NTP REPORT ON CARCINOGENS BACKGROUND DOCUMENT for SOLAR RADIATION AND EXPOSURE TO SUNLAMPS OR SUNBEDS

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Report on Carcinogens Listing for Solar Radiation and Exposure to Sunlamps or Sunbeds

Carcinogenicity

Solar radiation is *known to be a human carcinogen*, based on human studies which clearly indicate a causal relationship between exposure to solar radiation and cutaneous malignant melanoma and non-melanocytic skin cancer. Some studies suggest that solar radiation may also be associated with melanoma of the eye and non-Hodgkin's lymphoma. Simulated solar radiation is carcinogenic in experimental animals (IARC V.55, 1992).

Exposure to sunlamps or sunbeds is *known to be a human carcinogen*, based on both human and animal studies. Recent human studies have shown that exposure to sunlamps or sunbeds is associated with cutaneous malignant melonoma (Swerdlow et al., 1988; Walter et al., 1990; Autier et al., 1994; Westerdahl et al., 1994). Exposure-response relationships were observed for increasing duration of exposure, and effects were especially pronounced in individuals under 30 and those who experienced sunburn. Malignant melanoma of the eye is also associated with use of sunlamps. In contrast, there is little support for an association of exposure to sunlamps or sunbeds with non-melanocytic skin cancer (IARC V.55, 1992).

Sunlamps and sunbeds emit radiation primarily in the ultraviolet A (UVA) and ultraviolet B (UVB) portion of the spectrum. Numerous studies have shown that broad spectrum UV radiation, UVA radiation, UVB radiation, and UVC radiation are carcinogenic in experimental animals. There is evidence for benign and malignant skin tumors and for tumors of the cornea and conjunctiva in mice, rats, and hamsters. UV radiation also causes a wide spectrum of DNA damage resulting in mutations and other genetic alterations in a variety of *in vitro* and *in vivo* assays for genotoxicity, including assays using human skin cells (IARC V.55, 1992).

Listing Criteria from the Report on Carcinogens, Eighth Edition

Known To Be A Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans which indicates a causal relationship between exposure to the agent, substance or mixture and human cancer.

Reasonably Anticipated To Be A Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding factors, could not adequately be excluded, or

There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors: (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site or type of tumor, or age at onset; or

There is less than sufficient evidence of carcinogenicity in humans or laboratory animals, however; the agent, substance or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either a known to be human carcinogen or reasonably anticipated to be human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

1.0 INTRODUCTION

1.1 Physical Properties

Solar radiation from the sun includes most of the electromagnetic spectrum (IARC, 1992). The position of ultraviolet radiation (UVR) in the electromagnetic spectrum is shown in Figure 1-1 (NASA, 1996); see also Figure 1 in the IARC monograph p. 44. Table 1-1 shows different bands within the optical radiation spectrum, with UV light being the most energetic and biologically damaging. UV light is divided into UVA, UVB, and UVC. UVA is the most abundant of the three, representing 95% of the solar UV energy to hit the equator, and UVB represents the other 5%. The short wavelength UVC rays are absorbed by ozone, molecular oxygen, and water vapor in the upper atmosphere so that measurable amounts from solar radiation do not reach the earth's surface (Farmer and Naylor, 1996).

Table 1-1. Regions of the Optical Radiation Spectrum (ACGIH, 1996)

Region	Wavelength Range
Ultraviolet (UV)	100 to 380-400 nm
UV-C[a]	100 to 280 nm
UV-B[a]	280-315 nm
UV-A[a]	315-400 nm
Visible (Light)	380-400 to 760-780 nm
Infrared (IR)	760-780 nm to 1 mm
IR-A	760-780 nm to 1.4 μm
IR-B	1.4-3.0 μm
IR-C	3.0 μm to 1 mm

a = photobiological designations of the *Commission Internationale de l'Eclairage* (CIE, International Commission on Illumination)

1.2 Photobiological and Photochemical Activity

Molecules that absorb UV and visible light contain moieties called chromophoric groups in which electrons are excited from the ground state to higher energy states. In returning to lower energy or ground states, the molecules generally re-emit light (Dyer, 1965). Molecules sensitive to UV light absorb and emit UV light at characteristic maximum wavelengths (λ), often expressed as λ_{max}.

Photochemical and photobiological interactions occur when photons of optical radiation react with a photoreactive molecule, resulting in either a photochemically altered molecule or two dissociated molecules (Phillips, 1983; Smith, 1989; both cited by IARC, 1992). To alter molecules, a sufficient amount of energy is required to alter a photoreactive chemical bond (breaking the original bond and/or forming new bonds). Photon energy is expressed in electron volts (eV). A wavelength of 10 nm corresponds to a photon energy of 124 eV; and 400 nm, to an energy of 3.1 eV (WHO, 1979; cited by IARC, 1992). The quantum yield of a photochemical or photobiological reaction is defined as the number of altered molecules produced relative to the number of absorbed photons (Phillips, 1983; cited by IARC, 1992). The efficacy of a

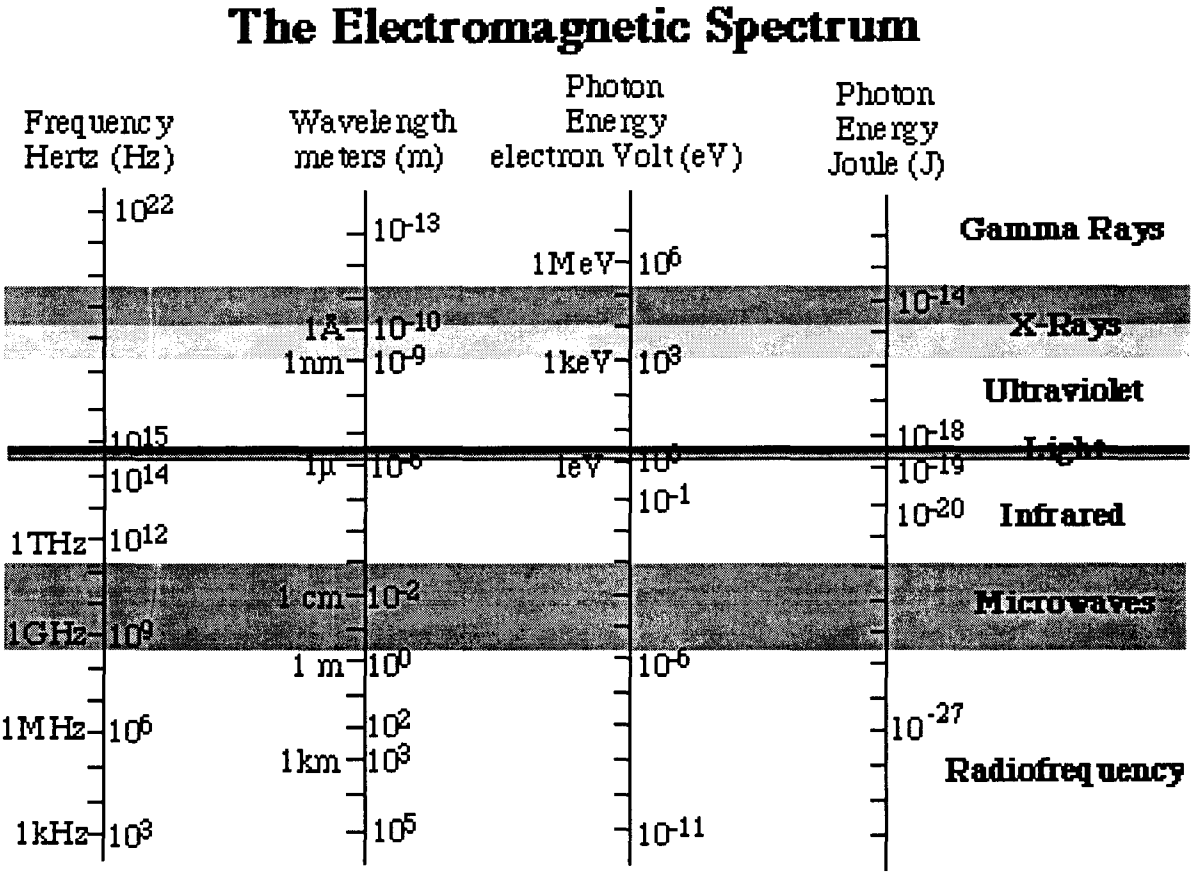
photochemical interaction per incident quantum and the photobiological effects per unit radiant exposure are widely variable, depending on wavelength. The action spectrum is characterized by the quantitative plot of such spectral variation, usually normalized to unity at the most effective wavelength (Jagger, 1985; cited by IARC, 1992, p. 44).

