Ultraviolet Radiation Related Exposures

Introduction

Ultraviolet radiation (UVR) is electromagnetic radiation found between X-rays and light in the electromagnetic spectrum. It is emitted by the sun and artificial devices, including sunbeds or sunlamps. UVR can be divided into UVA, UVB, and UVC components.

Solar radiation and exposure to sunlamps or sunbeds were first listed in the *Ninth Report on Carcinogens* (2000) and broad-spectrum UVR and its components ultraviolet A radiation (UVA), ultraviolet B radiation (UVB), and ultraviolet C radiation (UVC) were first listing in the *Tenth Report on Carcinogens* (2002). Much of the evidence for listing the various UVR related-exposures applies to more than one type of UVR, thus the profiles for these listings are discussed together. Evidence for the carcinogenicity of broad-spectrum UVR comes from studies on solar radiation and exposure to sunlamps or sunbeds. Similarly, studies to evaluate the carcinogenicity of solar radiation in animals and to determine the mechanism(s) by which it causes cancer (mechanistic studies) involve exposure to broad-spectrum UVR or its UVA, UVB, or UVC components. Use of sunlamps or sunbeds entails exposure to ultraviolet radiation. Evidence for the carcinogenicity of the UVR-related exposures is discussed separately and follows this introduction. However, most of the information on additional information relevant to carcinogenicity, properties, use, production, exposure, and regulations is common to all listings for exposures related to UVR and therefore has been combined into one section following the carcinogenicity discussions. The listings for exposures related to UVR are as follows:

- Solar radiation is *known to be a human carcinogen*
- Exposure to sunlamps or sunbeds is *known to be a human carcinogen*
- Broad-spectrum UVR is *known to be a human carcinogen*
- Ultraviolet A radiation is *reasonably anticipated to be a human carcinogen*
- Ultraviolet B radiation is *reasonably anticipated to be a human carcinogen*
- Ultraviolet C radiation is *reasonably anticipated to be a human carcinogen*

Solar Radiation

Known to be a human carcinogen
First Listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Solar radiation is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, which indicate a causal relationship between exposure to solar radiation and skin cancer (both cutaneous malignant melanoma and non-melanocytic skin cancer). Some studies suggest that solar radiation also may be associated with melanoma of the eye and non-Hodgkin's lymphoma (IARC 1992).

Exposure to Sunlamps or Sunbeds

Known to be a human carcinogen
First Listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Exposure to sunlamps or sunbeds is *known to be a human carcinogen*, based on sufficient evidence of carcinogenicity from studies in humans, which indicate a causal relationship between exposure to sunlamps or sunbeds and human cancer. Sunlamps and sunbeds emit primarily UVA and UVB radiation. Epidemiological studies have shown that exposure to sunlamps or sunbeds increases the risk of malignant melanoma (Swerdlow *et al.* 1988, Walter *et al.* 1990, Autier *et al.* 1994, Westerdahl *et al.* 1994, Chen *et al.* 1998, Walter *et al.* 1999, Westerdahl *et al.* 2000). The longer the exposure, the greater the risk, especially in people exposed before the age of 30 or people who have been sunburned. Malignant melanoma of the eye also is associated with use of sunlamps (IARC 1992).

Broad-Spectrum UVR

Known to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Broad-spectrum UVR is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans that show a causal relationship between exposure and human cancer. Epidemiology studies have shown that exposure to broad-spectrum UVR (solar radiation) causes skin cancer (both melanocytic and non-melanocytic). Studies of humans exposed to solar radiation, artificial devices emitting broad-spectrum UVR, or devices emitting predominantly UVA or UVB all contribute to these conclusions. Evidence that the broad-spectrum UVR component of solar radiation is carcinogenic comes from (1) studies of human cancer associated with exposure to devices that emit artificial broad-spectrum UVR, (2) the fact that tumors develop at the same sites both in humans exposed to sunlight and in animals exposed to broad-spectrum UVR from artificial sources, and (3) mechanistic studies in which human tissue was exposed to artificial sources of broad-spectrum UVR.

