factors was conducted in Torino, Italy between May 1984 and October 1986. The authors identified 208 incident cases in the "Registro Tumori Piemonte" registry and selected 416 controls from National Health Service files. Of these, 15 cases and 21 controls had used UVA lamps for tanning purposes. The risk for melanoma from this exposure was 0.9 (CI, 0.4–2.0) after adjustment for age, hair colour, skin reaction, sunburn in childhood and education level. The use of sunlamp for tanning was very rare in Italy during the study period, and the authors warned about the consequent lack of power of the study.

Walter et al. (1990): A case–control study, designed specifically to investigate the melanoma risk associated with artificial UV exposure, was conducted in southern Ontario, Canada between October 1984 and September 1986. Recruitment included 583 incident cases identified from pathology reports and 608 controls selected from property tax assessment rolls. Controls were matched to cases for sex, age and place of residence; 152 cases and 109 controls had ever been exposed to sunlamps or sunbeds. The risk for melanoma, adjusted for skin reaction to initial summer exposure, was 1.54 (CI, 1.16–2.05). The relative risk in the youngest age group (20–34 years) was 1.51 (CI, 0.82–2.77). When duration of exposure to tanning appliances was analysed by category (never; <12 months; ≥ 12 months), a significant trend was observed both for men ($p < 0.01$) and for women ($p = 0.04$). [This study was initially published in 1990 (Walter *et al.,* 1990). Further calculations with new adjustments were published in 1999 (Walter *et al.,* 1999).]

Westerdahl et al. (1994): A case–control study was conducted in Sweden between July 1988 and June 1990. The authors recruited 400 incident cases selected from the regional tumour registry, and 640 controls selected from the National Population Registry, aged 15 to 75 years. Controls were matched to cases for age, sex and place of residence. Of these, 111 cases and 159 controls had ever used sunbeds or sunlamps. The relative risk, adjusted for sunburns, hair colour, naevi number and sunbathing habits during summer, was 1.3 (CI, 0.9–1.8). Among individuals aged ≤ 30 years, the relative risk was 2.7 (CI, 0.7–9.8). When exposure exceeded 10 sessions per year, the risk for melanoma was significantly increased over that of never-users (OR, 1.8; CI, 1.0–3.2).

Holly et al. (1995): A case–control study on melanoma risk factors was conducted in San Francisco, USA between January 1981 and December 1986. The study was restricted to women aged 25–59 years. The authors recruited 452 incident cases ascertained through the SEER Registry for the San Francisco Bay area and 452 controls ascertained using telephone random digit dialling. Controls were frequency-matched to cases for age in 5-year categories. Exposure to sunlamps was investigated. No association was observed for ever using a sunlamp (crude OR, 0.94; CI, 0.74–1.2). [The Working Group noted that use of sunlamps by 63% of cases and 62% of controls, as presented in the text, would result in an odds ratio of 1.05 (CI, 0.79–1.38). Despite this inconsistency, it was decided to use the estimate given in the table.]

Chen et al. (1998): A case–control study was conducted in Connecticut, USA between January 1987 and May 1989. Using the population-based Rapid Case Ascertainment System, 624 incident cases were identified and 512 controls ascertained using telephone random digit dialling. Of these, 141 cases and 95 controls had ever used a sunlamp or sunbed. The risk for melanoma associated with sunlamp or sunbed exposure was 1.13 (CI, 0.82–1.54) after adjustment for age, sex, cutaneous phenotype index and recreational sun exposure index. In a stratified analysis, the relative risk associated with first exposure before age 25 years was 1.35 (CI, 0.88–2.08). No trend was observed in relation to duration of exposure to sunlamps or sunbeds.

Westerdahl et al. (2000): A case–control study was conducted in the South Health Care region of Sweden between January 1995 and June 1997. The authors recruited 571 incident cases identified in the regional tumour registry, and 913 controls matched for age and sex ascertained from the National Population Registry. Of these, 250 cases and 372 controls had ever used sunbeds. The risk for melanoma associated with sunbed exposure was 1.2 (CI, 0.9–1.6) after adjustment for age, sex, history of sunburn, hair colour, skin type and number of raised naevi. No change in the estimate was observed after adjustment for sunbathing habits. In a stratified analysis, there was a significant increase in risk when exposure took place before the age of 35 years (OR, 2.3; CI, 1.2–4.2). No trend relating to total duration of exposure was observed.

(c) Hospital- or clinic-based case–control studies

Klepp & Magnus (1979): A hospital-based case–control study was conducted in Oslo, Norway between January 1974 and May 1975. The authors enrolled 89 cases and 227 controls aged 20 years or more to evaluate possible etiological factors for melanoma. Cases were incident cutaneous melanomas from the Norwegian Radium Hospital; controls were other cancer patients in the same hospital. The self-administered questionnaire included a question about use of artificial UV lamps. No estimates were derived from the results because exposure to UV lamp was very rare, and there was no difference between cases and controls.

Gallagher et al. (1986): A case–control study was conducted in western Canada between April 1979 and March 1981. To study risk factors for melanoma, including host factors, sun exposure, and the use of oral contraceptive for women, 595 incidence cases from dermatology practice and 595 controls from provincial medical plans were recruited. Controls were matched to cases for age and sex. The recruitment was limited to individuals 20–79 years old. No estimate of the risk was presented. The study showed no association between sunlamp use and subsequent risk for melanoma (χ^2=6.1; 5 df; p=NS), including after stratifying by sex or by anatomical site exposed to the sunlamp.

Holly et al. (1987): A hospital-based case–control study was conducted in San Francisco (USA) between April 1984 and October 1987. To assess melanocytic naevi (dysplatic and non-dysplastic naevi) as risk factor for melanoma, 121 incident cases were recruited from a melanoma clinic at the University of California, San Francisco, and 139 controls were recruited among patients in another clinic at the same university. No estimate of the risk for melanoma associated with sunbed use was presented. The patients with cutaneous melanoma were similar to those in the control group with respect to their use of tanning salons.

Swerdlow et al. (1988): A hospital-based case–control study was conducted in Scotland (United Kingdom) between 1979 and 1984 to evaluate the role of fluorescent light and UV lamps on cutaneous melanoma risk. The authors recruited 180 incident cases from dermatology and plastic surgery units and 197 hospital inpatients and outpatients as controls excluding those with malignant disease. Analysis for exposure to tanning appliances was restricted to 120 controls without dermatological disease. Only 38 cases and 10 controls had ever used UV lamps or sunbeds (crude OR, 2.94; CI, 1.40–6.17). Data by age at first use (before and after age of 30 years) and by total number of hours of exposure (1–19 hours; ≥ 20 hours within the 5 years before presentation)

were also presented. A significant linear trend for duration of use was observed ($p<0.01$). Adjustment for hair colour, eye colour, skin type or sun exposure did not substantially change the estimates, while a small decrease was observed when adjusting for number of naevi.

MacKie et al. (1989): A hospital-based case–control study of melanoma was conducted in Scotland, United Kingdom in 1987. The authors identified 280 incident cases (99 men and 181 women) through the Scottish Cancer Registry; 280 controls (99 men and 181 women) were recruited at a hospital, excluding patients with dermatological illness. Controls were matched to cases for age and sex. In the questionnaire, one item investigated exposure to artificial UV radiation and use of sunbeds; 33 cases and 8 controls had been exposed to such sources. The odds ratio was stratified by sex and adjusted for total number of naevi, atypical naevi, freckling tendency, history of severe sunburns, tropical residence for more than 5 years and skin type. The adjusted odds ratios were 1.3 (CI, 0.2–7.9) for men and 1.2 (CI, 0.5–3.0) for women. Only 26 cases and 6 controls had used "modern sunbeds" once or twice weekly for at least 12 weeks. [Due to stratification by sex, two estimates from this study were used in the analysis.]

Beitner et al. (1990): A case–control study was conducted in Stockholm, Sweden between February 1978 and December 1983. The authors recruited 523 incident cases from the Department of Oncology at Karolinska Hospital and 505 controls selected from population registries. Controls were matched to cases for age and sex. No estimate of the risk was presented. No increase in the risk for developing cutaneous malignant melanoma was associated with frequent exposures to solaria.

Dunn-Lane et al. (1993): A hospital-based case–control study was conducted in Dublin, Ireland between 1985 and 1986. The authors recruited 100 incident cases from seven Dublin hospitals and 100 controls, admitted for limb injuries in the accident and emergency and orthopaedic departments, were recruited. Controls were matched to cases for age (within 5 years), sex and health broad area of residence. Seventeen cases and 15 controls had ever used sunbeds. The crude odds ratio [calculated by the Working Group] was 1.16 (CI, 0.54–2.47). [No estimates were reported by the authors.]

Garbe et al. (1993): A hospital-based case–control study evaluating risk factors for melanoma was conducted in Germany between 1984 and 1987. The authors studied 856 cases selected from the Central Malignant Melanoma Registry of the German Dermatology Society and 705 controls selected from outpatients presenting at dermatology clinics. Of these, 66 cases and 50 controls had ever used sunbeds. The relative risk for melanoma, adjusted for number of naevi, hair colour, skin type, age and study centre, was 1.5 (CI, 0.9–2.4). [The Working Group noted that the Central Malignant Melanoma Registry is a voluntary registry.]

Autier et al. (1994): A case–control study of melanoma was conducted in Europe (Germany, France, Belgium) from January 1991 onwards. The authors recruited 420 incident cases from dermatology practices and cancer centres; 447 controls were selected from neighbourhood by door-knock. Of these, 110 cases and 120 controls had ever been exposed to sunlamps or sunbeds. While there was no crude association with melanoma (OR, 0.97; CI, 0.71–1.32), in a stratified analysis total exposure to sunlamp or sunbed for tanning purposes for more than 10 hours and before 1980 showed an increased risk (OR, 2.12; CI, 0.84–5.37) after adjustment for age, sex, hair colour and number of holiday weeks per year. The risk for melanoma associated with sunlamp or sunbed use was significantly increased if exposures for more than 10 hours were accompanied by a burn to the skin (OR, 7.35; CI, 1.67–32.3).

Naldi et al. (2000): A hospital-based case–control study of melanoma was conducted in Italy between June 1992 and February 1995. The authors recruited 542 incident cases from oncology and dermatology centres, and 528 controls admitted to the hospital for a non-dermatologic or

non-neoplastic illness. Of these, 30 cases and 36 controls were ever exposed to sunbeds or sunlamps. The risk for melanoma, adjusted for age, sex, marital status, education, eye and skin colour, number of naevi, freckles density, sunburns and number of sunny vacations, was 0.78 (CI, 0.45–1.37).

Kaskel et al. (2001): A hospital-based case–control study of melanoma was conducted in Munich, Germany between June 1996 and April 1997. The authors recruited 271 prevalent cases (diagnosed from 5 years to 6 months before inclusion) from the Tumour Centre in Munich, and 271 controls from hospital departments of general surgery and ophthalmology. Controls were matched to cases for age (in 5-year categories), sex and place of residence. Among the 56 factors explored, one item investigated exposure to UV radiation or UV beds more than 5 times per year compared with 5 times per year or less. In the analysis of discordant pairs, the crude risk for artificial UV exposure was 1.0 (CI, 0.6–1.8).

Bataille et al. (2004): A hospital-based case–control study of melanoma was conducted in the North East Thames region (United Kingdom) between August 1989 and July 1993. The authors recruited 413 cases and 416 controls aged 16 to 75 years old. Incident cases of histologically confirmed melanomas were recruited from hospitals and general practices. Controls were also recruited through hospitals and general practices, excluding patients attending for a skin disease. One hundred cases and 110 controls had ever been exposed to sunbeds. The risk for melanoma associated with sunbed use was 1.19 (CI, 0.84–1.68), after adjusting for age and sex. Further adjustment for skin type and other sun exposure measures did not affect the results. In a stratified analysis, if sunbed exposure took place before the age of 45 years, the relative risk was 1.2 (CI, 0.76–1.90). No trend toward increased risk was observed with increasing lifetime duration of exposure.

Bataille et al. (2005): A case–control study designed specifically to investigate melanoma risk associated with sunbed exposure was conducted in Belgium, France, the Netherlands, Sweden and the United Kingdom between December 1998 and July 2001. The authors recruited 597 incident cases from dermatology or oncology clinics or identified through pathology laboratories. The method of recruitment of 622 controls differed according to each centre: population register in Sweden, neighbourhood controls in Belgium and France, and general practices in the Netherlands and the United Kingdom. Of these, 315 cases and 354 controls had ever used sunbeds. The risk for melanoma associated with sunbed use was 0.9 (CI, 0.71–1.14) when adjusting for age, sex and skin type. If exposure to tanning appliances occurred before age 15 years, the relative risk was 1.82 (CI, 0.92–3.62). No trends in risk for melanoma were observed with increasing lifetime exposure or with increasing time since first exposure. No association was observed when stratifying by type of sunbed. [A companion paper warned about potential biases that could have occurred in this study: selection bias of controls and misclassification of cases who tended to underreport their exposure (deVries *et al.,* 2005)].

Of these 23 studies, 4 studies were excluded—in accordance with the selection criteria—because they did not include estimates of the relative risk for cutaneous melanoma associated with exposure to tanning appliances (Klepp & Magnus, 1979; Gallagher *et al.,* 1986; Holly *et al.,* 1987; Beitner *et al.,* 1990).