UVB is considered to be the major cause of skin cancer despite its not penetrating the skin as deeply as UVA or reacting with the epidermis as vigorously as UVC. UVB's reactivity with macromolecules combined with depth of penetration make it the most potent portion of the UV spectrum biologically with respect to short-term and long-term effects. UVA, while possibly not as dangerous, also induces biological damage (Farmer and Naylor, 1996).

Photobiological reactions of concern for skin cancer risk due to UV light exposure are the reactions with the main chromophores of the epidermis—urocanic acid, DNA, tryptophan, tyrosine, and the melanins. DNA photoproducts include pyrimidine dimers, pyrimidine-pyrimidone (6-4) photoproducts, thymine glycols, and DNA exhibiting cytosine and purine damage and other damage such as DNA strand breaks and cross-links and DNA-protein cross-links. The different DNA photoproducts have varying mutagenic potential (IARC, 1992).

UV-induced DNA photoproducts produce a variety of cellular responses that contribute to skin cancer. Unrepaired DNA photoproducts may result in the release of cytokines that contribute to tumor promotion, tumor progression, immunosuppression, and the induction of latent viruses (Yarosh and Kripke, 1996). These and other photobiological reactions initiated by exposure to UVR as well as DNA damage repair to reverse DNA photoproducts are described more fully in Sections 6 and 7 and the IARC monograph (IARC, 1992).

Figure 1-1. The Electromagnetic Spectrum



Unit Abbreviations:

THz	terahertz	Å	Angstrom	MeV	Mega (or Million) electron Volts
GHz	gigahertz	nm	nanometer	keV	kilo-electron Volts
MHz	megahertz	μ	micron		
kHz	kilohertz	cm	centimeter		
		km	kilometer		

Source: NASA, 1996

2.0 HUMAN EXPOSURE

2.1 Use

Aside from the many benefits of sunlight/solar radiation, artificial sources of UVR are used for cosmetic tanning, promotion of polymerization reactions, laboratory and medical diagnostic practices and phototherapy, and numerous other applications as described in IARC (1992, pp. 58-70).

2.2 Sources

Ultraviolet light is naturally emitted by the sun and artificially from lamps such as tungsten-halogen lamps, gas discharge, arc, fluorescent, metal halide, and electrodeless lamps (IARC, 1992, pp. 58-59) and lasers such as the 308-nm XeCl (xenon chloride) excimer and the 193-nm ArF (argon fluoride) excimer (Sterenborg et al., 1991).

The use of sunlamps and tanning beds is as a cosmetic source. The latter chiefly emit UVA (315-400 nm) although certain lamps that emitted considerable UVB and UVC radiation were more common before the mid-1970s (IARC, 1992, pp. 60-62). However, UVB produces a better tan than UVA and recently, at least in the United States and United Kingdom, use of sunlamps with more UVB radiation has become widespread (Wright et al., 1997; cited by Swerdlow and Weinstock, 1998). Low-pressure mercury vapor lamps, sunlamps, and black-light lamps are considered to be low-intensity UV sources. High-intensity UV sources include high-pressure mercury vapor lamps, high-pressure xenon arcs, xenon-mercury arcs, plasma torches, and welding arcs. Three different UVA phosphors have been used in sunlamps sold in the United States over the past 20 years, producing emission spectra that peak at 340 nm, 350 nm, or 366 nm. Two modern U.S. sunlamps evaluated by the FDA emitted 99.0% and 95.7% UVA and the rest UVB radiation (<320 nm). A new high-pressure UVA sunbed with eighteen 1600-W filtered arc lamps emitted 99.9% UVA. An older-type sunlamp used more than 20 years ago (UVB/FS type) emitted 48.7% UVA (Miller et al., 1998).

2.3 Exposure

2.3.1 Environmental Exposure

2.3.1.1 Solar Radiation

The greatest source of human exposure to UVR is solar radiation; however, the exposure varies with the geographical location. With decreasing latitude or increasing altitude, there is greater exposure; for every 1000 feet above sea level, a 4% compounded increase exists. Decreases in the stratospheric ozone caused by chemicals generating free radicals increase UVR exposure. Heat, wind, humidity, pollutants, cloud cover, snow, season, and the time of day also affect UVR exposure (Consensus Development Panel, 1991). IARC (1992) gives several other environmental sources for UVR on pages 50-58 of the monograph.

Although use of sunscreen is known to protect from skin damage induced by UVR, sunscreen use has not become habitual by a large fraction of the U.S. population. For example, Newman et al. (1996) surveyed a random sample of persons in San Diego, a location with one of the highest incidences of skin cancer in the United States. Sunscreen was used only about 50% of the time on both skin and body by tanners, about 40% of the time on the face, and 30% of the time on the body.

2.3.1.2 Sunlamps or Sunbeds

Most bulbs sold in the United States for use in sunbeds emit "substantial doses of both UVB and UVA" (Swerdlow and Weinstock, 1998, citing "personal communication from industry sources"). Many of the home and salon devices in the 1980s emitted both UVA and UVB radiation, but current devices emit predominantly UVA (FTC, 1997; Sikes, 1998).

FDA scientists calculated that commonly used fluorescent sunlamps would deliver 0.3 to 1.2 times the annual UVA dose from the sun to a typical tanner requiring 20 sessions at 2 minimal erythema doses (MED) per session. The common sunlamps would deliver to a frequent tanner (100 sessions at 4 MED/session) 1.2 to 4.7 times the UVA received annually from solar radiation. The frequent tanner would receive 12 times the annual UVA from solar radiation from the recently available high-pressure sunlamps (Miller et al., 1998).

In 1987, an American Academy of Dermatology (AAD) survey found that, although 96% of the U.S. population surveyed knew that sun exposure causes cancer, one-third of the adults responding develop tans. By 1987, the indoor tanning industry was one of the fastest growing in the United States (Sikes, 1998). Surveys of U.S. telephone book Yellow Pages found 11,000 indoor tanning facilities in 1986 and more than 18,000 facilities in 1988. About 11% of women and 6% of men were frequent patrons (Research Studies-SIS, 1989). New York State alone was estimated to have 1300 commercial tanning facilities in 1993 (Lillquist et al., 1994). By 1995, indoor tanning facilities were a $1 billion industry serving 1 million patrons a day (Guttman, 1995). About 1 to 2 million patrons visit tanning facilities as often as 100 times per year (Sikes, 1998).

A 1990 survey of 1,564 holders of drivers' licenses residing in New York State outside of the New York City area, who were aged 17 to 74 years, were white, and had never had skin cancer, found that 21.5% of the respondents had ever used sun lamps (28.1% among those 16 to 24 years old) but that only 2.3% used sun lamps at least once a month. Ever users were more likely to be women, younger, and never married or divorced or separated (Lillquist et al., 1994). Surveys in the early 1990s of adolescents who had ever used tanning devices have found about twice as many girls as boys among the users (33% vs. 16% and 18.5% vs. 7.4%) (Banks et al., 1992; Mermelstein and Riesenberg, 1992; both cited by Lillquist et al., 1994).

Up to 25 million persons per year in North America are currently estimated to use sunbeds. Teenagers and young adults are prominent among users. A study of high school students in St. Paul, Minnesota, found that 34% had used commercial sunbeds at least 4 times in the past year. Fifty-nine percent of the users reported some skin injury. A 1995 U.S. survey found that commercial tanning salon patrons included 8% aged 16 to 19 years and 42% aged 20 to 29 years; 71% were female (Hurt and Freeman, undated; cited by Swerdlow and Weinstock, 1998).

Wisconsin dermatologists, ophthalmologists, and emergency room personnel reported treating 372 patients with ocular and/or dermal injuries from artificial tanning devices in a 12-month survey ca. 1990. Of these patients, 53% to 65% were exposed to tanning beds or booths and 17 to 35% were exposed to reflector bulb lamps. In the group of 155 emergency room patients with first or second degree skin burns from artificial tanning, 58% were burned at tanning salons and 37% were burned at home (Garrett, 1990). Although FDA has mandated rules that require that tanning equipment labeling warn about overexposure, skin cancer, possible premature skin aging, and photosensitivity with certain cosmetics and medications, a Public Interest Research Group survey of 100 tanning salons in 8 states and the District of Columbia

found 183 tanning devices without the required warnings (Cosmetic Insiders' Report, 1991). Sikes (1998) stated, without attribution, that tanning devices caused 1,800 reported injuries in 1991, mostly in persons aged 15 to 24 years old. A survey of 31 tanning salons in 1989 in the greater Lansing, Michigan, area, population 450,000, found that 87% of the facilities offered their clients "tanning accelerators." Respondents at five establishments stated that their tanning accelerators contained psoralens, but this could not be confirmed (Beyth et al., 1991).