Broad-spectrum UVR is absorbed by DNA and causes direct and indirect DNA damage with the potential to result in mutations, as demonstrated by mechanistic studies using human tissue. Mutations found in the *p53* tumor suppressor gene of human skin cancer are specific for broad spectrum UVR-induced damage.

The findings in humans are supported by evidence in experimental animals. Exposure to broad-spectrum UVR caused skin tumors (papilloma and squamous cell carcinoma) and eye tumors (spindle-cell sarcoma) in albino rats and skin tumors (fibrosarcoma and/or squamous-cell carcinoma) in mice, hamsters, and opossums (IARC 1992).

UVA

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVA is *reasonably anticipated to be a human carcinogen* based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals. Epidemiological studies on the effects of sunlight or artificial broad-spectrum UVR cannot identify effects due specifically to UVA, UVB, or UVC exposure. However, information about the specific effects of UVA, UVB, and UVC exposure can be inferred by comparing the results of human epidemiology studies of broad-spectrum UVR exposure with the results of studies on the effects of specific broad-spectrum UVR components in experimental animals and human tissues.

In studies where most of the UVR exposure was to UVA (i.e., exposure to solar radiation or UVA-emitting sunbeds), there was an increased risk of skin cancer. Westerdahl *et al.* (2000) studied exposure to sunbeds emitting mainly UVA (with 0.1% to 2.1% UVB) and found an increased risk of melanoma. The available data from experimental animals show that exposure to UVA caused skin tumors in mice (squamous-cell carcinoma and papilloma) and fish (melanoma) (IARC 1992).

UVB

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVB is *reasonably anticipated to be a human carcinogen* based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals. Mechanistic studies with human tissue have demonstrated that the UVB component in solar radiation is absorbed by DNA, resulting in DNA damage that leads to the characteristic *p53* gene mutations observed in human skin cancer. However, epidemiologic studies linking these exposures to skin cancer are limited because they lack information on the specific wavelengths of UVR to which the individuals were exposed. Although increased skin cancer is clearly associated with exposure to UVB (as a component of solar radiation or from sunlamps used before the early 1970s), the people in these studies also were exposed to other components of broad-spectrum UVR. Therefore, the studies could not distinguish between the effects of UVB and other components of UVR. Sunlamps used in the early 1970s produced significant amounts of UVB (22 to 40%); one study found that exposure to UVB-emitting sunlamps increased the risk of malignant melanoma of the skin (Chen *et al.* 1998). In experimental animals, prolonged exposure to devices emitting primarily UVB caused skin tumors in rats (papilloma), mice (squamous-cell carcinoma, fibrosarcoma, papilloma, and keratoacanthoma), guinea pigs (fibroma and trichofolliculoma), and opossums (melanocytic hyperplasia and melanoma) (IARC 1992).

UVC

Reasonably anticipated to be a human carcinogen
First Listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVC is *reasonably anticipated to be a human carcinogen* based on limited evidence from mechanistic studies with human tissue and sufficient evidence from studies in experimental animals. Human studies, including those with cultured human cells, have shown that exposure to UVC causes DNA damage. UVC is absorbed by DNA and causes damage similar to that caused by UVB. However, no epidemiological studies have adequately evaluated UVC carcinogenicity in humans. UVC is absorbed by the ozone layer and does not contribute to solar exposure. In studies of exposure to artificial devices emitting UVC, the devices also emitted other components of UVR. Exposure to high doses of radiation from devices emitting primarily UVC caused skin tumors in rats (keratoacanthoma-like tumors) and mice (squamous-cell carcinoma and fibrosarcoma) (IARC 1992).