Another study (Walter *et al.,* 1990) which presented an evaluation of "ever" versus "never" exposed to artificial UV radiation was excluded because it involved the same population as a later publication (Walter *et al.,* 1999); moreover, it presented crude rather than adjusted relative risks. However, the estimate for "first exposure before age 35 years" from the early publication (Walter *et al.,* 1990) was included in the relevant section.

Quantitative approach: meta-analysis

(a) Evaluation of exposure: Four types of exposure to indoor tanning appliances were evaluated:
- "ever" versus "never";
- "first exposure before age 35 years" versus ''never".

In addition, another concept was considered in order to make a comparison between recent and distant exposures:

- "exposure distant in time" versus "never";
- "exposure recent in time" versus "never".

A dose-response model was not considered for this meta-analysis because of the heterogeneity among the categories of duration and frequency of exposure used by different authors.

(b) Study characteristics: Table 7 provides an overview of all the studies retrieved, including the 19 studies reporting estimates that could be included in the meta-analysis (for a total of 7 355 cases). The first (published in 1981) and the last (published in 2005) studies included were published more than 20 years apart. Three case–control studies presented a time lag between first recruitment year and publication of 10 years or more.

Fifteen studies were carried out in European countries, four of which were in Scandinavian countries; two were conducted in the United States, one in Canada and one in Australia. The mean latitude of the study centres was 50° (range 25º–59º); eight studies were conducted in countries with average latitude below 50°.

(c) Types of estimate presented: Since melanoma is a rare disease, we ignored the distinction between the various estimates of relative risk (i.e. odds ratio, rate ratio, risk ratio), and all measurements were interpreted as odds ratios.

Except for the studies by Kaskel *et al.* (2001) and by Veierød *et al.* (2003), all studies presented estimates for "ever" versus "never" exposed to artificial UV radiation (Table 8). Thirteen of 19 studies presented positive estimates for "ever" versus "never" exposed to sunbed/sunlamps, but only four were statistically significant. For seven of these studies it was possible to obtain only crude relative risks, one adjusted for age and sex only.

The cohort study (Veierød *et al.,* 2003) presented an estimate for the widest age interval included (10–39 years), only for the comparison "≥ 1 time per month" versus "never/rarely". One study (Kaskel *et al.,* 2001) presented an estimate only for the comparison ">5 times per year" versus "≤ 5 times per year".

Five studies (Swerdlow *et al.,* 1988; Walter *et al.,* 1990; Chen *et al.,* 1998; Westerdhal *et al.,* 2000; Bataille *et al.,* 2005) also presented an estimate for first exposure at age ≤ 35 years (Table 9). Veierød *et al*. (2003) presented relative risks for "≥ 1 time per month" versus "never" in the age period 20–29 years; Westerdhal *et al*. (1994) presented estimates of "ever" versus "never" for individuals younger than 30 years. All relative risks were adjusted for confounders related to sun exposure or sun sensitivity, except in the study by Walter *et al.* (1990). All these estimates were considered for the evaluation of "first exposure before age 35 years" versus "never".

Five studies investigated time since exposure (Table 10) and reported estimates that allowed comparisons between recent and distant exposure: number of years of exposure before presentation (Swerdlow *et al.,* 1988; Bataille *et al.,* 2005), number of years since last exposure (Walter *et al.,* 1990) and age at first exposure (Autier *et al.,* 1994; Chen *et al.,* 1998).

(d) Selection of data and methods of analysis: Every measure of association adjusted for the maximum number of confounding variables and corresponding confidence interval were transformed into log RR, and the corresponding variance was calculated using the formula proposed by Greenland (1987). Where no estimates were given, crude estimates were calculated from tabular data, using Asymptotic Mantel-Haenszel estimates to evaluate the 95% CI of the log odds ratio.

Most estimates included all subjects, combining sexes. One study presented results separately for women and men with no combined data; both estimates were included (MacKie *et al.,* 1989).

The homogeneity of the effects across studies was assessed using the large sample test based on the Chi-square statistic (Chi). Since the Chi-square test has limited power, we considered statistically significant heterogeneity at the P=0.10 level of association. A further measure of heterogeneity, H (the square-root of Chi-square divided by its degrees of freedom), has been considered in order to make comparisons between heterogeneities of pooled estimates summarizing

Table 7. Characteristics of studies considered for the meta-analysis on melanoma

Reference	Country	First Year	Number		Histological diagnosis	Participation of controls (%)
			Cases	Controls		
Cohort study						
[1]Veierød *et al*. (2003)	Norway, Sweden	1992	187	106 379[2]	HC invasive M	54.5[3]
Population-based case–control studies						
[1]Adam *et al*. (1981)	UK	1971	169	207	HCM	68
Gallagher *et al*. (1986)	Western Canada	1979	595	595	M excluding LMM and ALM	48
[1]Holman *et al*. (1986)	Australia	1982	511	511	HC pre-invasive/ invasive M	69
[1]Osterlind *et al*. (1988)	Denmark	1985	474	926	HCM excluding LMM	81.7
[1]Zanetti *et al*. (1988)	Italy	1984	208	416	M *in situ* and all other histology	68.2
Beitner *et al*. (1990)	Sweden	1978	523	505	HCM (SSM, NM, LMM, unclassif. MM)	96.2
Walter *et al*. (1990)	Canada	1984	583	608	HCM *in situ* and Hutchinson's freckle, LMM	81
[1]Westerdahl *et al*. (1994)	Sweden	1990	400	640	Invasive M	77.4
[1]Holly *et al*. (1995)	USA	1986	452	930	HCM	77
[1]Chen *et al*. (1998)	USA	1989	624	512	HC first primary invasive M	70
[1]Walter *et al*. (1999)	Canada	1986	583	608	HCM *in situ* and Hutchinson's freckle, LMM	81
[1]Westerdahl *et al*. (2000)	Sweden	1997	571	913	HC first primary invasive M	68
Other case–control studies						
Klepp & Magnus (1979)	Norway	1974	78	131	M	NR
Holly *et al*. (1987)	USA	1984	121	139	NM or SSM	NR
[1]Swerdlow *et al*. (1988)	UK	1988	180	120	Primary M	NR
[1]MacKie *et al*. (1989)	UK	1987	280	180	Invasive M	NR
[1]Dunn-Lane *et al*. (1993)	UK	1986	100	100	M excluding LMM and ALM	NR
[1]Garbe *et al*. (1993)	Germany	1987	280	280	M	NR
[1]Autier *et al*. (1994)	Belgium, France & Germany	1991	420	447	HCM	78
[1]Naldi *et al*. (2000)	Italy	1993	542	538	M	NR
[1]Kaskel *et al*. (2001)	Germany	1996	271	271	HCM	NR
[1]Bataille *et al*. (2004)	UK	1993	413	416	M including *in situ* and LMM	NR
[1]Bataille *et al*. (2005)	UK	1998	597	622	HC first primary invasive M excluding LMM	NR

[1]included in the meta-analysis; [2]cohort size; [3]response rate.

ALM, acral lentiginous melanoma; HC, histologically confirmed; LMM, lentigo maligna melanoma; M, melanoma; MM, malignant melanoma; NM, nodular melanoma; NR, not reported; SSM, superficial spreading melanoma.

Table 8. Estimates included in the evaluation of an association of ever use of indoor tanning facilities and risk for melanoma

Reference	Exposure comparison	Relative risk (95% CI)	Adjustment
Adam *et al*. (1981)	Ever use of sunlamps *vs* never	2.93 (1.16–7.40)	Crude
Holman *et al*. (1986)	Ever use of sunlamps *vs* never	1.1 (0.6–1.8)	Crude
Osterlind *et al*. (1988)	Ever use of sunbeds *vs* never	0.73 (0.53–1.01)	Crude
Swerdlow *et al*. (1988)	Ever use of UV lamps/ sunbeds *vs* never	2.94 (1.41–6.17)	Crude
Zanetti *et al*. (1988)	Use of UVA lamp for tanning purpose: yes/no	0.9 (0.4–2.0)	Age, hair colour, skin reaction, sunburn in childhood, education level
MacKie *et al*. (1989) (men)	Ultraviolet use: some *vs* none	1.3 (0.2–7.9)	Naevi, freckles, sunburns, tropical residence, phototype
MacKie *et al*. (1989) (women)	Ultraviolet use: some *vs* none	1.2 (0.5–3.0)	Naevi, freckles, sunburns, tropical residence, phototype
Dunn-Lane *et al*. (1993)	Ever use of sunbeds *vs* never	1.16 (0.54–2.47)	Crude
Garbe *et al*. (1993)	Use of sunbeds: yes/no	1.5 (0.9–2.4)	Age, naevi, hair colour, phototype, study centre
Autier *et al*. (1994)	Ever exposed to sunlamps/sunbeds *vs* never	0.97 (0.71–1.32)	Crude
Westerdahl *et al*. (1994)	Ever exposed to sunbeds/sunlamps *vs* never	1.3 (0.9–1.8)	Sunburns, hair colour, naevi, sunbathing
Holly *et al*. (1995) (women)	Ever use of sunlamps *vs* never	0.94 (0.74–1.2)	Crude
Chen *et al*. (1998)	Ever use of sunlamps *vs* never	1.13 (0.82–1.54)	Sex, age, phenotype, recreational sun exposure
Walter *et al*. (1999)	Ever use of sunbeds/sunlamps *vs* never	1.54 (1.16–2.05)	Sex, age, skin reaction to initial summer sun exposure
Naldi *et al*. (2000)	Ever use of sunbeds/sunlamps *vs* never	0.78 (0.45–1.37)	Sex, age, skin, hair, eye, naevi, freckles, sunburn, number of sunny vacations
Westerdahl *et al*. (2000)	Ever use of sunbeds *vs* never	1.2 (0.9–1.6)	Sunburns, hair colour, skin type, raised naevi
Kaskel *et al*. (2001)	Artificial UV radiation/UV beds: >5/year *vs* ≤5/year	1.00 (0.6–1.8)	Crude
Veierød *et al*. (2003) (women)	Solarium use : ≥1/month *vs* never/rarely	1.55 (1.04–2.32)	Age, region of residence, hair colour, sunburns, summer vacations
Bataille *et al*. (2004)	Ever use of sunbeds *vs* never	1.19 (0.84–1.68)	Sex, age
Bataille *et al*. (2005)	Ever use of sunbeds or sunlamps *vs* never	0.90 (0.71–1.14)	Sex, age, skin phototype

Table 9. Estimates included in the evaluation of an association of first use of indoor tanning facility in youth and risk for melanoma

Reference	Definition	Relative risk (95% CI)	Adjustment
Swerdlow *et al.* (1988)	Age at first exposure <30 years *vs* never	3.8 (0.9–16.5)	Naevi, skin type, hair and eye colour, sun exposure
Walter *et al.* (1990)	Age at first use <30 years *vs* never	1.67 (1.17–2.39)	Age
Westerdahl *et al.* (1994)	Ever use of sunbed at age younger than 30 years	2.7 (0.7–9.8)	Sunburns, hair colour, naevi, sunbathing
Chen *et al.* (1998)	Age at first use of sunlamp < 25 years *vs* never	1.35 (0.88–2.08)	Sex, age, phenotype index, recreational sun exposure
Westerdahl *et al.* (2000)	Age at first exposure ≤ 35 years *vs* never	1.6 (0.9–2.9)	Sunburns, hair colour, skin type, naevi
Veierød *et al.* (2003)	Exposure at age 20–29: ≥ 1 time/month *vs* never	2.58 (1.48–4.50)	Age, region of residence, sunburns, summer vacations
Bataille *et al.* (2005)	Ever sunbed use before age 15 years *vs* never	1.82 (0.92–3.62)	Age, sex, skin type

Table 10. Estimates included in the evaluation of an association of distant and recent exposure and risk for melanoma

Reference	Definition	Relative risk (95% CI)	Adjustment
Swerdlow *et al.* (1988)	Less than 5 years before presentation *vs* never	1.9 (0.6–5.6)	Age, sex, residence
	More than 5 years before presentation *vs* never	9.1 (2.0–40.6)	
Walter *et al.* (1990)	Less than 5 years since last use *vs* never	Men, 1.52 (0.56–4.25) Women, 1.24 (0.67–2.31)	Age
	More than 5 years since last use *vs* never	Men, 2.00 (1.21–3.34) Women, 1.53 (0.96–2.46)	
Autier *et al.* (1994)	First use in 1980 or later (≥ 10 hr of exposure for tanning purposes)	0.99 (0.49–2.00)	Age, sex, hair colour, holiday weeks spent in sunny resorts
	First use before 1980 (≥ 10 hr of exposure for tanning purposes)	2.12 (0.84–5.37)	
Chen *et al.* (1998)	First use after 1970	1.15 (0.64–2.07)	Sex, age, phenotype index, recreational sun exposure
	First use before 1970	1.33 (0.84–2.12)	
Bataille *et al.* (2005)	< 6 years between first sunbed use and interviews	0.91 (0.58–1.42)	Sex, age, skin type
	≥ 15 years between first sunbed use and interviews	0.97 (0.70–1.34)	

different numbers of studies. Greater values of H indicate larger heterogeneity (Higgins & Thompson, 2002).

The summary relative risk was estimated by pooling the study-specific estimates by random effects models even when heterogeneity was found to be not significant and H was very low, in order to be conservative and to enable generalization of the results. For mixed effects models, SAS was used (SAS Institute Inc. SAS Windows version 8.02, 1999, Cary, NC) with PROC MIXED (van Houwelingen *et al.,* 2002). These models allowed taking into account between-study variability and non-independence of estimates originating from the same study.