2.3.2 Occupational Exposure

Many occupations, e.g., agricultural, construction, and road work laborers, spend a large component of their work day outdoors. Outdoor workers, therefore, are the largest occupational group exposed to solar UVR. Occupational exposure to artificial UVR occurs in industrial photo processes, principally UV curing of polymer inks, coatings, and circuit board photoresists; sterilization and disinfection; quality assurance in the food industry; medical and dental practices; and welding. Welders are the largest occupational group with artificial UVR exposure. However, only arc welding processes produce significant levels of UVR. UVR from welding operations is produced in broad bands whose intensities depend on factors such as electrode material, discharge current, and gases surrounding the arc (NIOSH, 1972). [OSHA regulations required many protective measures to reduce UVR exposure of workers engaged in or working in the vicinity of arc welding operations. See the Regulations section.] IARC (1992) describes on pages 66-70 of the monograph details of these occupational exposures to artificial UVR.

A study conducted on laboratory UV lasers such as those used in cornea shaping and coronary angioplasty showed that the relative risk may increase to a level comparable to that of individuals with an outdoor profession (Sterenborg et al., 1991).

Applying a mathematical power model based on human data, Lytle et al. (1992) suggested that there is an increased risk of squamous cell carcinoma (SCC) from exposure to UV-emitting fluorescent lamps. The estimates of annual incidence of new SCC, for indoor workers exposed to UV light, indicated that an exposure to typical fluorescent lighting (unfiltered by a clear acrylic prismatic diffuser) may add 3.9% (1.6%-12%) to the potential risk from solar UVR, thus resulting in an induction of an additional 1500 (600-4500) SCC per year in the United States. There is a small increased risk of SCC from exposure to UV-emitting fluorescent lamps, when compared to 110,000 SCC caused by solar exposure.

NIOSH (1972) estimated that 211,000 workers in the manufacturing industries (Standard Industrial Codes [SICs] 19-39) were exposed to UVR; 49,000, in the transportation and communication industries (SICs 40-49); 17,000, in the wholesale, miscellaneous retail, and service stations categories (SICs 50, 59, 55); and 41,000, services industries (SICs 70-89). The sources considered were arc welding, air purifiers, and sanitizers.

2.4 Regulations and Criteria

The U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) have promulgated regulations concerning sunlamp products and UV lamps intended for use in sunlamp products. Manufacturers must notify CDRH of product defects and repair and replacement of defects. CDRH issues written notices and warnings in cases of noncompliance. Several performance requirements must be met by sunlamp products (21 CFR 1040.20), including irradiance ratio limits, a timer system, protective eyewear to be worn during

product use, compatibility of lamps, and specific labels. The label should include the statement "DANGER—Ultraviolet radiation" and warn of the dangers of exposure and overexposure.

OSHA requires extensive UVR protective measures of employees engaged in or working adjacent to arc welding processes. Arc welding emits broad spectrum UVR. Workers should be protected from the UVR by screening, shields, or goggles. Employees in the vicinity of arc welding and cutting operations should be separated from them by shields, screens, curtains, or goggles. If possible, welders should be enclosed in individual booths. In inert-gas metal-arc welding UVR production is 5 to 30 times more intense than that produced by shielded metal-arc welding. OSHA-required protective measures in shipyard employment and marine terminals include filter lens goggles worn under welding helmets or hand shields and protective clothing that completely covers the skin to prevent UVR burns and other damage (OSHA, 1998a, 1998b, 1998c).

ACGIH (1996) has set various Threshold Limit Values (TLVs®) for skin and ocular exposures. TLVs® for occupational exposure are determined by these parameters:

1. "For the near UV spectral region (320 to 400 nm), total irradiance incident upon the unprotected eye should not exceed 1.0 mW/cm^2 for periods greater than 10^3 seconds (approximately 16 minutes) and for exposure times less than 10^3 seconds should not exceed 1.0 J/cm^2."
2. Unprotected eye or skin exposure to UVR should not exceed 250 mJ/cm^2 (180 nm) to $1.0x10^5$ mJ/cm^2 (400nm) for an 8-hour period. The TLVs® in the wavelength range 235 to 300 nm are 3.0 (at 270 nm) to 10 mJ/cm^2.
3. Effective irradiance for broad band sources must be determined by using a weighting formula.
4. "For most white-light sources and all open arcs, the weighting of spectral irradiance between 200 and 315 nm should suffice to determine the effective irradiance. Only specialized UV sources designed to emit UV-A radiation would normally require spectral weighting from 315 to 400 nm."
5. The permissible ultraviolet radiation exposure for unprotected eye and skin exposure may range from 0.1 $\mu W/cm^2$ (8 hours/day) to 30000 $\mu W/cm^2$ (0.1 sec/day).
6. "All of the preceding TLVs® for UV energy apply to sources which subtend an angle less than 80°. Sources which subtend a greater angle need to be measured only over an angle of 80°."

ACGIH (1996) added that even though conditioned (tanned) individuals may not be any more protected from skin cancer, they can tolerate skin exposure in excess of the TLV without erythemal effects. NIOSH criteria for a recommended standard for occupational exposure to UVR are practically identical to those given in ACGIH items 1 and 2 above (NIOSH, 1972).

The Federal Trade Commission (FTC) investigates false, misleading, and deceptive advertising claims about sunlamps and tanning devices (FTC, 1997).

The American Medical Association passed a resolution in December 1994 that called for a ban of the use of suntan parlor equipment for nonmedical purposes. Dermatologists have urged the FDA to take action to discourage use of suntan parlors and suntan beds (Blalock, 1995). Currently, the FDA Center for Devices and Radiological Health and the Centers for Disease Control and Prevention (CDC) encourage avoidance of sunlamps and sunbeds (AAD, 1997).

Although 27 states and municipalities had promulgated some regulations on indoor tanning facilities by late 1995, they are seldom enforced (Blalock, 1995). The American Academy of Dermatology's Tanning Parlor Initiative provides a manual giving instructions on petitioning state, regional, and local governments on this issue and examples of regulatory legislation (Dermatology Times, 1990).

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 5—PART 5—DELEGATIONS OF AUTHORITY AND ORGANIZATION. Subpart B—Redelegations of Authority from the Commissioner of Food and Drugs.	
	21 CFR 5.37—Sec. 5.37 Issuance of reports of minor violations. Promulgated: 48 FR 8441, Mar. 1, 1983, as amended through 62 FR 67271, Dec. 24, 1997.	Sec. 21 CFR 5.37(b)(5)(ii): U.S. FDA officials of the Center for Devices and Radiological Health (CDRH), Regional Food and Drug Directors, and other listed officials are authorized to perform all the functions of the Commissioner of Food and Drugs under section 539(d) of the FFD&CA regarding the issuance of written notices or warnings when their functions relate to manufacturers of sunlamp products and UV lamps intended for use in any sunlamp product as defined in 21 CFR 1040.20(b).
	21 CFR 5.89—Sec. 5.89 Notification of defects in and repair and replacement of, electronic products. Promulgated: 48 FR 56948, Dec. 27, 1983, as amended through 62 FR 67271, Dec. 24, 1997.	Sec. 5.89(a)(2) lists CDRH and other officials authorized to perform all functions of the Commissioner of Food and Drugs relating to notification of defects in, noncompliance of, and repair or replacement or refund for manufacturer's UV lamps for sunlamps under Section 359 of the Public Health Service Act and under Secs. 1003.11, 1003.22, 1003.31, 1004.2, 1004.3, 1004.4, and 1004.6
	21 CFR 878—PART 878—GENERAL AND PLASTIC SURGERY DEVICES. Subpart E—Surgical Devices.	

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
F D A	21 CFR 878.4635—Sec 878.4635 Ultraviolet lamp for tanning. Promulgated: 55 FR 48400, Nov. 20, 1990, as amended at 59 FR 63010, Dec. 7, 1994.	This section defines a UV lamp for tanning as a device using UVR to tan the skin. Such a device is designated as Class I, exempt from premarket notification procedures given in 21 CFR 807.
	21 CFR 1000—PART 1000—GENERAL. Subpart B—Statements of Policy and Interpretation.	Tanning and therapeutic lamps are UVR sources subject to the regulations of this part.
	21 CFR 1000.15—Sec. 1000.15 Examples of electronic products subject to the Radiation Control for Health and Safety Act of 1968.	
	21 CFR 1002—PART 1002—RECORDS AND REPORTS. Subpart A—General Provisions.	Specifies record and reporting requirements falling under other subparts of 21 CFR 1002 for sunlamps.
	21 CFR 1002.1—Sec. 1002.1 Applicability. Promulgated: 60 FR 48382, Sept. 19, 1995; 61 FR 13423, March 27, 1996.	
	21 CFR 1040—PART 1040—PERFORMANCE STANDARDS FOR LIGHT-EMITTING PRODUCTS.	Sunlamps and UV lamps for use in sunlamp products are lamps producing UVR in the wavelength interval 200-400 nm in air. A sunlamp product is defined as any electronic product designed to incorporate one or more UV lamps and intended for irradiation of any part of the human body to induce skin tanning. The regulation in 21 CFR 1040.20(ii) (c) specifies performance requirements including an irradiance ratio limit: the ratio irradiance at >200-260nm / irradiance at >260-320 nm may not exceed 0.003 at any distance and direction.
	21 CFR 1040.20—Sec. 1040.20 Sunlamp products and ultraviolet lamps intended for use in sunlamp products. Promulgated: 50 FR 36550, Sept. 6, 1985.	