Subgroup analyses and meta-regressions were carried out to investigate inter-study heterogeneity (Colditz *et al.,* 1995). Heterogeneity was investigated by looking at all factors concerning the type of study, analysis, exposure and features of the population that could influence the estimates. Studies conducted in different populations living at substantially different latitudes were not included in the heterogeneity analysis that evaluated latitude.

A sensitivity analysis was conducted to evaluate the stability of the pooled estimates and the influence of individual studies. To verify whether publication bias might affect the validity of the estimates, funnel plots were plotted using Copas and Shi's method (Copas & Shi, 2001) and the funnel plot regression of Ln(RR) on the sample size, weighted by the inverse of the pooled variance (Macaskill *et al.,* 2001).

(e) Pooled estimates: Results of the meta-analysis of all studies included are shown in Table 11 and Figure 2. Between-study heterogeneity was found significant for being "ever" versus "never" exposed to artificial UV (Chi=35.40, degrees of freedom (d.f.) =19, P=0.013). The pooled estimate indicated a borderline-significant positive association between "ever" versus "never" use of sunlamps/sunbed and melanoma (RR, 1.15; CI, 1.00-1.31).

When "first exposure before age 35 years" was analysed, a significant 75% increase in risk was detected (Table 11; Figure 3) and the Chi-square testing heterogeneity was non-significant (Chi = 4.95, d.f . = 6, P = 0.55) and H (= 0.91) was smaller than the value obtained for "ever" versus "never" (H = 1.37).

The number of studies presenting an assessment of time since exposure was low (n = 5); however all studies presented greater estimates for exposures more distant in time compared to more recent exposures. Heterogeneity was greater for "distant exposure" (H = 1.65 and Chi =13.63, d.f. = 5, P = 0.018) than for "recent exposure" (H = 0.67 and Chi = 2.52, d.f. = 5, P = 0.81).

It is interesting to note that exposures more distant in time led to an increased risk compared with recent exposures, consistently with the higher risk for "first exposure before age 35 years" versus "never" compared to "ever" versus "never".

In order to decrease the influence of biases, estimates were calculated including only the cohort and population-based case–control studies (Table 12). The pooled relative risks were very similar apart from wider confidence intervals.

Table 11. Meta-analysis of all studies included

Exposure	Number of studies	Summary relative risk (95% CI)	Heterogeneity[1]	
			P-value χ^2	H
Ever use of indoor tanning facility	19	1.15 (1.00–1.31)	0.013	1.37
First exposure in youth	7	1.75 (1.35–2.26)	0.55	0.91
Exposure distant in time	5	1.49 (0.93–2.38)	0.018	1.65
Exposure recent in time	5	1.10 (0.76–1.60)	0.81	0.67

[1]The degrees of freedom for the Chi-square are given by the number of databases included minus one, not by the number of studies.

Figure 2. Relative risk for cutaneous melanoma associated with ever use of indoor tanning equipment: estimates of 19 studies and summary estimate

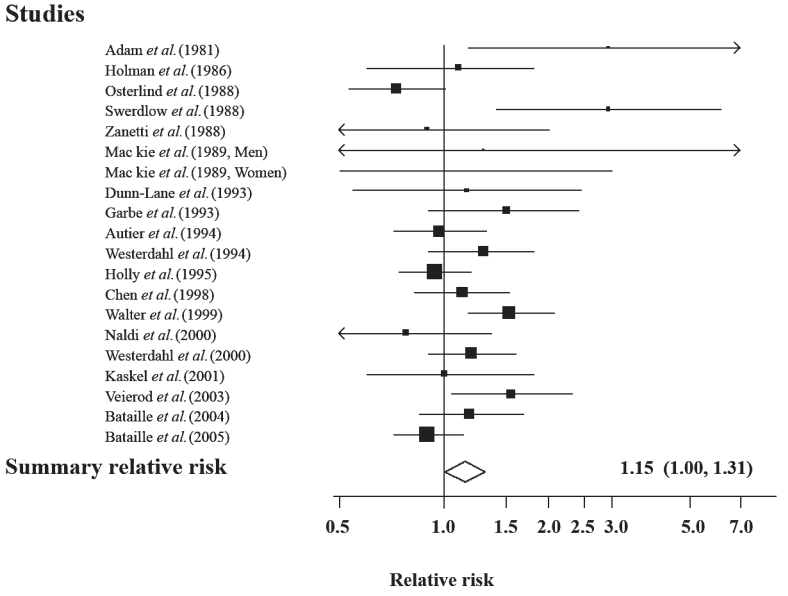


Figure 3. Relative risk for cutaneous melanoma associated with first use of indoor tanning equipment at age <35 years: estimates of 7 studies and summary estimate

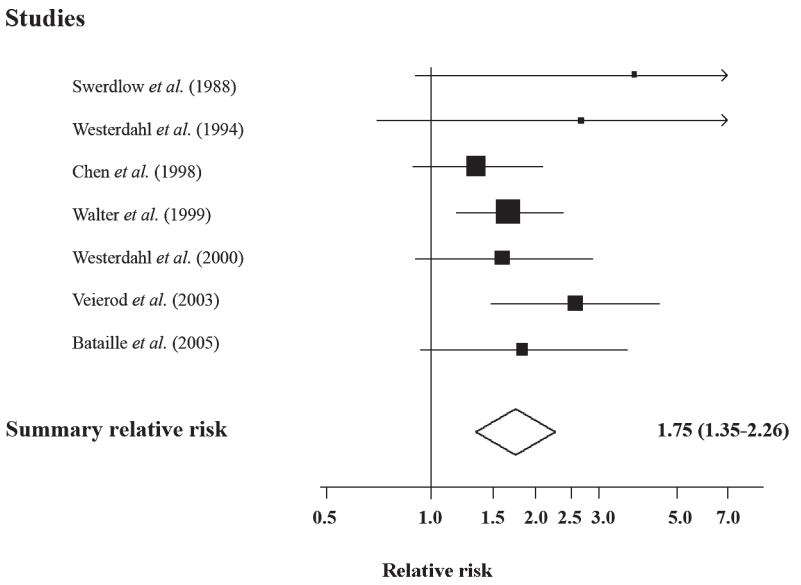


Table 12. Meta-analysis of the cohort and population-based case–control studies included

Exposure	Number of studies	Summary relative risk (95% CI)	Heterogeneity	
			P-value χ^2	H
Ever use of indoor tanning facility	10	1.17 (0.96–1.42)	0.011	1.540
Age at first exposure in youth	5	1.71 (1.25–2.33)	0.435	0.973
Exposure distant in time	2	1.58 (0.25–9.98)[1]	0.502	0.830
Exposure recent in time	2	1.24 (0.52–2.94)	0.762	0.521

[1]The confidence interval is very wide because this analysis includes only 2 studies, one of which has two estimates.

(f) Heterogeneity analysis: For the comparison of "ever" versus "never", which included the largest number of studies, several factors that could influence the variability among estimates were investigated. This analysis revealed that studies with a longer time lag between the first year of recruitment and publication (≥ 10 years) presented higher estimates (Table 13). (The cohort study was excluded from this analysis because of the nature of the study design.)

Studies carried out in countries at higher latitudes presented higher relative estimates than did studies carried out at lower latitudes (Table 13 and Figure 4).

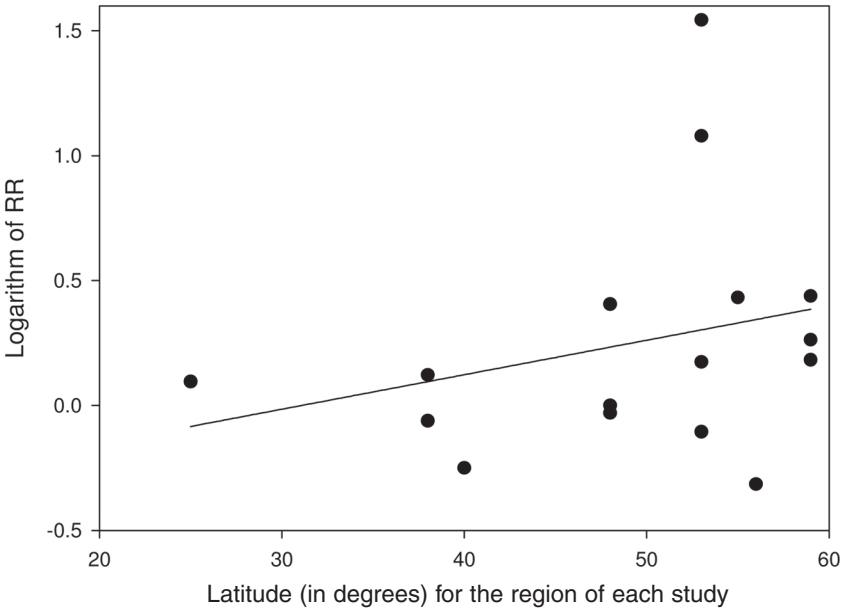
Adjustment for confounders related to sun exposure and sun sensitivity led to a higher pooled estimate compared with studies considering only crude relative risks or relative risks adjusted only for age and sex (Table 13). In the analysis restricted to the eight studies that adjusted for confounders related to sun exposure and sun sensitivity, the pooled relative risk remained similar to the summary estimate for all 19 studies but the confidence interval widened (RR, 1.19; CI, 0.33–4.30). The difference between adjusted and crude pooled relative risks may not be due to the adjustment in itself but to the fact that well-conducted studies usually adjust for sun exposure and sun sensitivity, which could be an indicator of the quality of the analysis.

(g) Sensitivity analysis: A series of analyses were performed to test the stability and sensitivity of the analysis (Table 14). Inclusion criteria were tested by including the estimates reported by Walter and colleagues in 1990 instead of those reported in 1999. Also, the studies that did not report any relative risk (Klepp & Magnus, 1979; Gallagher *et al.,* 1986; Holly *et al.,* 1987; Beitner *et al.,* 1990) were included by imputing the

Table 13. Heterogeneity analysis

Parameter analysed	Number of studies	Pooled relative risk (95% CI)	Heterogeneity
			P-value χ^2
Number of years between recruitment and publication ≥ 10	3	1.38 (0.25–7.46)	0.16
Number of years between recruitment and publication <10	15	1.06 (0.50–2.27)	0.14
Estimate adjusted for phototype/sun exposure/sunburns	10	1.19 (0.45–3.12)	0.17
Crude estimate or estimate adjusted for age and sex only	9	1.03 (0.31–3.40)	0.018
Latitude of study centre <50°	8	1.08 (0.31–3.78)	0.73
Latitude of study center >50°	11	1.20 (0.41–3.46)	0.003

Figure 4. Correlation between latitude of study centre and relative risk for melanoma associated with use of indoor tanning facilities



missing estimates from data available in the reports. Where no data at all were presented but an indication of non-significant effect was given, a relative risk of 1 and a standard error equal to the mean standard error of the other studies was considered. The pooled relative risks did not change considerably (Table 14).

In order to verify the stability of the results, a new analysis was carried out taking out the estimate from the cohort study (Veierød *et al.,* 2003). The pooled relative risk showed a wider confidence interval.

The definitions used to evaluate the risk for "first exposure before age 35 years" differed for two studies: one study presented an estimate of "ever" versus "never" for individuals aged ≤ 30 years (Westerdahl *et al.,* 1994); the other study (Veierød *et al.,* 2003) presented two estimates: "ever" versus "never" at age 10–19 years and "≥ 1 time/month" versus "never" at age 20–29 years. For the latter study, the estimate including a larger number of individuals (age group 20–29 years) was used for the main analysis of "first exposure before age 35 years" (only 4 cases were in the exposed group for the estimate at age 10–19 years). When both studies were excluded, the pooled estimate did not change considerably (Table 14).

For the evaluation of recent and distant exposures, Autier et al. (1994) reported estimates by several substrata; for the main analysis we selected the adjusted relative risk evaluating exposure for tanning purposes and for a duration of 10 hr or more. Crude relative risks obtained by merging all categories were: for "distant exposure", 1.22 (CI, 0.79–1.88) and for "recent exposure", 0.82 (CI, 0.56–1.19). Thus the pooled relative risk for "distant exposure" remained greater than that for "recent exposure" (data not shown).

Analysis by Funnel plot regression gave no indication of publication bias ("ever used sunbed/sunlamps", P = 0.80; "first exposure before age 35 years", P = 0.10). In addition, analysis by the Copas and Shi method of trends in the funnel plots (Figures 5 and 6) gave an indication of non-significant asymmetry ("ever used sunbed/sunlamps", P = 0.37; "first exposure before age 35 years", P = 0.15).

Discussion

To establish a causal link between exposure to tanning appliances and melanoma occurrence, studies should show whether there are dose–effect relationships and whether exposures distant in time are

Table 14. Sensitivity analysis

Parameter analysed	Inclusion criteria	Number of studies	Summary relative risk (95% CI)	P-value χ^2 Heterogeneity
Ever use of indoor tanning facility	Including study by Walter *et al.* (1990)	19	1.15 (1.00–1.32)	0.007
	Including all studies considered	23	1.14 (1.00–1.30)	0.045
	Excluding the cohort study by Veierød *et al.* (2003)	18	1.11 (0.97–1.26)	0.019
First exposure in youth	Excluding the cohort study by Veierød *et al.* (2003)	6	1.64 (1.22–2.20)	0.743
	Including only those studies with a specific definition of first exposure (studies by Veierød *et al.* 2003 and Westerdahl *et al.,* 2000 excluded)	5	1.65 (1.17–2.32)	0.709

more strongly associated with melanoma than are recent exposures. The latter point is important, as there is most probably a latency period between exposure and melanoma, thus the carcinogenic effect of more recent exposures would not yet be detectable. Also, since the fashion of using indoor tanning facilities has been increasing steadily, a lack of distinction between distant and recent exposures may mask an actual increase in risk.

Experimental and epidemiological studies provide evidence that susceptibility to UV radiation is greater at younger ages (mainly in childhood and adolescence) than at older ages (see page 8; Autier & Doré 1998; Whiteman *et al.,* 2001). Hence, data analysis should identify whether exposure to tanning appliances starting at younger ages was more strongly associated with melanoma than exposure starting at older ages.

The UV emission spectrum of UV lamps in indoor tanning appliances has changed over time: before 1980, many UV lamps produced large amounts of UVC and UVB, whereas most UV tanning appliances used after 1985 mainly emitted in the UVA range (see page 3).

(a) Case–control studies: Case–control studies of melanoma providing results on use of indoor tanning facilities have been of variable study design, and many of them only included one question on exposure to tanning appliances. Some positive or negative associations between exposure to tanning appliances and risk for melanoma may have been due to statistical fluctuations (i.e. alpha or beta errors) or to design effects.

In some studies, melanoma patients (i.e. cases) were derived from a small number of dermatologic clinics, and subjects without melanoma (i.e. controls) were derived from hospital wards or outpatient clinics. This way of selecting cases and controls is prone to many biases: for instance, control subjects could suffer from a disease associated with higher or lower propensity to engage in indoor or outdoor tanning.

Users of indoor tanning facilities have been shown to have a greater-than-average propensity to engage in intentional sun exposure (Autier *et al.,* 1991), and may have characteristics of inherited sun sensitivity different from the rest of the population (see page 9). Hence, a possible association between exposure to tanning

Figure 5. Investigation by Funnel plot representation of a possible publication bias in the studies of risk for melanoma associated with use of indoor tanning facilitites included in the meta-analysis

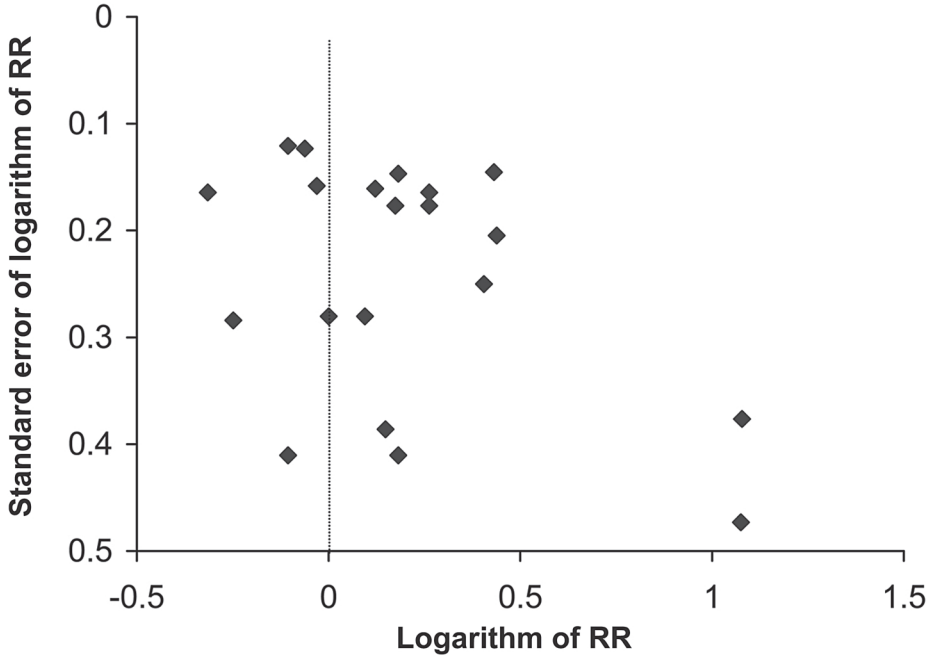
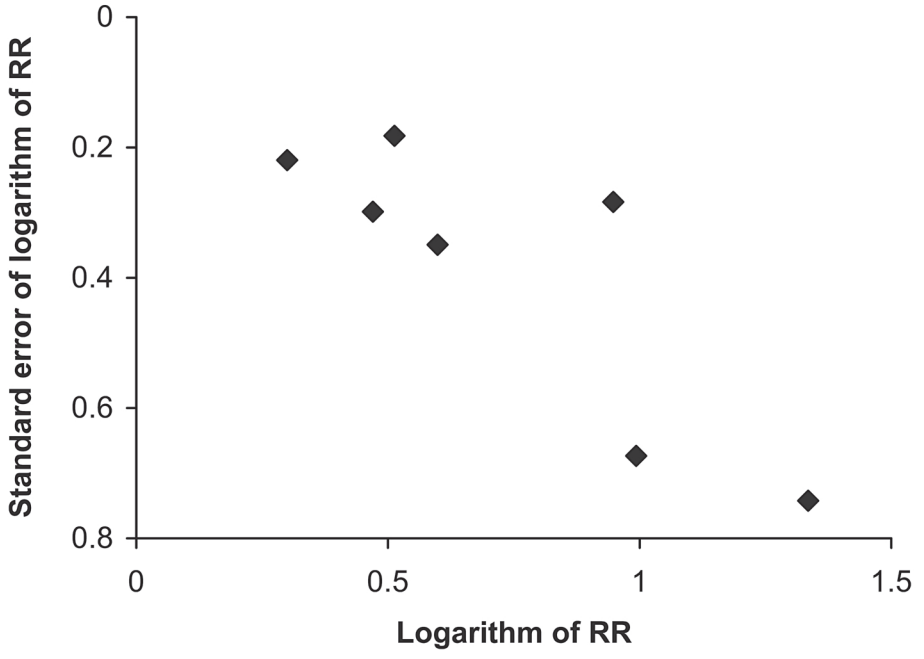


Figure 6. Investigation by Funnel plot representation of a possible publication bias in the studies of risk for melanoma associated with first use of indoor tanning facilities in youth



appliances and risk for melanoma could in fact be due to greater sun exposure than average, or to greater use of indoor tanning facilities by subjects naturally more prone to melanoma. To reduce the effect of these confounding factors on risk estimates, it was necessary to adopt statistical methods (e.g. a multivariate logistic regression model) allowing the calculation of estimated risks adjusted for both sun exposure history and host characteristics.

In order to examine the consistency of the data on exposure to tanning appliances and risk for melanoma provided by case–control studies, we selected those studies among the 19 studies included in the meta-analysis (see Tables 7 and 8) that had a section specifically exploring exposure to tanning appliances and results adjusted for (intermittent) sun exposure and sun sensitivity (Autier *et al.,* 1994; Westerdahl *et al.,* 1994; Chen *et al.,* 1998; Westerdahl *et al.,* 2000).

Table 15 presents adjusted relative risks for melanoma associated with exposure to tanning appliances, showing some statistically significant dose–effect relationship for two studies (Autier *et al.,* 1994; Westerdahl *et al.,* 1994), a borderline statistically significant dose–effect relationship in one study (Chen *et al.,* 1998), and one study with a non-significant dose–effect relationship (Westerdahl *et al.,* 2000).

Two of the four studies (Autier *et al.,* 1994; Chen *et al.,* 1998) showed that the highest risk for melanoma was associated with exposure to tanning appliances more distant in time (Table 10). Three studies (Westerdahl *et al.,* 1994; Chen *et al.,* 1998; Westerdahl *et al.,* 2000) showed that melanoma risk was highest when exposure to tanning appliances started at younger ages, i.e. before approximately 35 years old (Table 9). However, most associations with exposure distant in time and with younger age at start did not reach statistical significance because of the low number of subjects in the relevant categories of exposure. Statistical significance first emerged when all data were combined in a meta-analysis, resulting in a greater number of subjects in relevant categories of exposure and thus higher statistical power (see page 30).

(b) Prospective study: The Norwegian-Swedish study (Veierød *et al.,* 2003) is the only published prospective cohort study of environmental risk factors for melanoma. Women in Norway and Sweden (N=106 379) were followed for an average of 8.1 years from 1991 until 1999. The study showed consistent associations between host characteristics of inherited sun susceptibility, sunburn history, sun exposure, exposure to tanning appliances and cutaneous melanoma. During follow-up, 187 cases of melanoma were diagnosed. After adjustment for intermittent sun exposure and host characteristics, the adjusted relative risk for melanoma was 1.55 (CI, 1.04–2.32) among the 18% of women aged 10–39 years who reported having used sunbeds at least once a month when they were 10–19, 20–29 or 30–39 years old. Twelve sunbed sessions per year correspond to the typical tanning programme proposed by many commercial tanning facilities. Thus the 55% increase in melanoma risk was related to 40 hours or more of exposure to tanning appliances, assuming an average of 20 minutes per session. In that respect, the levels of exposure to tanning appliances reported in this prospective study were more comparable with levels reported in surveys carried out in European countries than those reported in case–control studies.

In the Scandinavian countries, use of indoor tanning facilities has been popular since the late 1970s, and the prevalence of use of indoor tanning facilities in those countries is the highest in the world. In the Norwegian-Swedish prospective study, the highest risk for melanoma was found in women who used indoor tanning facilities at least once per month when they were 20 to 29 years old (RR, 2.58; CI, 1.48–4.50), and the lowest risks were found for exposure to tanning appliances at least once a month during the third (RR, 1.42; CI, 0.93–2.16) or the fourth decade of life (RR, 1.67; CI, 0.93–2.99). These results support the hypothesis by which a latency period is needed before the impact of exposure to tanning appliances on melanoma incidence becomes apparent. It also underlines the greater vulnerability of younger subjects to harmful effects of sunbeds.

Table 15. Duration of exposure to indoor tanning facilities and risk for melanoma in selected case–control studies[1]

Reference Place & years of study Numbers of cases/control		Duration of exposure	Cases	Controls	Estimated risk	95% CI
Autier *et al.* (1994)		Never used	310	327	1.00	Ref.
Belgium, France, Germany,	Exposure starts	< 10 hours	36	45	0.75	0.46–1.25
1991–92	≥ 1980	≥ 10 hours	19	18	0.99	0.49–2.00
420/447[2]	Exposure starts	< 10 hours	16	15	1.00	0.47–2.13
	< 1980	≥ 10 hours	18	7	2.12	0.84–2.12
Westerdahl *et al.* (1994)		Never used	282	479	1.0	Ref.
Sweden, 1988-90		1–3 sessions/year	44	67	1.1	0.7–1.9
400/640		4–10 sessions/year	30	55	1.1	0.7–1.9
		>10 sessions/year	41	33	1.8	1.0–3.2
Chen *et al.* (1998)		Never used	483	417	1.00	Ref.
Connecticut, USA, 1987–89		< 10 sunlamp uses	76	50	1.25	0.84–1.84
624/512		≥ 10 sunlamp uses	63	40	1.15	0.60–2.20
Westerdahl *et al.* (2000)		Never used	319	538	1.0	Ref.
Sweden, 1995–97		1–125 uses	22	32	2.8	1.0–7.8
571/913		126–250 uses	34	31	3.1	1.3–7.1
		> 250 uses	31	37	1.5	0.7–3.2

[1] Duration of exposure, relative risk, and 95% confidences as in published reports. All estimated risks are adjusted for age, sex, natural sun sensitivity and recreational sun exposure.

[2] The 21 cases and 35 controls who were exposed to sunlamp or sunbed for non-tanning purposes are not reported in this Table.

(c) Methodological aspects of case–control and prospective cohort studies: Case–control studies are prone to two biases inherent in the design. First, since data are collected retrospectively (when cases already know they have a melanoma), the associations found could be the result of recall bias, as melanoma patients might have been more likely to remember past exposures to artificial UV sources (Walter *et al.,* 1990). Second, the selection of controls may have included subjects more (or less) inclined to have had more frequent exposure to tanning appliances than average (selection bias).

Among the four case–control studies selected in Section (a) of this section, three studies (Autier *et al.,* 1994; Westerdahl *et al.,* 1994, 2000) used measures to control for recall bias. Autier *et al.* (1994) focused on recall bias in the training of the interviewers: neither interviewers nor subjects were informed of the study's objective. Westerdahl *et al.* (1994) used a questionnaire with many variables and stated that at the time of the interview (1988 to 1990), the population was unaware of the relationship between exposure to artificial UV radiation for tanning purposes and malignant melanoma. Westerdahl *et al.* (2000) used identical procedures of data collection for cases and controls, and collected information from melanoma patients shortly after diagnosis.

Selection bias of controls was not likely to have occurred in any of the four selected case–control studies: three studies (Westerdahl *et al.,* 1994, 2000; Chen *et al.,* 1998) were based on population-based melanoma registries and sampling of control subjects. The study by Autier *et al.* (1994) selected cases from multiple sources (hospital, clinics and melanoma registries), and controls were chosen in the neighbourhood of cases according to rigorous contact procedures (Grimes & Schulz, 2005).