REGULATIONS

	Regulatory Action	Effect of Regulation/Other Comments
FDA		Other performance requirements include a timer system, appropriate protective eyewear to accompany the product, compatibility of lamps and specific labeling. The label should include a statement beginning with "DANGER—Ultraviolet radiation..." and warn of the dangers of overexposure (eye and skin injury and allergic reactions) and repeated exposure (premature aging). The instructions should recommend exposure positions and exposure schedule, describe proper operation of the product, and instruct how to obtain repairs and replacement components.
NIOSH	1972 Criteria for a Recommended Standard....Occupational Exposure to Ultraviolet Radiation. NIOSH Publication No. 73-11009, NTIS No. PB-214268	For the spectral region of 315 to 400 nm: For periods greater than 1,000 s = 1.0 mW/cm^2; for periods less than or equal to 1,000 s = 1,000 $mW\text{-}s/cm^2$ (1.0 J/cm^2). For spectral region of 200 to 315 nm, consult the criteria document.

3.0 HUMAN STUDIES

3.1 Solar UV Radiation

Most of the human literature through 1991 on the relationship of solar radiation to cancer was thoroughly evaluated by IARC (1992, pp. 73-130). IARC concluded that there was *sufficient evidence* in humans for the carcinogenicity of solar radiation and that it caused cutaneous malignant melanoma (CMM) and nonmelanocytic skin cancer. On the basis of animal and human data, IARC concluded that *solar radiation is carcinogenic to humans* (Group 1).

Four recent studies have investigated the relationship of solar radiation to non-Hodgkin's lymphoma (NHL) (Table 3-1). Bentham (1996) reported on 55,818 NHL cases registered in the *Atlas of Cancer Incidence in England and Wales,* 1968-1985, which covers 59 counties in England and Wales. The cases were compared to weighted samples of all other registered cancers, adjusting for age and sex. Exposure was defined as the estimated levels of solar UVR, by county, calculated from a model using data on latitude and cloud cover. After adjusting for social class and agricultural employment, the relative risk (95% confidence interval [CI]) of NHL for the highest versus the lowest UVR group was 1.34 (1.32-1.37).

Newton et al. (1996 lett.) used a large, population-based cancer registry containing occupational information to compare 428 registered NHL cases , who had outdoor occupations in England, 1981-1987 to NHL cases with any occupation. After adjusting for age, social class, and cancer registry of origin, the proportional registration ratios (95% CI) were 95 (86-105) for men

and 156 (103-228) for women (a 56% excess of NHL), suggesting an association of NHL with outdoor occupation in women but not in men.

Hartge et al. (1996) examined geographic patterns of mortality rates for CMM, nonmelanocytic skin cancer, and NHL in U.S. whites, 1950-1980. Although rates for both types of skin cancer were higher in the southern half of the United States, the rate for NHL was lower. Annual ambient levels of solar UVB radiation were estimated for each state, adjusting for latitude, altitude, and cloud cover. Mortality from both types of skin cancer, by state, had a positive linear relationship with solar UVB radiation ($p<0.0001$), while mortality from NHL was negatively related to solar UVB radiation ($p<0.0001$).

McMichael and Giles (1996) used data on age-standardized cancer incidence rates during 1978-1987 in Caucasian populations around the world to examine the correlation of NHL incidence rates with estimates of UVB radiation. The association of UVB radiation with NHL in men ($r = 0.50$, $p<0.001$) was weaker than the association with CMM ($r = 0.75$, $p<0.001$); results were similar in women. Data on age-, sex-, and time-standardized incidence rates for Caucasian populations showed that the correlation of NHL with CMM was 0.41 ($p<0.014$) for men and 0.29 ($p<0.099$) for women. They also observed that British migrants to Australia had NHL and CMM rates intermediate between that of the population of England and Wales and the Australian-born population.

These results provide limited support for an association of NHL with exposure to solar radiation.

3.2 Nonsolar UV Radiation

IARC also reviewed studies of cancer and nonsolar UVR (1992, pp. 130-134). The IARC Working Group concluded that there was *limited evidence* in humans for the carcinogenicity of exposure to UVR from sunlamps and sunbeds and *inadequate evidence* in humans for the carcinogenicity of exposure to fluorescent lighting. On the basis of human and animal data, IARC concluded that UVA, UVB, and UVC radiation are *probably carcinogenic to humans* (Group 2A), that use of sunlamps and sunbeds entails exposures that are *probably carcinogenic to humans* (Group 2A), and that exposure to fluorescent lighting is *not classifiable as to its carcinogenicity to humans* (Group 3).

Three studies published after the IARC review have investigated the effect of exposure to sunlamps or sunbeds on cancer incidence. Autier et al. (1994) conducted a case-control study in Belgium, France, and Germany, which examined the relationship between cutaneous malignant melanoma and exposure to sunlamps or sunbeds. The cases were 420 consecutive patients who were 20 years old or more and had nonpigmented skin. Controls with no history of skin cancer were randomly chosen from the same municipalities as the cases and matched on age and gender. Response rates were 92% for cases and 78% for controls. Exposure was estimated by home interviews using a structured questionnaire, and categorized by purpose: tanning or nontanning. The crude odds ratio for ever exposure was 0.97 (95% CI, 0.71-1.32). After adjusting for age, sex, hair color, and average time per year spent in sunny holiday resorts, the odds ratio for at least 10 hours' exposure for tanning purposes starting before 1980 was 2.12 (95% CI, 0.84-5.37). The adjusted odds ratio for at least 10 hours' exposure for tanning purposes in subjects who experienced skin-burn was 7.35 (95% CI, 1.67-32.3).

A Swedish case-control study (Westerdahl et al., 1994) examined the relationship between malignant melanoma and exposure to sunlamps or sunbeds. Incident cases (400), aged 15-75 years, were selected from a population-based regional tumor registry. Controls (640) were randomly selected from the National Population Registry of the same region, and matched to the cases on age, gender, and parish. Response rates were 89% for cases and 77% for controls. Exposure to sunlamps and sunbeds was determined by mailed questionnaires. After adjusting for skin and hair color, history of sunburn, number of raised nevi, family history of malignant melanoma, and frequency of summer sunbathing, the odds ratio for ever exposure was 1.3 (0.9-1.8). The adjusted odds ratio for 10 or more exposures per year was 1.8 (95% CI, 1.0-3.2). The adjusted odds ratio for subjects less than 30 years old was 7.7 (95% CI, 1.0-63.6), and a significant dose-response was demonstrated ($p = 0.02$); in older individuals the odds ratio was smaller and nonsignificant. The risk was greater for melanoma on the trunk (adjusted odds ratio, 4.2; 95% CI, 1.6-11.0) than for melanoma on the extremities, head, or neck (adjusted odds ratio, 1.1, 95% CI 0.6-2.3), indicating that the risk depends on the site of exposure.

A Canadian case-control study (Bajdik et al., 1996) examined the relationship between basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) and exposure to nonsolar UVR. Male cases of BCC (226) and SCC (180) from the Alberta Cancer Registry were compared to 406 age-matched male controls randomly selected from Alberta's health insurance plan subscriber list. Response rates were 70-80% for both cases and controls. Exposure to various nonsolar UVR sources (fluorescent lighting, sunlamps, welding torches, mercury vapor lamps, printing/photocopying lights, UV lamp treatments, UV/black lights, and horticultural growth-inducing lights) was determined by home interviews using a structured questionnaire. After adjusting for ethnic origin, skin and hair color, and occupational sun exposure, ever exposure to sunlamps was associated with a small, nonsignificant elevation in risk for both types of cancer [odds ratio for BCC, 1.2 (95% CI, 0.7-2.2); odds ratio for SCC, 1.4 (95% CI, 0.7-2.7)]. No other type of exposure was associated with either type of cancer, but the number of subjects reporting most exposures was small.