The prospective cohort study assessed exposure to tanning appliances retrospectively

but before diagnosis of melanoma. Thus, this study was less prone to interview and selection biases at the inception of the cohort.

Taken together, the four case–control studies selected and the prospective study offer the conclusion that the increased melanoma risk was associated with exposure to tanning appliances (mainly when exposure started before the age of approximately 35 years) and the observed positive associations are not entirely due to recall or selection biases.

(d) Type of artificial UV light: Only one study (Chen *et al.,* 1998) collected information concerning the type of appliance used by showing subjects pictures of various types of indoor tanning appliances (e.g. desktop models, floor models, beds, walk-in booths). The study found a non-significant elevated risk for melanoma associated with the use of desktop sunlamps and heavyweight floor-model sunbeds and a statistically significant tripled risk associated with use of more than two types of sunlamps, compared with no use of sunlamps.

Before 1980, exposure to artificial UV radiation was more likely to take place at home with appliances that emitted large amounts of UVB radiation, whereas exposure in the 1980s increasingly occurred in commercial salons using appliances that emitted mainly UVA. The prospective study provided evidence that the increased melanoma risk associated with exposure to tanning appliances was not due to the type of UV lamps used before 1983 (Veierød *et al.,* 2004).

Basal cell and squamous cell carcinomas

Description of studies

Nine case–control studies have addressed the possible association of artificial UV exposure with either BCC or SCC of the skin. All studies reported a risk estimate, except one (Boyd *et al.,* 2002), which was therefore excluded. A further three studies that did not distinguish between these two major types of skin cancer (O'Loughlin *et al.,* 1985; Herity *et al.,* 1989; Hogan *et al.,* 1991) were also excluded from review because BCCs and SCCs have different aetiologies, thus leaving five studies under consideration (Table 16).

Aubry & MacGibbon (1985): The earliest case–control study that addressed the possible

Table 16. Characteristics of case–control studies included in the meta-analysis on non-melanoma skin cancers

Reference	Country	Number of cases	Number of controls	Source	
				Cases	Controls
Aubry & McGibbon (1985)	Canada	SCC: 92	174	Hospital	Hospital
Bajdik *et al.* (1996)	Canada	BCC: 226 SCC: 180	404	Cancer registry	Population, health insurance
Corona *et al.* (2001)	Italy	BCC: 166	158	Hospital	Hospital
Karagas *et al*. (2002)	USA	BCC: 601 SCC: 292	539	Dermatology department	Population, Dept. of Transportation, Medicare
Walther *et al.* (2004)	Germany	BCC: 213	411	Hospital	Hospital

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

association of artificial UV exposure and squamous cell carcinoma was conducted in Montreal, Canada. Its overall aim was to assess risk factors for SCC of the skin with a particular focus on potential carcinogenic occupational exposures. Eligible cases were histologically diagnosed with primary invasive cutaneous SCC in 1977–78 in 12 hospitals in the Montreal region; 2 controls per case with no known history of skin cancer, matched for sex, age and hospital of case diagnosis, were selected from those diagnosed in the same period with specified dermatologic conditions. Data on standard risk factors for skin cancer were collected including skin type, occupational and nonoccupational sun exposure as well as ever-use of long- and round-tube sunlamps. The final study population, aged 65 years on average, comprised 30% of all eligible patients. There were 92 SCC cases, 4 of whom reported any exposure to a long-tube sunlamp, and 174 dermatological controls, one of whom was so exposed, giving an odds ratio of 13.4 after adjusting for age, sex, eye and hair colour, ethnicity, and nonoccupational sun exposure ($p < 0.008$). (Round-tube sunlamp results were not reported.) [This study was conducted almost 30 years ago among elderly people; the Working Group noted major drawbacks, including a hospital-based study population, controls with skin conditions and a very low response rate. The risk estimates were based on a single exposed control, and no details of artificial UV exposure were obtained.]

Bajdik et al. (1996): Another study carried out in Canada that aimed to assess phenotypic, solar and non-solar risk factors for BCC and SCC of the skin in men in the province of Alberta also asked about exposure to non-solar UV light. Cases were men with a first BCC or SCC histologically diagnosed in 1983–84 and ascertained through the Alberta Cancer Registry. Controls were matched for age within 2 years from the Alberta health insurance plan subscriber list. Through personal interviews, information about non-solar UV exposure such as exposure to welding torches, UV lights and sunlamps was obtained, as well as standard risk factors. Results were based on 226 BCC cases (72% of those ascertained), 180 SCC cases (80%), and 406 eligible controls (71%). Ever-use of a sunlamp was reported by 8% of controls (33 of 404) and 9% of BCC cases (23 of 226), giving an odds ratio of 1.2 (CI, 0.7–2.2); ever-use was reported by 10% of SCC cases (18 of 180), with odds ratio of 1.4 (CI, 0.7–2.7). Risk estimates were adjusted for age, skin and hair colour, ethnicity and lifetime occupational sun exposure. [While this study was population-based, it was conducted 20 years ago, was restricted to men of unreported but likely older ages, and no details of artificial UV exposure were available.]

Corona et al. (2001): A more recently conducted hospital-based case–control study of causes of BCC in Italy assessed non-solar factors as well as phenotypic and solar factors. Cases of histologically-confirmed BCCs diagnosed in 1995–1997 were ascertained on random days of the week through a hospital for skin diseases in Rome. Controls diagnosed with minor skin disorders (e.g. warts, naevi) were drawn from the same hospital but excluded if they had a history of skin cancer or UV therapy. Questionnaire data collected face-to-face included artificial UV exposure as well as standard risk factors regarding phenotype and patterns of sun exposure. Ever-use of a sunbed or sunlamp was reported by 20% of controls (31 of 158) and 11% of BCC cases (17 of 166). After adjustment for age, sex, family history of skin cancer, outdoor work and beach exposure in youth, the relative risk estimate for BCC was 0.6 (CI, 0.3–1.2). [This study, carried out 10 years ago, had major shortcomings through its design, namely a convenience sampling frame of adult dermatologic patients. No details of exposure to tanning appliances were obtained.]

Karagas et al. (2002): A case–control study conducted in the USA among New Hampshire residents assessed risk for BCC and SCC in relation to exposure to artificial UV tanning appliances, among other factors. Cases of skin cancer diagnosed in 1993–1995 were ascertained through a network of dermatologists and pathology laboratories. Controls were a frequency-matched sample of residents drawn from the Department of Transportation listing (< 65 yrs) or Medicare program list (> 65 yrs). Sunlamp/tanning bed use

and age at first and last use as well as standard skin-cancer risk factor data were obtained through personal interviews. The study population comprised 603 BCC cases and 293 SCC cases (78% of those eligible) and 540 (60%) eligible controls. Fourteen percent of controls (75 of 539), 21% (127 of 601) of BCC cases and 22% (63 of 229) of SCC cases reported any exposure to tanning appliances. After adjustment for age, sex and sun sensitivity, risk estimates associated with ever-use of a sunlamp in relation to BCC were 1.5 (CI, 1.1–2.1) and to SCC, 2.5 (1.7–3.8), and were similar in men and women. There was a non-significant trend toward increased risk with younger age at first use for SCC. Risks were increased for both BCC (OR, 1.6; CI, 1.1–2.3) and SCC (OR, 2.9; CI, 1.8–4.7) for first use more than 20 years previous to enrolment (before 1975). [The strengths of this study conducted 10 years ago were its population-based design and its availability of some quantitative data regarding sunlamp use. It lacked power to explore the associations with age at first use versus years since first exposure, and no data were available about frequency of use.]

Walther et al. (2004): The most recently published study of the association of artificial UV radiation and BCC was conducted in Germany, based on 213 patients with BCC diagnosed in the previous 5 years and 411 controls from the same dermatology department as the cases or the general surgery department of the same hospitals. During an interview patients were asked about number of times a year they used indoor tanning facilities. On crude analysis there was no association between recent history of BCC and use of indoor tanning facilities more than 5 times a year (OR, 0.7; CI, 0.3–1.5).

Meta-analysis

The meta-analysis was based on the five studies reporting type-specific risk estimates (Table 17). Chi-squared test and random effect models were used to assess heterogeneity, as described on page 26. Pooled relative risks suggested a significant effect of exposure to indoor tanning facilities for SCC, but not for BCC (Table 18).

The effect estimate seen for BCC was not much influenced by the estimate reported by Corona *et al.* (2001), which indicated a protective effect of artificial UV radiation for BCC (the weight of this study was the lowest [w = 8.0]). As above, this study was not specifically designed to investigate exposure to artificial UV radiation, thus radiation exposure data were not detailed. Excluding this publication from the analysis changed the pooled relative risk for BCC, although not substantially (pooled RR, 1.39; CI, 0.14–13.51).

Regarding SCC as an outcome, the study by Aubry & MacGibbon (1985) reported findings for only one type of sunlamp (long-tube type) and was hospital-based. The weight of this study was the lowest of this group (w=0.74); nevertheless, the pooled relative risk for SCC excluding this study was neither stronger not more significant (pooled RR, 2.16; CI, 0.24–19.53).

Funnel plot regression gave indication of no publication bias (P=0.77 and 0.26 for BCC and SCC, respectively) but results based on so few estimates are not reliable.

The study by Karagas *et al*. (2002) gave the most detailed results and the trends were consistent with the results reported for melanoma. The weight of this study was the highest (w = 23.8 for SCC and w = 36.8 for BCC) and therefore its results were the most influential.

Quality of studies

Only one case–control study (Karagas *et al.,* 2002) had a section designed specifically to explore sunlamp/sunbed use in more detail than never/ever use. Results were adjusted for sun sensitivity but not for sun exposure since adjustment for sun exposure did not change the risk estimates. Study participants who reported using sunlamps or sunbeds were more likely to be women, to be aged under 50 years, to have sun-sensitive skin, more painful sunburns and a history of frequent sunbathing (> 4 times per year) than non-users. Based on age at first use, the relative risks for BCC and SCC were found to increase by 10% (OR, 1.1; CI, 0.9–1.5) and 20% (OR, 1.2; CI, 0.9–1.6) respectively, for each decade younger the person was at first use of an indoor tanning facility. The effects of age at first use could

Table 17. Estimates included in the evaluation of an association of ever use of indoor tanning facilities and risk for non-melanoma skin cancers

Reference	Exposure	Diagnosis	Relative risk (95% CI)	Adjustment
Aubry & McGibbon (1985)	Long-tube sunlamp use	SCC	13.4 (1.4–130.5)	Age, sex, eye and hair colour, ethnicity, non-occupational sun exposure
Bajdik *et al.* (1996)	Ever use of sun-lamps	BCC SCC	1.2 (0.7–2.2) 1.4 (0.7–2.7)	Age, ethnic origin, skin and hair colour, occupational sun exposure
Corona *et al.* (2001)	Sun bed or sun-lamp use	BCC	0.6 (0.3–1.2)	Age, sex, pigmentary traits, family history skin cancer, outdoor work, number of weeks spent at beach before age 20 years
Karagas *et al.* (2002)	Any tanning device use	BCC SCC	1.5 (1.1–2.1) 2.5 (1.7–3.8)	Age, sex, sun sensitivity
Walther *et al.* (2004)	Exposure ≥ 5 times/year to artificial UV radiation/-UV sunbeds	BCC	0.7 (0.3–1.5)	Crude

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

not be distinguished from years since first use because of the relatively small number of cases in the study, and there were no semi-quantitative measurements of artificial UV exposure (e.g. number of sessions per month, duration of use).

Other sources of exposure to artificial UV radiation

Medical Use

Light treatment has been used for a large number of medical conditions (see page 4), most particularly for psoriasis.

(a) PUVA therapy in psoriasis patients: Most long-term studies looking at risk for skin cancer resulting from exposure to UV treatment collected data from a significant number of psoriasis patients treated with PUVA (see page 4 (b)). There is clear evidence that PUVA increases the risk for SCC with a relatively short latency period, although it is difficult to distinguish the contribution of PUVA from other factors, given that treated patients have usually received multiple carcinogenic treatments. For example, SCC in psoriatic patients treated with PUVA commonly have UV signature mutations rather than PUVA signature mutations (Kreimer-Erlacher *et al.,* 2003), suggesting that PUVA may act as a promoter rather than an initiator.

Two large cohorts of psoriasis patients have been followed up since the 1970s: one of 4799 patients in Sweden (Lindelof *et al.,* 1999) and another of 1380 patients in the USA (Stern, 2001). In the Swedish cohort the relative risk for SCC was 5.6 in men (CI, 4.4–7.1) and 3.6 in women (CI, 2.1–5.8). In the cohort in the USA, one fourth of patients who received more than 2000 J/cm^2 developed an SCC (Stern & Laird,

Table 18. Meta-analysis of studies of exposure to artificial UV radiation and risk for non-melanoma skin cancers

Diagnosis	Number of studies	Summary relative risk (95% CI)	P-value χ^2 Heterogeneity
SCC	3	2.25 (1.08–4.70)	0.10
BCC	4	1.03 (0.56–1.90)	0.06

BCC, basal cell carcinoma; SCC, squamous cell carcinoma

1994). The same authors subsequently carried out a meta-analysis of their own data and all published studies with more than 150 patients (Stern & Lunder, 1998), and found that patients exposed to high doses of PUVA (more than 200 treatments or more than 2000 J/cm^2) had a 14-fold higher risk for SCC than those with <100 treatments or <1000 J/cm^2 exposure. The risk is further increased when the patients have also received methotrexate at some time (Stern & Laird, 1994) and is greater still with the use of cyclosporine (Marcil & Stern, 2001). There is no evidence to date that bath PUVA increases the risk for SCC (Hannuksela-Svahn *et al.,* 1999) but the data available relate to only 944 patients who received relatively low total PUVA doses.

The risk for melanoma after PUVA treatment is more controversial. In the cohort in the USA, discussed above, an increased risk for melanoma has been reported (Stern, 2001). Of the 822 participants with long-term follow-up, 44% had at least 200 PUVA treatments and therefore are called high exposure patients. Sixteen of the 1380 patients developed an invasive melanoma and 6 developed a melanoma in situ. The authors reported a 10-fold increase in the incidence of invasive melanoma compared with population rates in the 27 months prior to publication of the article. Within the cohort, the risk for melanoma was greater in those with fair skin (Fitzpatrick skin type) and those who received high doses of PUVA (incidence rate ratio, 2.6; CI, 1.0–6.6) for more than 200 treatments compared with less than 200. The risk also appeared to have a long latency in that an elevation in risk appeared only after 15 years. There did not appear to be any increased risk in patients who were also treated with ionizing radiation or methotrexate.

The Swedish cohort (Lindelof *et al.,* 1999) reported no increased risk for melanoma. This study was much larger than the study in the USA and the patients were tracked using the Swedish Cancer Registry, thereby allowing "complete" follow-up. Of the 2343 men in the cohort, 8 developed a melanoma compared with the 7.3 expected, and of the 2456 women, 7 developed a melanoma compared with the 6.3 expected. The length of follow-up was impressive in this cohort, as the average length was 16 years and 1038 patients had been followed for more than 19 years.

Given the considerable size and the duration of follow-up of the Swedish cohort, the findings from this cohort are the more persuasive of the two studies. The difference in findings, however, remains unexplained. In the Swedish cohort a proportion of patients had had bath PUVA, which tends to be associated with lower UVA doses. There were differences in the treatment protocols as well (Honigsmann, 2001), in that in Europe schedules are individualized after light testing, more commonly resulting in reduced time to clearing and lower doses per treatment course. These differences may explain the discrepant risk estimates, but it cannot be excluded that the data from the study in the USA are subject to bias, not least because follow-up was substantially incomplete.

Overall, there is a postive association between PUVA and risk for SCC and there appears to be a dose–response effect. The risk was greater for fair-skinned people. The risk for melanoma is much less clear, even in fair-skinned populations. The positive dose-response relationship in the study in the USA supports the interpretation that the association is causal. It seems likely, however, that the risk is associated with high doses of PUVA, is relatively small and is observed after a long latency.

The data from PUVA studies are important in that they include large numbers of people who were studied prospectively. They cannot however be extrapolated to exposure to tanning appliances because of the presence of psoralen. Furthermore, the total UV dose received by psoriasis patients is considerably less than that received by long-term users of indoor tanning facilities.

(b) Broadband and narrow-band UVB in psoriasis patients: The evidence relating to long-term risk for skin cancer after UVB therapy is scanty. In the PUVA cohort study from the United States, there was no discernible additional effect of exposure to UVB (Stern & Laird, 1994). In a study of psoriatics treated with coal tar and UVB in the 1950s followed up for 25 years, there was no demonstrable increased risk for skin cancer, though the numbers treated were relatively small (n = 280) (Pittelkow *et al.,* 1981). In a small study of 195 German psoriatics treated with broadband (n = 69) or narrow-band UVB (n =126) from 1994 to 2000 only one skin cancer had occurred by 2004. This was an in-situ melanoma which developed in the same year that narrow-band UVB therapy was begun (Weischer *et al.,* 2004). Though these data are reassuring they cannot exclude a small increased risk nor a large increased risk in patients treated with high doses.

(c) UV treatment of other skin diseases: The immunomodulatory effects of UV radiation are utilized in the treatment of a variety of skin diseases other than psoriasis. Many of the patients treated are at increased risk for skin cancer even without PUVA because of the nature of their dermatosis (e.g. vitiligo). Others are at further increased risk because of immunosuppression which may both characterize the skin disease and its treatment, such as graft versus host disease (GVHD) (Furlong *et al.,* 2002) or cutaneous T-cell lymphoma.

A series of 103 patients with steroid-resistant GVHD treated with PUVA received a mean dose of 41 J/cm^2 between 1994 and 2000. Only one SCC has developed in this cohort to date (Furlong *et al.,* 2002).

PUVA is also very useful, although not curative, in the treatment of cutaneous T cell lymphoma (CTCL) when it is commonly used as part of multi-modality treatment programmes with other drugs contributing to risk such as cytotoxics (McGinnis *et al.,* 2003). Narrow-band UVB has been reported to be as effective as PUVA in the treatment of early CTCL in one retrospective study (Diederen *et al.,* 2003). There is no doubt that in this patient population there was an increased risk for SCC but it is difficult to apportion risk to PUVA. The risk for melanoma was reported in a very small series of patients and therefore cannot be assessed (McGinnis *et al.,* 2003).

Lighting

(a) Fluorescent tubes: Household lights emit significant amounts of UV radiation (Sayre *et al.,* 2004) and several case–control studies have addressed risk for melanoma associated with such exposure. The earliest study suggested an elevated risk associated with exposure to fluorescent lights at work (Beral *et al.,* 1982) but all subsequent studies failed to identify such a risk (Rigel *et al.,* 1983; Osterlind *et al.,* 1988; Walter *et al.,* 1992; Holly *et al.,* 1995).

(*b) Full spectrum lamps:* No data were available to the Working Group regarding exposure to full-spectrum lamps intended for domestic and public use and risk for skin cancer.

Effects of artificial UV radiation not relevant to skin carcinogenesis

Cutaneous diseases

Skin ageing

Skin ageing is a phenomenon comprising intrinsic processes that are largely genetically determined and extrinsic ageing (or photo-ageing) that is largely related to sun exposure (Jenkins, 2002). Both UVB (Del Bino *et al.,* 2004) and UVA (Marrot *et al.,* 2004) are held to be mediators of these effects. Intrinsic ageing is characterized by thinning of the skin accompanied by reduction in collagen levels. These changes are thought to result at least in part from diminished cellular proliferative activity in the skin (inevitable cellular senescence) and from increased expression of enzymes that degrade the collagen, such as the metallo-proteinases (Jenkins, 2002). The process is undoubtedly complex, and one of the drives to cellular senescence may be chronic exposure to oxidative stress.

The changes resulting from sun exposure that are perceived as ageing are loss of elasticity, pigmentary change and deep wrinkling (Leyden, 1990). Most of these changes result from damage to the dermis, which is visible histologically as elastotic material. This material is comprised of degenerate elastic fibres and newly synthesized dysfunctional elastotic material. Similarly there appears to be a reduced amount of collagen I in the dermis and increased amounts of degenerate collagen. The metallo-proteinases mediate this degradation, at least in part, and their activity appears to be increased both by age and by sun exposure. Increased age is associated with a diminished ability to repair damage induced by exposure to UV radiation (Takahashi *et al.,* 2005).

Comparatively few epidemiological studies have addressed photo-ageing of the skin, not least because of the difficulties of measuring it accurately. Some authors have suggested that ultrasound measurement is of value (Gniadecka & Jemec, 1998); others have used silicone (Green, 1991; Fritschi *et al.,* 1995) to create moulds to allow an estimate of the topography of the skin, a method which appears to be better evaluated. A large study performed in Queensland, Australia demonstrated premature ageing of the skin in a population excessively exposed to the sun (Green, 1991). This was more marked in men who reported outdoor work or leisure, and especially those with fair skin. The presence of photo-ageing was correlated with skin cancer. The relationship between non-melanoma skin cancer and solar keratoses is held to be clear and straightforward (Green *et al.,* 1999). Experimental studies on UV exposure and photo-ageing have been reviewed (IARC, 1992).

Very few studies have investigated the relationship of artificial UV exposure to ageing in humans. Lentigos similar to PUVA freckles have been reported to be induced by exposure to tanning appliances (Roth *et al.,* 1989; Kadunce *et al.,* 1990), which is of concern given the evidence that the risk for skin cancer is increased in PUVA patients. A number of case reports have described an extreme form of cutaneous ageing which resulted from very frequent exposure to tanning appliances in fair-skinned people (Poh-Fitzpatrick & Ellis, 1989). There have been no informative epidemiological studies of the role of indoor tanning facilities in the induction of photo-ageing.

There is some evidence that cigarette smoke exacerbates photo-ageing of the skin (IARC, 2004; Placzek *et al.,* 2004).

Other skin diseases caused or exacerbated by exposure to UV radiation

A wide variety of dermatoses are exacerbated by sun exposure, such as atopic eczema or psoriasis if sunburn occurs. Some skin diseases are directly provoked by sun exposure, the most common of which is polymorphic light eruption, which is common in women. It has been reported in around 20% of healthy women (Millard *et al.,*

2000). Variants occur, such as a blistering eruption seen on the ears in childhood or actinic prurigo, where itchy papules and nodules develop after sun exposure. Such photodermatoses are a nuisance but otherwise relatively trivial problem. Exposure to tanning appliances may precipitate such dermatoses (O'Toole & Barnes, 1995). Medical use of artificial UV radiation may be used to control polymorphic light eruption if used carefully as a means of desensitization.

Photosensitivity is usual in patients with lupus even in the absence of a history of a sun-evoked eruption (Sanders *et al.,* 2003), and light testing reveals that the majority of patients react to both UVA and UVB (Sanders *et al.,* 2003). The cutaneous manifestations of lupus are also commonly precipitated by exposure to the sun. Phototesting with artificial UV radiation sources has been reported to provoke cutaneous lupus (Marguery *et al.,* 2005), and therefore it seems likely that it may also be provoked by other sources of artificial radiation such as tanning appliances.

More significant photodermatoses occur more rarely, such as chronic actinic dermatosis, in which persistent sun-induced eczema occurs. It is a rare condition, usually seen in elderly men. It may develop from an allergic dermatitis for example to pollen or fragrances.

Much more significant are the porphyrias in which sun exposure may trigger photosensitivity. The varieties that induce photosensitivity are variegate porphyria (Mustajoki, 1980) (most common in South Africans of Dutch descent), erythropoietic porphyria (Goerz, 1979) and porphyria cutanea tarda (PCT). PCT is the most common and in 80% of cases occurs because of exposure to estrogens or alcohol. Use of indoor tanning facilities or other artificial UV sources — even fluorescent lights — by patients with latent porphyria is potentially very serious as a result of the possible induction of sunburn.

The overall dose of UVB and UVA incurred by most people using bright light therapy is likely to be considerably less than that received by psoriasis patients treated with PUVA. Exposure is also likely to be limited to the face. It seems likely therefore that the theoretical risk will relate to non-melanoma skin cancer rather than melanoma, but there are no relevant data from epidemiological studies at present to inform. It would seem very reasonable however to conclude that lamps emitting low levels of UVA would be preferred to those emitting higher levels.

Case reports also suggest that use of indoor tanning facilities is associated with development of drug-induced photodermatoses and exacerbation of lupus erythematosus (Spencer & Amonette, 1995).

Drug-induced photosensitivity

A variety of commonly used drugs increase cutaneous sensitivity to the sun and to artificial UV sources, and are predicted therefore to increase the risk for skin cancer. Most drugs have a phototoxic effect rather than a photo-allergenic one (Moore, 2002). Oral photosensitisers include tetracyclines, amioderone, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) and chlorpromazine (Moore, 2002). Diuretics, antibiotics and NSAIDs are very widely used drugs, and their phototoxic effects therefore have the potential to affect a significant proportion of the population. Topical agents include plant-derived photosensitisers (psoralens) such as bergamot, widely used in perfumed products. Use of perfumes has the potential to increase the photo-damaging effects of indoor tanning appliances.

Effects on the eyes

Cataract

Conditions linked to sub-chronic and chronic exposure to solar UV include pterygium and SCC affecting the cornea; cataract, affecting the ocular lens; and acute macular degeneration affecting the retina (Tomany *et al.,* 2004). Of these, cataracts of the nuclear and cortical types are the most widespread and serious UV-related eye conditions. There is an inverse association between latitude of residence and cataract surgery in Medicare program data from the USA (Javitt & Taylor, 1994), and epidemiological studies conducted in Australia, China, and the USA (see Taylor, 1994, for review) support a role of UV exposure in cataract development. Risk for

cortical cataract (opacity of the outer lens) is related to increasing cumulative UVB exposure, while risk for nuclear cataract (opacity of the central lens) has been shown to be significantly increased with increasing UV exposure in young adulthood, consistent with the successive laying down with age of outer lens fibres on the cortical layer exposed in earlier life (Neale *et al.,* 2003). With regard to artificial UVB, there is sufficient experimental evidence that exposure causes cortical lens opacity in the eyes of laboratory animals (IPCS, 1994).

Intraocular melanoma

Early-life exposure to sunlight may be important in the development of intraocular melanoma (Tucker *et al.,* 1985; Seddon *et al.,* 1990), more specifically of choroidal melanoma (Moy, 2001). This is consistent with the observation that after childhood most UV radiation is screened by the lens (Zigman, 1983; Lerman, 1984).