Table 3-2 summarizes the evidence from nine studies regarding the association of CMM with exposure to sunlamps or sunbeds, including seven reviewed in the IARC monograph (1992) and two reviewed above. Results of the first five studies listed are essentially negative. However, most of these studies have limited power to evaluate the association, due to small sample size and/or small numbers of exposed individuals. Moreover, cases in most of these studies were recruited before use of sunlamps and sunbeds became widespread in the 1980s, but CMM has a relatively long latency. Three of the studies evaluated only sunlamp exposure, but sunbeds may provide higher UVR exposure. Thus, the negative evidence is weak. In contrast, the four positive studies were reasonably large and had sufficient numbers of exposed individuals; most cases were recruited in the mid-1980s or later; and exposure to both sunlamps and sunbeds was evaluated. The positive results of these studies are unlikely to be due to confounding since their analyses adjusted for exposure to solar radiation as well as skin and hair coloring and other risk factors for CMM. Three of the studies found a dose-response for increasing duration of exposure. Taken together, these studies provide strong evidence for an association of exposure to sunlamps or sunbeds with CMM.

Four studies have also found an association of melanoma of the eye with exposure to sunlamps or sunbeds, with statistically significant odds ratios of 1.4 to 3.7 (reviewed by IARC, 1992).

In contrast, three studies reviewed by IARC (1992) and one described above (Bajdik et al., 1996) failed to find associations of nonmelanocytic skin cancer with exposure to sunlamps or sunbeds. However, all four considered very few exposed subjects and recruited cases in 1985 or earlier.

3.3 Potential Confounding of the Association Between Exposure to Sunlamps or Sunbeds and Cutaneous Malignant Melanoma by Exposure to Solar Radiation

Individuals who use sunlamps or sunbeds for tanning purposes are also likely to expose themselves to solar radiation in order to tan. Thus, exposure to solar radiation may confound the relationship between exposure to sunlamps or sunbeds and cutaneous malignant melanoma. Three of four recent studies of the relationship have addressed this issue. Swerdlow et al. (1988) adjusted for sun exposure as well as numbers of nevi, skin type, and hair and eye color; relative risks [95% confidence interval (CI)] for <3 months, 3 months to 1 year, and >1 years of use, compared to never use, were 0.7 (0.1-3.8), 3.1 (1.0-9.9), and 3.4 (0.6-20.3). Although the estimates were imprecise because of small numbers, there was a significant trend with increasing duration of use ($p<0.05$). Autier et al. (1994) stratified on purpose of exposure (non-tanning vs. tanning), cumulative hours of exposure (<10 vs. 10+), and experience of sunburn (no vs. yes) and adjusted for average number of holiday weeks in sunny resorts as well as age, sex, and hair color; among the group with 10+ hours of exposure for tanning purposes who experienced sunburn, the adjusted odds ratio (95% CI) for exposure was 7.35 (1.67-32.3), compared to no exposure. Westerdahl et al. (1994) stratified on site of melanoma and adjusted for history of frequent sunbathing as well as family history of melanoma, history of sunburn, hair color, and raised nevi; among those with melanoma on the trunk, odds ratios (95% CI) for 1-3, 4-10, and >10 exposures per year, compared to no exposure, were 1.1 (0.5-2.2), 1.3 (0.6-3.2), and 4.2 (1.6-11.0). There was a significant trend with increasing number of exposures ($p<0.04$). These adjustments are somewhat crude, and the studies are hampered by small numbers, so uncontrolled confounding by exposure to solar radiation cannot be completely ruled out. Nevertheless, results from these three studies suggest that exposure to sunlamps or sunbeds is an independent risk factor for cutaneous malignant melanoma. Since UV radiation is presumably the relevant exposure underlying both solar radiation and sunlamps or sunbeds, the two exposures may have an additive effect on the risk of melanoma.

Table 3-1. Human Studies of the Relationship Between UV Radiation Exposure and Non-Hodgkin's Lymphoma

Design	Exposed Subjects/ Cases: source/no./ response rate	Controls: source/no./ response rate	Exposure: level/duration/ measurements	Exposure Categories	Potential Confounders Controlled For? [Y or N]	Odds Ratio (95% CI)	Effect of Confounders	Evidence for Dose-Response	Reference
case control	registered cases of non-Hodgkin's lymphoma in 59 counties of England and Wales; from the *Atlas of Cancer Incidence in England and Wales*	all other cancers (weighted sample)	cases registered from 1968 to 1985 age and sex-adjusted odds ratio for lymphoma in each county estimated levels of solar UVR from model that used data on latitude and cloud cover	NA	1) social class [Y] 2) agricultural employment [Y]	1.27 (1.24-1.29, p<0.001) before adjustment for confounders obtained by comparing risk of non-Hodgkin's lymphoma in a particular county with its risk in all other counties	odds ratio increased: 1.34 (1.32-1.37, p = 0.004) after adjustment for confounders	incidence of non-Hodgkin's lymphoma significantly associated with solar UV radiation	Bentham (1996)
cohort	registered cases of non-Hodgkin's lymphoma in U.K. outdoor workers from population-based cancer registry, adjusted for confounders Men-401 cases (age 20-74) Women-27 cases (age 20-74)	registered cases of non-Hodgkin's lymphoma in workers of all occupations from population-based cancer registry occupational information retrieved for 252,663 men and 119,227 women in registry; no. of cases with only non-Hodgkin's lymphoma NR	cancer registered from 1981-1987 outdoor workers defined by using the Southhampton occupational classification	1) outdoor occupation 2) all occupations	1) age: considered five-yr age groups [Y] 2) sex [Y] 3) social class: considered six classes [Y] 4) cancer registry of origin [Y]	adjusted proportional registration ratio (95% CI): Men: 95 (86-105) Women: 156 (103-228)	sex: significant increase (56%) for women but not men other confounder effects NR	incidence of non-Hodgkin's lymphoma higher among female outdoor workers compared to females in all occupations; outdoor workers have more exposure to solar UVR unknown reason for sex difference	Newton et al. (1996 lett.)

Table 3-1. Human Studies of the Relationship Between UV Radiation Exposure and Non-Hodgkin's Lymphoma (Continued)

Design	Exposed Subjects/ Cases: source/no. /response rate	Controls: source/no. /response rate	Exposure: level/duration/ measurements	Exposure Categories	Potential Confounders Controlled For? [Y or N]	Odds Ratio (95% CI)	Effect of Confounders	Evidence for Dose-Response	Reference
Descriptive	U.S. mortality rates for non-Hodgkin's lymphoma 1) 1950-1980 white population 2) 1970-1989 white population 3) 1978-1988 white males	NA	estimated average ultraviolet B (UVB) level in each state 1) examined U.S. geographic variation of lymphoma mortality rates 1950-1980 2) examined U.S. geographic variation of lymphoma mortality rates 1970-1989 3) fitted regression model with state-specific UVB as independent variable, state mortality rates for white men as dependent variable	NA	1) sex [Y]	NA	none	1) no consistent latitude gradient 2) no consistent latitude gradient 3) correlation coefficient statistically significant ($p<0.001$)	Hartge et al. (1996)
Descriptive	1) non-Hodgkin's lymphoma (NHL) incidence rates in Caucasian populations, classified by dominant latitude 2) world population cancer registries (age 30-74) 3) cancer incidence data from population-based registry in Australia	NA	1) relationship of NHL incidence rates to ambient UVR level in developed countries (latitude converted to estimates of UVB exposure) 2) correlation between percentage increases in NHL and malignant melanoma (MM) incidences during 1970-85 3) changes in incidence of NHL and MM in several migrant populations	NA	1) sex [Y] 2) race; race separately analyzed only for correlations between time trends in MM and NHL	NA	1) the correlation between MM and NHL was significant ($p<0.05$) for men but not women in Caucasian populations 2) the correlation between MM and NHL was stronger for a subset of male Caucasians than in all populations combined	1) moderate positive correlation between ambient UVR level and NHL incidence: correlation coefficient for men or women statistically significant ($p<0.001$) 2) moderate positive correlation between percentage increases in the incidence of MM and NHL for all populations minus Black, Maori, Indian ($p<0.05$ for men or women) 3) British migrants to higher UVR Australia have higher incidence rates of NHL	McMichael and Giles (1996)

NA=not applicable; NR=not reported

Table 3-2. Association of Cutaneous Malignant Melanoma (CMM) with Use of Sunlamps and Sunbeds