Welding equipment and tanning appliances are sources of intense UV radiation. Five out of eight epidemiologic studies found a significantly increased risk for ocular melanoma with welding exposure, with relative risks ranging from 1.9 to 10.9 (Tucker *et al.,* 1985; Holly *et al.,* 1990; Seddon *et al.,* 1990; Siemiatycki, 1991; Ajani *et al.,* 1992; Holly *et al.,* 1996; Guenel *et al.,* 2001); in contrast, one study conducted in nine European countries found an increased risk only in one country (Lutz *et al.,* 2005).

Four case–control studies have examined the risk for intraocular melanoma in relation to exposure to UV radiation from sunlamps (Table 19). While the earliest study only found a non-significant trend in risk according to frequency of sunlamp use (Tucker *et al.,* 1985), the three more recent studies consistently found an increased relative risk, ranging from 1.7 to 3.6 (Holly *et al.,* 1990; Seddon *et al.,* 1990; Vajdic *et al.,* 2004).

UV exposure and vitamin D

Vitamin D is an essential nutrient, generally quantified by measuring circulating levels of 25-hydroxyvitamin D. There are three major sources of vitamin D: photosynthesis in the skin, ingestion in the diet and oral supplementation. Worldwide, photosynthesis from sunlight is the most common source of vitamin D.

Vitamin D formation by photosynthesis

Previtamin D3 is produced from 7-dehydroxycholesterol (provitamin D_3) by the direct photolytic action of UVB. The precursor, 7-dehydroxycholesterol, is abundant in human skin although levels decrease with age (Holick *et al.,* 1989). On exposure of the skin to sunlight, 7-dehydroxycholesterol in epidermal and dermal cells absorbs UVB radiation to form previtamin D_3. Previtamin D_3 is thermodynamically unstable and is rapidly transformed by rearrangement of its double bonds to form vitamin D_3 (here called vitamin D) before entering the circulation. Vitamin D is a prohormone that is converted by 25-hydroxylation in the liver to the intermediate metabolite 25-hydroxyvitamin D, which is the main circulating and storage form. With physiological demands for calcium and phosphorus, 25-hydroxyvitamin D undergoes 1α-hydroxylation in the kidney to form the active hormone, 1,25-dihyroxyvitamin D. Blood levels of 25-hydroxyvitamin D reflect the availability of vitamin D (Osborne & Hutchinson, 2002).

Main target organs for 1,25-dihydroxyvitamin D include the intestine, kidney and bone, but nuclear receptors have been found in over 30 different tissues, reflecting its many other actions besides parathyroid activity and serum calcium homeostasis, analogous to those of classical steroid hormones. 1,25-dihydroxyvitamin D is also an antiproliferative, prodifferentiation and proapoptotic agent (Osborne & Hutchinson, 2002).

Dietary sources of vitamin D

There are only a few foods (cod liver oil, oily fish such as salmon, mackerel and sardines) that are naturally rich in vitamin D, so in many countries where oily fish are not widely consumed, food fortification or vitamin supplements may be needed. In a global review of vitamin D intake, wide variations were found in food fortification practices and contributions from supplement use

Table 19. Case–control studies of exposure to artificial UV radiation and risk for intraocular melanoma

Reference	Location, Period of Recruitment	Cases and Controls	Age (years)	Adjusted Relative Risk	Characteristics Assessed	Comments
Tucker *et al.* (1985)	Philadelphia, PA, USA, January 1974–June 1979	444 intraocular melanoma (1 hospital) 424 hospital controls with detached retina, matched on age, sex and period of diagnosis	NR	1.4 (0.9–2.2); with cataract: 2.3 (0.9–5.9) without cataract: 1.2 (0.7–2.0)	Eye colour, complexion and hair colour, corrective lenses, sun exposure during leisure time, sun protection, years lived in the South	Telephone interview (45 min.); estimates adjusted for history of cataract; sunlight exposure is an important risk factor for intraocular melanoma (persons born in the South: RR 2.7 (1.3–5.9). Trend in RR according to frequency of sunlamp use rising to twofold for frequent use (P=0.10)
Holly *et al.* (1990)	11 Western States, USA, January 1978–February 1987	407 cases (Ocular Oncology Unit, UCSF); 870 controls (random digit dialling in the same geographic area as the patients), 2 age/sex matched controls per patient	20–74	Exposure to UV or blacklight: 3.59 (1.57–8.70) Welding burn, sunburn to eye, snow blindness: 7.17 (2.5–20.57)	Eye and hair colour, naevi, freckles, tendency to sunburn, other eye conditions, tobacco, coffee, tea, alcohol	Telephone interview; adjustment on eye colour, coffee, effect of 0.5 h exposure to midday summer sun, other UV exposure.
Seddon *et al.* (1990)	New England, USA all USA	197 cases 385 matched population controls (random digit dialling) 337 cases; 800 sibling controls	17–88	Use of sunlamps: 3.4 (1.1–10.3); with random digit dialled controls 2.3 (1.2–4.3) with sibling controls	Ancestry from Northern or Southern latitudes, latitude of residence, skin colour, naevi	Only choroid and ciliary body melanomas. 2 independent comparisons. Occasional or frequent versus never use.
Vajdic *et al.* (2004)	Australia, 1996 –1998	290 cases (246 with melanoma of choroid or ciliary body); 893 population controls (electoral rolls)	19–79	Use of sunlamps: 1.7 (1.0–2.8) Welding: 1.2 (0.8–1.7)	Eye colour, host characteristics, lifetime residence, work calendar, sun exposure, sun protective wear	Population-based prospective recruitment of cases (all ophthalmologists and cancer registries). Telephone interview. Risk increases with increasing duration of use and is greater for exposures begun before the age of 21 years and after 1980. Sunlamp use or welding not associated with iris or conjunctival melanoma.

NR, not reported.

(Calvo *et al.,* 2005). In Canada and the USA, where fortification is mandatory for staple foods such as milk and margarine and optional for other classes of food, vitamin D intake was generally 2–3 μg higher than in either Australia, Ireland, Scotland or the United Kingdom where fortification of staples like margarine and breakfast cereals is optional, or European and other countries where food fortification is restricted. Mean daily vitamin D intakes were reported to be highest in young adult Caucasian men and women in North America (8.1 and 7.3 μg/d) due to milk fortification and in Japanese women (7.1 μg/d) due to high fish consumption. Norwegian men and women, who also have high fish consumption, had higher levels (6.8 and 5.9 mg/d) than their British counterparts (4.2 and 3.7 μg/d). Contributions by dietary supplements to mean daily vitamin D intakes ranged from 49% in Norwegian women to 12% in British men, and on average contributions from supplements increased with age and were more common in women (Calvo *et al.,* 2005).

Vitamin D and exposure to artificial UV radiation for tanning purposes

Available data are inadequate to assess the effect of exposure to UV in indoor tanning facilities on vitamin D status. Our current understanding of the photosynthesis of vitamin D in the skin would suggest that this type of artificial UV exposure would be effective in induction of vitamin D photosynthesis only to the extent that it contains UVB, as opposed to UVA radiation. Practically speaking, the usefulness of these facilities for correcting vitamin D insufficiency is limited by the inability of consumers to ascertain the UVB flux to which they are being exposed in a tanning session, the expense and inconvenience of these sessions compared with oral vitamin D supplementation, and the other health consequences of using these facilities, as outlined in the other chapters of this document.

The nature of the network of photo- and thermoreactions that are involved in vitamin D synthesis in vitro is well established. As measured in vitro the greatest sensitivity of the conversion of 7-dehydroxycholesterol to previtamin D lies in the UVB part of the solar spectrum, 280–320 nm. It is therefore similar to the erythema action spectrum, except for a sharper downturn in provitamin D absorptivity in the UVA spectral region from a maximum at 282 nm (Galkin & Terenetskaya, 1999).

Seasonal and latitude variations in UVB intensity markedly affect vitamin D synthesis, with lowest relative production occurring at high latitudes during winter months. Also, ageing decreases the capacity of skin to produce vitamin D (Holick *et al.,* 1989). Finally, compared with fair-skinned people, those with darkly pigmented skin are less efficient at producing vitamin D and require 10–50 times the level of sun exposure to produce the same amount (Clemens *et al.,* 1982). In addition to season, latitude, ageing, and skin pigmentation, vitamin D photosynthesis may be influenced by factors that affect the intensity of skin exposure to UVB.

For light-skinned adults, a few minutes per day with the face and hands in bright sunshine is sufficient to cover daily needs in vitamin D. Intense UVB exposure may generate little vitamin D beyond that achieved by more modest exposure because previtamin D and vitamin D can readily convert to other photoproducts that have little or no vitamin D action.

Vitamin D and xeroderma pigmentosum patients

A further indication that necessary amounts of vitamin D may be provided through dietary sources comes from a study of patients suffering from xeroderma pigmentosum, a rare disease associated with a deficiency in UV-induced DNA lesion repair (Setlow *et al.,* 1969), and characterized by extreme sensitivity to sunlight (Kraemer *et al.,* 1994). To prevent the development of skin cancers at an early age, these patients wear protective clothing and use sunscreens when outdoors. A six-year follow-up study of eight children with xeroderma pigmentosum showed a normal vitamin D intake and that normal vitamin D levels can be maintained in ambulatory patients despite rigorous sun protection (Sollitto *et al.,* 1997).

Summary and conclusion

Summary

UV radiation wavelengths range between 100 nm and 400 nm and are broadly categorised into UVA (>315–400 nm), UVB (>280–315 nm) and UVC (100–280 nm). The portion of solar UV radiation that reaches the earth's surface is composed predominantly of UVA and less than 5% UVB.

The sun is the main source of UV for most individuals. Sources of artificial UV radiation are used during indoor tanning, for medical applications and in some occupations. Indoor tanning facilities in general deliver higher relative intensities and higher proportions of UVA compared with solar UV radiation, but there are wide variations.

Several national and international organisations have presented recommendations regarding the use of indoor tanning facilities, but few countries regulate access and use.

The few studies that have addressed the biological changes in the skin induced by indoor tanning have shown that they are similar to those induced by sunlight.

Many studies have substantiated the carcinogenic effects of UV radiation. Experimental studies in humans have shown that in the basal layers of the epidermis, where melanocytes are located, UVA induces more DNA damage than does UVB.

Both UVA and UVB radiation can affect the immune system: while UVB induces immunosuppression at both the local and systemic levels, UVA does not induce systemic immune suppression. Exposure to tanning appliances has also been shown to induce changes in the skin immune system, including reduced skin test responses, changes in lymphocyte populations, and depression of NK cell activity.

Prevalence of indoor tanning varies greatly between countries; it is widespread in Northern Europe and North America, particularly among women and young people. Indoor tanning has increased considerably since the early 1980s. Several studies show common use by adolescents, and sometimes by children. The most frequent motivations for indoor tanning are the acquisition of a so-called "safe" tan and skin preparation before sun exposure. Limited evidence suggests that compliance with recommendations and regulations by indoor tanning facility operators and customers is poor.

Twenty-three published studies (22 case–control, one cohort) in light-skinned populations investigated the association between indoor tanning and risk for melanoma, and 7 case–control studies for keratinocytic skin cancers. Characterisation of exposure was highly variable across reports.

The summary relative risk for ever versus never use of indoor tanning facilities from the 19 informative studies was 1.15 (1.00–1.31). When the analysis was restricted to the nine population-based case–control studies and the cohort study, the summary relative risk was 1.17 (0.96–1.42). There was no consistent evidence for a dose–response relationship between indoor tanning exposure and risk for melanoma.

All studies that examined age at first exposure found an increased risk for melanoma when exposure started before approximately 30 years of age, with a summary relative risk estimate of 1.75 (1.35–2.26).

Studies on exposure to indoor tanning appliances and squamous cell carcinoma found some evidence for an increased risk for squamous cell carcinoma, especially when age at first use was below 20 years. Studies on basal cell carcinoma did not support an association with use of indoor tanning facilities.

Investigation of the association between indoor tanning and skin cancers poses challenging problems, as the fashion of indoor tanning is still very recent. Associations after long latency periods, such as may be expected for melanoma and basal cell carcinoma, may not yet be detectable.

Artificial UV sources are used to treat a variety of skin conditions, predominantly psoriasis.

Broadband UVB has been used for many years and, more recently, narrow-band UVB, but there are few data on which to base estimates of risk for skin cancer. PUVA therapy increases the risk for squamous cell carcinoma. Data concerning the risk for melanoma as a result of PUVA therapy are conflicting, but to date it seems likely that any increased risk for melanoma is small and that the latency is in excess of 20 years.

Case reports suggest that use of indoor tanning facilities is associated with the development of drug-induced photodermatoses and exacerbation of lupus erythematosus.

UV exposure is related to eye damage, including cataracts, corneal squamous cell carcinoma and ocular melanoma. Several epidemiological studies have shown an association between artificial UV exposure and ocular melanoma, especially if exposure occurred in adolescence or young adulthood.

Sources of vitamin D include photosynthesis in the skin in response to exposure to UVB radiation, oral intake from consumption of food and dietary supplements. In cases of insufficiency, supplementation through oral intake is recommended. Indoor tanning may produce vitamin D photosynthesis in the skin depending on the amount of UVB radiation, if any, in their emission spectrum, although the emission spectrum is generally unknown to consumers and operators.

Conclusion

The use of indoor tanning facilities is widespread in Europe and North America, and this impels consideration of the risk for adverse health consequences, particularly melanoma. Consideration is hampered by the relative recency of widespread use and the limitations of available studies.