Reference, Location, Years Subjects Recruited	Number of Cases/ Controls	Exposure, Percent Exposed (Case/Control)	Risk for Ever Use	Dose-Response (Duration)	Comments
Gallagher et al. (1986) W. Canada 1979-1981	595/595	Sunlamp, Percent exposed not available	No association	Not considered	No association in men or women No association with site of use
Holman et al. (1986) W. Australia 1980-1982	511/511	Sunlamp 9 overall	1.1 (0.6-1.8)	Not considered	
Elwood et al. (1986) England 1981-1984	83/83	Sunlamp or tanning studio 15/12	No association	Not considered	Average exposure 2.3 h
Østerlind et al. (1988) Denmark 1982-1985	474/926	Sunlamp or sunbed 45/42	No association	Not considered	No association with number of times used
Zanetti et al. (1988) N. Italy 1984-1986	208/416	Sunlamp 7/5	0.9 (0.4-2.0)[a]	Not considered	
Swerdlow et al. (1988) Scotland 1979-1984	180/120	Sunlamp or sunbed 21/8	2.9 (1.3-6.4)[b]	$p<0.05$	Greater risk for first use before age 30 (OR 3.8) Greater risk for use >5 years previously (OR 9.1) No variation in risk by site or subtype

Table 3-2. Association of Cutaneous Malignant Melanoma (CMM) with Use of Sunlamps and Sunbeds (Continued)

Reference, Location, Years Subjects Recruited	Number of Cases/ Controls	Exposure, Percent Exposed (Case/Control)	Risk for Ever Use	Dose-Response (Duration)	Comments
Walter et al. (1990) Ontario 1984-1986	583/608	Sunlamp or sunbed M: 24/14 W: 28/21	M: 1.88 (1.20-2.98) W: 1.45 (0.99-2.13)	M: p<0.01 W: p<0.04	Dose-response for amount of use Greater risk for face/head/neck/arms than trunk or extremities Greater risk for LMM+HMF Greater risk for home use Greater risk for first use before age 30 Greater risk for last use ≥5 years previously
Autier et al. (1994) Belgium, France, Germany 1991+	420/447	Sunlamp or sunbed 26/27	0.97 (0.71-1.32)	Not considered	For 10+ h exposure, first exposure before 1980, exposure for tanning purposes, OR = 2.12 (0.84-5.37)[c] For 10+ h exposure, experience of sunburn, exposure for tanning purposes, OR = 7.35 (1.67-32.3)[c]
Westerdahl et al. (1994) Sweden, 1988-1990	400/640	Sunlamp or sunbed 30/25	1.3 (0.9-1.8)[e]	p<0.06	For individuals <30, OR = 2.7 (0.7-9.8); p for dose-response <0.02 Greater risk for trunk than head or extremities

[a] Adjusted for age, education, coloring, childhood sunburn

[b] Adjusted for age, sex, and city

[c] Adjusted for age, sex, coloring, weeks per year in sunny holiday resorts

[d] Adjusted for coloring, raised nevi, history of sunburn, history of frequent summer sunbathing

4.0 EXPERIMENTAL CARCINOGENESIS

This background document primarily focuses on human carcinogenesis. Therefore, experimental animal carcinogenesis studies were not included. Evidence for experimental carcinogenesis induced by UVR is covered in the IARC monograph (1992, pp. 139-161; see Appendix A).

5.0 GENOTOXICITY

Evidence for the genetic toxicity of solar and nonsolar UVR (UVA, UVB, and UVC) in prokaryotes, lower eukaryotes, mammalian systems *in vitro* and *in vivo*, and in humans has been thoroughly covered in the IARC Monograph, Volume 55 (1992, pp. 194-215; see Appendix A).

6.0 OTHER RELEVANT DATA

6.1 Absorption

Ultraviolet radiation (UVR) is absorbed by the skin and eyes in a wavelength-dependent manner. A tissue chromophore must absorb radiation in order to express photochemical or photobiological effects (IARC, 1992).

6.1.1 Epidermal Chromophores (IARC, 1992, pp. 165-166)

Urocanic acid (λ_{max}, 277 nm at pH 4.5), DNA (λ_{max}, 260 nm at pH 4.5), tryptophan (λ_{max}, 280 nm at pH 7), tyrosine (λ_{max}, 275 nm at pH 7), and melanins are the main chromophores in the epidermis (Morrison, 1985; cited by IARC, 1992). The epidermis can be divided into two parts; the inner part composed of living cells in the process of differentiation and an outer part, called the stratum corneum, in which the cells are fully differentiated and dead (IARC, 1992). Two isomers of urocanic acid exist in the epidermis, mainly in the stratum corneum. Exposure to UVR converts the *trans*-isomer of urocanic acid to the *cis*-isomer (Morrison, 1985; cited by IARC, 1992). Tryptophan and tyrosine in proteins absorb UVR throughout the epidermis. Melanocytes produce melanins, which absorb broadly over the UV spectrum (IARC, 1992, pp. 165-166).

6.1.2 Human Epidermal and Dermal Damage

A study on the cumulative damage in human skin caused by UVA wavelengths found that chronic damage has different spectral dependence, the dermal damage from UVA has a broad action spectrum, and the action spectrum is different from the acute erythema spectrum. Indices of cumulative photoperturbation were measurements of epidermal changes (stratum corneum thickening, viable epidermal thickening sunburn cell production) and dermal alteration (lysozyme deposition, inflammation). All UVA bands induced the dermal markers, but wavelengths > 400 nm caused no cutaneous alterations. UVA wavelengths between 320 and 345 nm were more effective than longer wavelengths in producing viable epidermal thickening (Lavker and Kaidbey, 1997).

6.1.3 Ocular Damage

Transmission of UVR in the cornea was maximal at 380 nm (80%); in the aqueous humor, 400 nm (90%); in the lens, 320 nm; and in the vitreous humor, 350 nm (80%) (Boettner and Wolter, 1962; cited by IARC, 1992, p. 166). Increasing age leads to decreasing transmission through the lens of UVR at 300-400 nm (Lerman, 1988; cited by IARC, 1992 p. 166).

6.2 Immunosuppression

The cutaneous immune system is altered by acute, low-dose exposure to UVB radiation in at least two ways: contact hypersensitivity is impaired and antigen-specific tolerance is induced (Streilein et al., 1994a).

6.2.1 Contact Hypersensitivity Impairment

UV-irradiated skin was treated with a contact sensitizer that should have induced a contact hypersensitivity (CH) response but did not (Toews et al., 1980; cited by Kripke, 1991). Human subjects were dosed with a topical application of dinitrochlorobenzene (DNCB) and 4 daily exposures to UVB radiation. Thirty days later another application of DCNB at a different site on the body yielded no response in 40% of the subjects, while 60% had typical CH responses (Rae et al., 1989; Yoshikawa et al., 1990; both cited by Streilein et al., 1994a). In mice a similar effect was seen when one population of mice lost CH responsiveness upon exposure to UVB and another population's CH response was resistant to UVB (Streilein and Bergstresser, 1988; Yoshikawa and Streilein, 1990; cited by Streilein et al., 1994b), supporting the belief that UVR studies in mice can be relevant in humans. IARC (1992) reviews contact hypersensitivity impairment on pp. 175-176 of the monograph.

6.2.2 Antigen-Specific Tolerance

UV-induced tumors are rejected upon transplantation into normal syngeneic hosts because they are highly antigenic, but they grow well in recipients with a suppressed immune system (Kripke, 1974; cited by IARC, 1992). Cytolytic T lymphocytes mediate immunologic rejection of these tumors with the assistance of natural killer and cytotoxic T cells (Fortner and Kripke, 1977; Fortner and Lill, 1985; Streeter and Fortner, 1988a, b; all cited by IARC, 1992). Exposure to UVR induces T-suppressor lymphocytes, which block the normal immunological surveillance system, allowing the antigenic UV-induced tumors to grow (Fisher and Kripke, 1977; Spellman et al., 1977; Fisher and Kripke, 1978; Spellman and Daynes, 1978; all cited by IARC, 1992). Exposure to UVC (from low-pressure mercury discharge lamps) (Lill, 1983; cited by IARC, 1992), UVB (De Fabo and Kripke, 1980; cited by IARC, 1992), large doses of UVA (Morison, 1986; cited by IARC, 1992), and sunlight (Morison and Kelley, 1985; cited by IARC, 1992) can induce suppressor cells. Long before the *de-novo* appearance of tumors, UVR exposure creates susceptibility to transplanted tumors (Fisher and Kripke, 1977; cited by IARC, 1992). IARC (1992) reviews antigen-specific tolerance on p. 180 of the monograph.

6.3 DNA Effects

Exposure of DNA to UVR leads to formation of many types of DNA photoproducts. Changes in wavelength alter the ratios of the products formed (IARC, 1992). A more detailed description of the photoproducts described in this subsection is provided by IARC (1992, pp. 185-189).

6.3.1 Pyrimidine Dimers

Thymine compounds dimerize in response to UVC via a cyclobutane ring involving carbons 5 and 6, which causes a loss of UV absorption (Beukers et al., 1958; Beukers and Berends, 1960; Wulff and Fraenkel, 1961; all cited by IARC, 1992). A wavelength-dependent equilibrium results from continued irradiation, with dimerization favored at wavelengths greater than 260 nm, when the ratio of dimer to monomer absorbance is small, while monomerization is favored when the ratio is larger (around 240 nm) (Johns et al., 1962; cited by IARC, 1992). Irradiated *Escherichia coli* DNA forms cytosine-thymine (cyt-thy), thymine-thymine (thy-thy), and cytosine-cytosine (cyt-cyt) cyclobutane-type dimers (Setlow and Carrier, 1966; cited by IARC, 1992). Under physiological conditions that produce uracil residues, cytosine moieties in dimers are deaminated and the rate could be more significant than previously believed (Fix, 1986; Tessman and Kennedy, 1991; both cited by IARC, 1992). Cyclobutane dimers can also be formed by exposure to UVB radiation by a mechanism that likely involves direct absorption (Ellison and Childs, 1981; cited by IARC, 1992). The excision repair mechanism, which is deficient in cells from most patients with xeroderma pigmentosum, removes cyclobutane-type dimers from DNA (Friedburg, 1984; Cleaver and Kraemer, 1989; both cited by IARC, 1992). Pyrimidine dimers are monomerized *in situ* by a photolyase in a specific photoreactivation (IARC, 1992). The IARC monograph reviews pyrimidine dimers on pp. 185-186.

6.3.2 Pyrimidine-Pyrimidone (6-4) Photoproducts

Acid hydrolyzates of DNA that was exposed to UVR contained the compound 6-4′-[pyrimidin-2′-one]thymine (thy(6-4)pyo) (Varghese and Wang, 1967; Wang and Varghese, 1967; both cited by IARC, 1992 pp. 186-187)). Products such as this, designated as (6-4) photoproducts, occurred at roughly the same frequency as cyclobutane dimers (Kraemer et al., 1988; cited by IARC, 1992).

6.3.3 Thymine glycols

After alkaline-acid degradation of human DNA from UV-irradiated cells, 5,6-dihydroxydihydrothymine type-lesions (thymine glycols) have been detected (Hariharan and Cerutti, 1976, 1977; cited by IARC, 1992). This class of UV photoproducts, thought to arise indirectly via the action of hydroxyl radicals, is structurally similar to a class of ionizing radiation products that is formed in this manner (IARC, 1992). Exposures in the UVB range of radiation increase the yield of thymine glycols relative to that of other UV-induced damage (Cerutti and Netrawali, 1979; cited by IARC, 1992). The lesions can be repaired by a glycosylase isolated from human cells (Higgins et al., 1987; cited by IARC, 1992). Thymine glycols are discussed by IARC (1992) on p. 187 of the monograph.

6.3.4 Cytosine Damage

Incision of cytosine photoproducts by human endonucleases was reported by Gallagher et al. (1989; cited by IARC, 1992, p. 188). The observed photoproducts were neither cyclobutane-type pyrimidine dimers nor (6-4) photoproducts, and they occurred with a frequency two orders of magnitude below that of pyrimidine dimers. Ultraviolet radiation (UVR) at 270 to 295 nm was optimal for induction of these lesions.

6.3.5 Purine Damage

Broad spectrum UV irradiation yields incision by endonuclease V at unidentified purine or purine-pyrimidine moieties (Gallagher and Duker, 1986; cited by IARC, 1992, p. 188) with a maximal induction at 260-300 nm (Gallagher and Duker, 1989; cited by IARC, 1992, p.188).

6.3.6 DNA Strand Breaks

Of all photoproducts induced by UVC radiation, those from single-strand breaks occur at the lowest proportion; however, strand breaks become more important at wavelengths of 290-400 nm (IARC, 1992). One strand break occurred at 313 nm for every 44 pyrimidine dimers in *E. coli* (Miguel and Tyrrell, 1983; cited by IARC, 1992), but at 365 nm only two pyrimidine dimers formed for each strand break (Tyrrell et al., 1974; cited by IARC, 1992). Both prokaryotes and eukaryotes can rapidly repair strand breaks (Tyrrell et al., 1974; cited by IARC, 1992). IARC (1992) discusses UVR-induced DNA strand breaks on pp. 188-189 of the monograph.

6.3.7 DNA-Protein Cross-Links

Eleven amino acids can be photochemically added to uracil with cysteine being the most reactive. Several cysteine-containing heteroproducts have been isolated and characterized (IARC, 1992 p. 189). Evidence suggests that wavelengths longer than 345 nm produce significant yields of DNA-protein cross-links in mammalian cells (Bradley et al., 1979; Peak and Peak, 1991; both cited by IARC, 1992).

6.3.8 Lethal Effects on Repair-Defective Bacteria

A comparative test of fluorescent lamps found that various lamps had lethal effects on repair-defective bacteria. DNA repair-defective *Salmonella* bacteria were killed by all lamps with relatively high UVB+UVC illuminance (> 0.5% UVB+UVC). Another repair-deficient bacterial species (an *E. coli* triple mutant) was killed by all lamps tested, even those that did not kill *Salmonella*, and single-hit exponential inactivation rates correlated to directly measured UVB+UVC output (Hartman and Biggley, 1996).

6.3.9 DNA Damage and Repair

A molecular epidemiology study reported that repair of UVR-induced DNA damage is reduced in basal cell carcinoma (BCC) cases relative to cancer-free controls (Grossman and Wei, 1995; Wei et al., 1995). Lymphocytes from BCC patients (n = 88) and controls (n = 135) were tested in a host cell reactivation assay that measured reporter gene expression in cells transfected with a recombinant DNA plasmid vector (pCMVcat) pre-exposed to UVR. The reporter gene was the enzyme chloramphenicol acetyltransferase (CAT) contained within the plasmid; repair of damaged genes was dependent on host cell DNA repair capacity. The host (human) cell DNA repair capacity was reflected by CAT activity in lymphocytes transfected with plasmids pre-exposed to one dose of nonsolar UVR (700 J/m^2) compared to reporter gene activity from plasmids unexposed to UVR. The results showed a statistically significant decrease (8.1%; $p<0.05$) in CAT activity (DNA repair capacity) between the BCC group and a control group (Grossman and Wei, 1995). A significantly increased risk of BCC was also observed among cases with low DNA repair capacity, when low capacity was defined as less than the median capacity of controls.

A similar study (Hall et al., 1994) found no statistically significant difference between DNA repair activity in lymphocytes from nonmelanocytic skin cancer cases and controls. Lymphocytes from cases (n = 86) and controls (n = 87) were cultured and transfected as described above, though samples were not immediately processed because of shipment delay.

A recent review of UV mechanisms of carcinogenicity concludes that UV-induced DNA photoproducts produce a variety of cellular responses that contribute to skin cancer (Yarosh and Kripke, 1996). Unrepaired DNA photoproducts cause the release of cytokines that contribute to tumor promotion, tumor progression, immunosuppression, and the induction of latent viruses. DNA repair enzymes are an important gene protection mechanism because they can reverse DNA photoproducts and block the carcinogenic responses triggered by cytokines.

7.0 MECHANISMS OF CARCINOGENESIS

7.1 Immunosuppression

trans-Urocanic acid is converted by UVB radiation to *cis*-urocanic acid, which has been reported to be immunosuppressive (Streilein, 1993; cited by Streilein et al., 1994b). *cis*-Urocanic acid causes a local accumulation and production of tumor necrosis factor-alpha (TNFα) (Streilein et al., 1994b), which seems to prevent induction of contact hypersensitivity (CH) by temporarily immobilizing factors within the skin (Streilein, 1993; cited by Streilein et al., 1994b). Cell markers for Langerhans cells disappear following exposure of the skin to UVR (Aberer et al., 1981; Hanau et al., 1985; both cited by Baadsgaard, 1991) and the antigen-presenting function of Langerhans cells is abrogated (Stingl et al., 1981; Gurish et al., 1983; Czernielewski et al., 1984; Sauder et al., 1983; all cited by Baadsgaard, 1991). When UV-irradiated epidermis, which is depleted of Langerhans cells, presents antigen, suppressor T-cell activation and tolerance to antigen result (Green et al., 1979; Toews et al., 1980; Sauder et al., 1981; all cited by Baadsgaard, 1991). The growth of immunogenic neoplasms induced by UVR in murine models requires the suppression of the immune system seen following exposure to UVR (Baadsgaard, 1991). A role for immunosuppression in carcinogenesis is supported by the fact that squamous cell carcinomas, basal cell carcinomas, and lentigo maligna melanomas all occur at higher incidences in immunosuppressed patients (Newell et al., 1988; Kinlen et al., 1979; Gupta et al., 1986; Hoxtell et al., 1977; Greene et al., 1981; all cited by Grabbe and Granstein, 1994) and these tumors generally occur in UV-exposed areas (Newell et al., 1988; Schmieder et al., 1992; both cited by Grabbe and Granstein, 1994).