Our systematic review of published studies, conducted mainly in North America and Europe, of the association of indoor tanning facility use with melanoma revealed an association of early age at first use (less than approximately 30 years) with melanoma risk. These studies consistently indicated a moderate strength of association, with a summary relative risk of 1.75 (1.35–2.26). The association with ever use of these facilities, or use more than 15 to 20 years prior to diagnosis of melanoma, was weak, and evidence regarding a dose–response relationship was scanty. The evidence is limited by variation in characterization of exposure, potential confounding by sun exposure or other variables, and the low power to detect associations that become evident only following a prolonged lag period after exposure.

The association between indoor tanning facility use and melanoma risk is consistent with the knowledge that melanoma is caused by exposure to solar radiation. Exposure to sunlight in childhood has been established as an important contributing factor for melanoma risk in adults. Although the contexts of exposure to sun and of indoor tanning differ, both deliver UV radiation, and the health effects would therefore be expected to be similar. The limited evidence for an association between indoor tanning and squamous cell carcinoma is consistent with the known association of sun exposure with that cancer. In light of the known effects of UV radiation on the skin, the biological plausibility of a causal association between use of indoor tanning facilities and risk for melanoma and squamous cell carcinoma is strong.

On balance, the evidence pertaining to the strength, consistency, dose–response and temporal sequence of the association of the use of indoor tanning equipment with melanoma risk, and of the coherence and biologic plausibility of the association, leads us to conclude that there is convincing evidence to support a causal relationship, particularly with exposure before the age of 35 years. This evidence is strongly suggestive and further studies could clarify our understanding of this association and allow more definitive conclusions.

We are cognizant of the importance of this issue for the health of light-skinned populations. The strength of the existing evidence suggests that policymakers should consider enacting measures, such as prohibiting minors and discouraging young adults from using indoor tanning facilities, to protect the general population from possible additional risk for melanoma.

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Appendix: European and international positions regarding artificial sources of UV radiation

Establishment of a standard for appliances designed specifically for tanning purposes

Appliances designed specifically for tanning purposes are defined in the international standard prepared by the International Electrotechnical Commission (IEC 60 335-2-27). This standard was first established in 1985 (IEC, 1987) and slightly modified in 1989 (2nd edition; IEC, 1989), in 1995 (3rd edition; IEC, 1995) and in 2002 (4th edition; IEC, 2003). The USA follow the recommendations of the Food and Drug Administration (US FDA, 1985), which were recently updated (Lim *et al.*, 2004; US FDA, 2004).

According to the 3rd edition of the IEC standard, appliances emitting UV radiation must belong to one of the types described below:

- Type UV-1 appliance: appliance with a UV source such that the biological effect is triggered by radiation wavelengths >320nm, and which is characterized by relatively high irradiance efficiency in the range 320–400nm.
- Type UV-2 appliance: appliance with a UV source such that the biological effect is triggered by radiation wavelengths above or below 320nm, and which is characterized by relatively high irradiance efficiency in the range 320–400nm.
- Type UV-3 appliance: appliance with a UV source such that the biological effect is triggered by radiation wavelengths above or below 320nm and which is characterized by restricted irradiance over the entire range of UV radiation.
- Type UV-4 appliance: appliance with a UV source such that the biological effect is triggered primarily by radiation wavelengths <320nm.

Table I shows the physical characteristics of the appliances.

According to the standard, "the appliances must not be toxic or represent similar hazard. The appliances emitting UV radiation must not emit radiation in dangerous amounts and their irradiance efficiency must be within the values specified in Table [I]". In addition, the standard states that the verification of conformity must be performed by 1) determining the ageing of the appliance before measurement and 2) respecting a distance of 0.3m.

The guidelines recommend that the exposure time for the first session on untanned skin should correspond to an effective dose not exceeding 100 J/m^2; this is approximately equivalent to 1 MED for subjects with sun-reactive skin type I. The annual exposure should not exceed an effective dose of 25 kJ/m^2 (IEC, 1989).

Although these guidelines form the basis of several national standards on the use of tanning appliances, it should be noted that variations exist; for example, in the Netherlands, Norway

Table I. Type of UV appliances according to their irradiance efficiency

Type of UV appliance	Irradiance efficiency in W/m	
	250 nm < λ < 320 nm	320 nm < λ < 400 nm
1	< 0.0005	≥ 0.15
2	0.0005 to 0.15	≥ 0.15
3	< 0.15	< 0.15
4	≥ 0.15	< 0.15

λ, radiation wavelength

and Sweden, certain UV appliances are not permitted. Regulations concerning the use of tanning appliances are in force in only a few countries, but many others have published advice on their use, including information on adverse effects, as well as guidelines on manufacturing standards.

In 2004, amendment 1 (2004-2007) to the 4th edition of the standard (2002-2009) added type-5 appliances to the standard: appliance with a UV source such that the biological effect is triggered by radiation wavelengths above or below 320nm and which is characterized by a relatively high irradiance efficiency over the entire range of UV radiation.

The second amendment is currently being voted internationally. This amendment would suppress the current classes and distinguish only two classes: appliances for sale to the general public (formerly type-3 appliances) and appliances for professionals making UV available to the public.

National and international scientific policies

Several international authorities have adopted a defined position regarding specifically the use of UV-emitting appliances for tanning purposes. These positions are almost invariably accompanied by recommendations targeted at the safety of customers.

ICNIRP

The International Commission on Non-Ionizing Radiation Protection (ICNIRP) is an independent group of experts convened to evaluate available data on the effects of non-ionizing radiation to humans. ICNIRP proposes exposure limits to UV radiation for the general population and in occupational settings for the eye and for the skin, for an 8-hour exposure period (ICNIRP, 2004).

In its statement relating to UV-emitting appliances for tanning purposes, ICNIRP, after considering the effects of UV radiation on the skin and the different types of existing appliances, concluded that use of UV-emitting appliances for tanning and other non-medical purposes should be discouraged. High-risk individuals must be particularly warned against the use of tanning appliances. These include:

- individuals with skin phototypes I and II;
- children and adolescents under the age of 18 years;
- individuals with a large number of naevi;
- individuals with a tendency to have freckles;
- individuals who had frequent sunburns during childhood;
- individuals with pre-malignant and malignant skin tumours;
- individuals with actinic skin ageing;
- individuals who have applied cosmetics on their skin; and
- individuals who are taking medication must seek advice from their doctor to determine whether their medication renders them more sensitive to UV.

If, in spite of the above-mentioned recommendations, individuals decide to use tanning appliances, a number of measures must be implemented to minimize the risk. These measures apply specifically to skin phototype I and II, children, individuals with increased sensitivity due to the use of medication or cosmetics, or individuals with a skin cancer-related pathology.

World Health Organization (WHO)

In 2003, WHO published a document entitled: "Artificial tanning sunbeds: risks and guidances" in the framework of the INTERSUN program (WHO, 2003). This document is based on recommendations cited by other organisations such as ICNIRP, EUROSKIN and the National Radiological Protection Board (NRPB), among others. Specifically, WHO recommends that costumers carefully read the recommendations and sign the consent form before each tanning session, so as to make them fully aware of their responsibilities.

EUROSKIN

EUROSKIN dedicated an international meeting to the problems arising from the use of tanning appliances. The outcome of the conference was published in the European Journal of Cancer Prevention (Greinert *et al*., 2001). The document presents general statements about individuals

who should avoid such practices, and makes specific recommendations on the information to be given to customers and on how to use UV-emitting appliances.

National Radiological Protection Board (NRPB)

In 2002, a group of public health scientists in the United Kingdom published a report through the National Radiological Protection Board on the health effects of UV radiation (NRPB, 2002). The document advises against the use of UV-emitting appliances for tanning purposes and recommends that the potential risks for detrimental health effects be clearly outlined to the users and to the general population at large.

National Toxicology Program (NTP)

In 2002, the National Toxicology Program in the USA published the 10th Report on Carcinogens (NTP, 2002) in which UVA, UVB and UVC radiations were included in the list of "known carcinogens to humans". One chapter of the document is dedicated to solar radiation and exposure to UV-emitting appliances. In fact, the American Medical Association had asked in 1994 for a complete ban of exposure to UV for non-medical purposes. In the USA, 27 states have a regulation regarding availability of indoor tanning facilities to the general population.

Regulations

Regulations and recommendations of health authorities from those countries where they are available are listed in Table II. The following findings can be highlighted:

For consumer safety reasons, Scandinavian countries authorise only type-3 appliances with an emission limit of 0.15 $W.m^{-2}$ for both UVA and UVB, i.e. a total UV intensity of 0.3 $W.m^{-2}$. Some countries specify that these appliances may also be sold to individuals.

The organisations responsible for radioprotection and the health authorities of five Scandinavian countries (Denmark, Finland, Iceland, Norway and Sweden) released a joint public health advice recommending that more stringent safety procedures be adopted regarding the use of UV tanning appliances. This advice is in line with the position of international (WHO, ICNIRP), European (EUROSKIN) and national organisations.

The countries that produce the majority of UV tubes and UV tanning appliances (Germany, Italy and the Netherlands) have no legislation limiting the manufacturers.

The USA has its own restrictive regulation imposed by the FDA.

The European Commission has raised a concern about the lack of upper limits for the dose rate of type-1 and type-2 appliances (Type-4 appliances are not concerned).

The legislation in Spain requires that each individual sign a book, a registry and a consent form, and be given a tanning booklet specifying the details of the sessions in accordance with the characteristics of the UV appliance. This initiative corresponds to the recommendations of WHO (WHO, 2003).

The maximal cumulative annual dose of UV radiation currently established at 15 $kJ.m^{-2}$ is calculated from the standard IEC 60 335-2-27. This cumulative dose by far exceeds the dose received from ambient natural UV. Finland wishes to set a maximal annual cumulative dose of 5 $kJ.m^{-2}$. In fact, the maximal annual cumulative dose should be adjusted to the phototype, i.e. 9 $kJ.m^{-2}$ (NMSC) for phototype II, 15 $kJ.m^{-2}$ (NMSC) for phototype III and 21 $kJ.m^{-2}$ (NMSC) for phototype IV.

It is noteworthy that few countries regulate indoor tanning, and when they do, regulations are mostly silent on use of these appliances by adolescents. According to a recent review by Dellavalle et al. (2003), only France has adopted the age of 18 years as the legal minimum age for indoor tanning. In the USA, only 6 states have in place minimum age limits for tanning patrons: California, Illinois, New Hampshire and North Carolina restrict access to individuals younger than 14 years old, while Texas and Wisconsin restrict access to adolescents younger than 13 and 16 years old, respectively (Francis *et al.*, 2005).

In France, technical controls are performed periodically in all registered tanning

Table II. Regulations and recommendations from health authorities in those countries where information is available

Austria	Presnorme Önorm S 1132 : "Safety rules during the use of solaria emitting UV radiations" (1 January 2002)
Belgium	"Royal decision on requirements for exploiting solaria" (2000)
Canada	Territory, Province and State Committee on radioprotection : "Guidelines to owners, operators and users of tanning salons". Enforcement of regulations enacted to implement the « law relating to appliances emitting radiations – RED Act : Regulations of sun lamps » (2002-2003)
Germany	Bundesamt für Strahlenschutz, Munich : "Certification of solaria" (proposal) Currently, UV exposure in solaria must respect the German standard DIN 5050-2 (June 1998)
Finland	Decree on the limitation of public exposure to non-ionising radiation (294/2002) chapter 4, "Ultraviolet radiation"; SS 9.1 "Safety of solaria" (1989); SONT 9.1 "Safety and control conditions of solaria" (project) (2003)
France	Decree n° 97-617 (30 May 1997) and regulations of 10 September 1997, 09 December 1997 and 16 September 2002 enacted to implement the law
Italy	Istituto Superiore di Sanità "Devices must conform to the technical norm IEC 60335-2-27" (1995–2003); detailed information available at http://www.iss.it/sitp/sole/abbrart/leggi.html
Netherlands	No formal regulation. Several reports from the Dutch Health Council (1987, 1994)
Norway	Regulations of 8 April 1983 for solaria/alpine sun. Delegation of authority regulation fixing by royal decree the usage of UV radiations for cosmetic purposes (01 July 1983)
Spain	19574 Royal decree 1002/2002 : "Regulation of sale and use of tanning appliances emitting UV radiations" (27 September 2002)
Sweden	Regulatory code concerning sunbeds (SSI FS 1998:2) "The regulation of tanning appliances used by the public fulfils the criteria of the standard EN 60335-2-27." (28 September 1998 and 03 November1 998)
USA	FDA Sunlamp Performance Standard 21CFR1040.20 combined with a guide (1986) on timers and frequency of exposure (updated 01 April 2004)

establishments since 1999. The proportion of establishments compliant with the technical requirements increased from 51% in 1999 to 72% in 2003. Periodic visits in 2002 and 2003 to additional establishments showed a compliance of 85% and 81%, respectively. Non-compliance was mainly for minor infractions (AFSSE, 2005).

In addition, the Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes (DGCCRF) proceeded to a series of controls and enquiries about indoor tanning facilities in 2002 and 2003. The following comments were noted: the facility operators are well informed of the regulations in place; the compulsory declaration was generally satisfactory; in most places, at least one person had the required qualifications, but the need for continuing education was not perceived clearly; information to the customers were usually available to the users, but information on risks was often lacking (AFSSE, 2005).