UVBR-induced immunosuppression, following suppression of the expression of the adhesion molecule ICAM-1, was associated with the formation of a significant number of cyclobutane-type pyrimidine dimers. This immunosuppression was blocked by treatment with photolyase, which removed the dimers (Stege et al., 1996; cited by Krutmann et al., 1996). DNA repair mechanisms then play a role in determining the susceptibility of a human cell to UV-induced immunosuppression (Krutmann et al., 1996).

7.2 Mutations

Section 6.3 discussed the various effects of UV light on DNA. The different photoproducts formed have varying mutagenic potentials. Cyclobutane thy-thy dimers, the major UV photoproducts, are only weakly mutagenic (Banerjee et al., 1988, 1990; cited by IARC, 1992), while the relatively minor (6-4) thymine-thymine photoproduct is highly

mutagenic, though less common (LeClerc et al., 1991; cited by IARC, 1992, p. 201). UV-induced cyclobutane dimer formation is directly involved in UV carcinogenesis. Such dimers prevent gene transcription. Malignant transformation of the cell may result when the affected gene is a growth regulating gene such as an oncogene or tumor suppressor gene. DNA repair mechanisms include excision repair and photoreactivation. In the latter, the photoreactivating enzyme repairs UVR-induced cyclobutane dimers. The enzyme is activated by long-wave UVA and visible irradiation. Thus, photoreactivation repairing cyclobutane dimers, effectively reduces the incidence of UV-induced tumors in the South American opossum *Monodelphis domestica* (Ley et al., 1991; cited by Grabbe and Granstein, 1994).

The mutagenicity also varies with the type of UVR. Peak et al. (1987; cited by Robert et al., 1996) found that the frequency of single-strand breaks per genome per lethal event was higher upon exposure of a human teratoma cell line to UVA than UVB and/or UVC radiation. This is consistent with the finding that UVA induces a greater proportion of rearrangements than UVB, 39% and 24%, respectively, possibly due to repair of single-strand breaks (Robert et al., 1996).

7.3 *p53* Tumor Suppressor

Mutations in the tumor suppressor *p53* gene have been found in human squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and actinic keratosis (AK) (Ziegler et al., 1993, 1994; Nelson et al., 1994; Kanjilal and Ananthaswamy, 1994; Kanjilal et al., 1995; Nataraj et al., 1995; all cited by Ananthaswamy and Kanjilal, 1996). Mutations associated with dipyrimidinic sites correspond to the UVB-induced DNA lesions cyclobutane pyrimidine dimers and (6-4) photoproducts and have been found in the *p53* gene in human skin cancer, indicating that UVR is causing the skin cancer (Brash et al., 1991; cited by de Gruijl, 1996).

Mutations in *p53* can be identified in the fourth week of chronic irradiation (Ananthaswamy et al., 1997). This fact combined with the identification of *p53* mutations in sun-damaged skin and pre-malignant AK (Ananthaswamy and Kanjilal, 1996) suggest that *p53* is mutated early in carcinogenesis. However, an analysis of fifty malignant melanomas led Hartmann et al. (1996) to the conclusion that mutations in *p53* probably do not play a major role in SCC or BCC. Another study by Matsumura et al. (1996) found *p53* mutations in BCC in areas of the body not exposed to much sunlight, leading to the authors' conclusion that additional factors other than UVR cause BCC in non-sun-exposed areas.

7.4 DNA Repair

Application of liposomes containing endonuclease V, an enzyme that repairs cyclobutane pyrimidine dimers, following UV irradiation, decreased the incidence of SCC in mice, demonstrating that unrepaired dimers are a direct cause of cancer in mouse skin (Yarosh et al., 1992). The dimers are repaired by nucleotide excision repair, which has been found in human cells (Regan et al., 1968; cited by Sutherland, 1996), and photorepair by photolyase or photoreactivating enzyme using visible or near-UV light as an energy source. Photorepair of cyclobutane pyrimidine dimers has been measured *in situ* in human skin (Sutherland et al., 1980; D'Ambrosio et al., 1981, 1983; all cited by Sutherland, 1996). Unrepaired DNA photoproducts from UV exposure cause the release of cytokines that contribute to tumor development and DNA repair enzymes can reverse this process (Yarosh and Kripke, 1996).

7.5 Signaling Molecules

Transcription of Ha-Ras, Raf-1, and MAP-2 genes is induced by exposure of HeLa cells to UVR. Ultraviolet radiation also activates Src tyrosine kinase, potentiates the activity of c-Jun by increasing its degree of phosphorylation (Devary et al., 1993; Radler-Pohl et al., 1993; both cited by Grabbe and Granstein, 1994), and induces c-Fos (Shah et al., 1993; cited by Grabbe and Granstein, 1994).

7.6 Other Mechanisms

Exposure of human skin to a combination of UVA and UVB radiation increases the amount of ascorbate free radical ($Asc^{\cdot-}$) fourfold, while exposure to visible light causes a twofold increase (Jurkiewicz and Buettner, 1996). UVB radiation activates nuclear factor B (NF-κB) in human epidermoid carcinoma cells and cytosolic extracts free of nuclei; however, scavenging of free radicals decreased this activation (Simon et al., 1994; cited by Pentland, 1996). Protein kinase C (PKC) mediates the activity of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) as a tumor promoter. Exposure to UVB has been shown to produce similar cellular effects and to increase levels of PKC at the membrane and in the cytosol (Matsui et al., 1996). Glutathione *S*-transferase activity, which may play a role in protecting skin from UVR, is decreased in skin tissue following chronic exposure to UVB (Seo et al., 1996). None of the investigators were able to define the relationship between any of these effects and carcinogenesis.

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APPENDIX A

Excerpts from the IARC Monograph on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Volume 55 (Solar and Ultraviolet Radiation) pp. 43-290, 1992

APPENDIX B

DESCRIPTION OF ONLINE SEARCHES FOR SOLAR RADIATION AND EXPOSURE TO SUNLAMPS OR SUNBEDS

DESCRIPTION OF ONLINE SEARCHES FOR SOLAR RADIATION AND EXPOSURE TO SUNLAMPS OR SUNBEDS

Searches were limited to 1991 [the year before the IARC Monograph (1992), which has an extensive literature review] through July 1997.

Online searches for UVR were performed in databases on the systems of the National Library of Medicine and STN International from 1991 to date. Toxicology information was sought in EMIC, EMICBACK, and TOXLINE. Searches for human studies focused on non-Hodgkin's lymphoma associated with exposure to solar radiation and on epidemiology of nonsolar UVR.

Regulatory information was obtained from the in-house FESA CD-ROM containing the latest *Code of Federal Regulations*, and the *Federal Register* pertaining to the titles 21 (FDA), 29 (OSHA), and 40 (EPA).

Review of 1200 life sciences journals for current awareness was done using Current Contents on Diskette® (and cumulative issues on CD-ROM).

APPENDIX C

REPORT ON CARCINOGENS (RoC), 9th EDITION
REVIEW SUMMARY

Report on Carcinogens (RoC), 9th Edition
Review Summary

Solar Radiation and Exposure to Sunlamps or Sunbeds

NOMINATION

Review based on letter from Dr. Hiroshi Yamasaki (IARC) recommending listing in the RoC based on IARC classification of UV Radiation as a known human carcinogen (IARC Vol. 55, 1992).

DISCUSSION

Studies of human exposure to Solar Radiation clearly indicate a causal relationship between exposure to solar radiation and cutaneous malignant melanoma and non-melanocytic skin cancer. Recent human studies have shown that exposure to sunlamps or sunbeds is associated with cutaneous malignant melanoma. Exposure-response relationships were observed for increasing duration of exposure, and effects were especially pronounced in individuals under 30 and those who experience sunburn. The NTP will review UV Radiation, including UVA, UVB and UVC, separately for possible listing in the RoC. The recommendations from the three NTP reviews of this nomination are as follows:

Review Committee	Recommendation	Vote
NIEHS (RG1)	list as known human carcinogen	11 yes/0 no
NTP EC Working Group (RG2)	Defer action*	7 yes/1 no
NTP Board RoC Subcommittee	list as known human carcinogen	6 yes/0 no

*RG2 voted in favor of motion to defer action on UV Radiation until the Background Document could be revised to address the full spectrum of UV Radiation, including UVA, UVB, and UVC.

Public Comments Received

A total of 26 public comments were received, all with common format stating no disagreement with listing exposure to sunlamps and sunbeds in the RoC but do not feel UV Radiation should be listed in any category.