Ultraviolet Radiation Related Exposures

Additional Information Relevant to Carcinogenicity

Broad-spectrum UVR causes skin cancer via DNA damage, suppression of the immune system, tumor promotion, and mutations in the *p53* tumor suppressor gene. Broad-spectrum UVR causes mutations in cultured human cells; the type of damage depends on the specific wavelength of UVR and whether the affected cells can repair the damage without error. DNA absorbs broad-spectrum UVR (mainly UVB and UVC), and this reaction yields products that can cause mutations (discussed below under "Properties"). UVB causes the following four major DNA base modifications (changes to DNA's structure) in people: cyclobutane-type pyrimidine dimers, (6-4) photoproducts, the corresponding Dewar isomers, and thymine glycols. Both UVA and UVB induce 8-hydroxydeoxyguanosine production from guanosine by the action of singlet oxygen (Griffiths *et al.* 1998).

UVA, UVB, and UVC as individual components of broad-spectrum UVR cause genotoxic damage in several *in vitro* test systems, including bacteria, yeast, rodent cells, and human cells. Moreover, exposure to each of the three components of broad-spectrum UVR causes DNA damage in humans. UVA's biological effects are indirect and largely the result of energy transferred through reactive oxygen intermediates (free radicals), whereas UVB and UVC are absorbed by DNA and directly damage DNA through base modifications. Based on the number of studies showing genetic damage, UVC is the strongest genotoxin of the three components of broad-spectrum UVR, and UVA is the weakest.

More than 90% of human squamous-cell carcinomas contain mutations of the *p53* tumor suppressor gene. These mutations were found in 74% of sun-exposed normal human skin and only 5% of unexposed skin, indicating a strong association with sun exposure. Observed *p53* gene mutations were most frequently C to T or CC to TT transitions at pyrimidine–pyrimidine sequences. These specific *p53* mutations now are considered a signature of broad-spectrum UVR carcinogenesis (Brash *et al.* 1991, Ziegler *et al.* 1993, Griffiths *et al.* 1998, Wikonkal and Brash 1999).

Exposure to solar radiation and broad-spectrum UVR alters immune function in humans and experimental animals (IARC 1992). Evidence that immunosuppression is related to skin cancer comes from the following observations: (1) immunosuppressed organ transplant recipients showed a marked increase in skin cancer, particularly squamous-cell carcinoma, (2) broad-spectrum UVR decreased the ability to mount a delayed-type hypersensitivity response, and (3) mice exposed to low levels of broad-spectrum UVR failed to reject highly immunogenic tumor cell lines (Quinn 1997).

Exposure of human skin grafts on mice to UVB radiation after pretreatment with the carcinogen dimethylbenz(*a*)anthracene causes human skin tumors (squamous-cell carcinoma, actinic keratoses, melanocytic hyperplasia, and melanoma) (Atillasoy *et al.* 1997). Exposure of human skin grafts on mice to UVB alone causes precancerous lesions (melanocytic hyperplasia).

Properties

Solar radiation includes most of the electromagnetic spectrum. Of the bands within the optical radiation spectrum, UVR is the strongest and most damaging to living things (IARC 1992). Broad-spectrum UVR includes wavelengths of light ranging from 100 to 400 nm. UVR is divided into wavelength ranges identified as UVA (315 to 400 nm), UVB (280 to 315 nm), and UVC (100 to 280 nm). Of the solar UV energy reaching the equator, 95% is UVA and 5% is UVB. No measurable UVC from solar radiation reaches the earth's surface, because the shortest UV wavelengths are completely absorbed by

ozone, molecular oxygen, and water vapor in the upper atmosphere (Farmer and Naylor 1996).

Molecules that absorb UVR and visible light (photoreactive molecules) contain segments that react with light (called chromophores), in which photons of light excite electrons from the ground state to higher-energy states. These molecules then generally re-emit light on returning to lower-energy or ground states (Dyer 1965). The various molecules sensitive to UVR differ in the wavelengths of UVR that they absorb and the light that they emit.

Photochemical and photobiological interactions occur when photons react with a photoreactive molecule, forming either an altered molecule or two separate molecules (Phillips 1983, Smith 1989). For such a reaction to occur, the photons must have enough energy to alter a photoreactive chemical bond (i.e., to break the original bond or form new bonds).

The photobiological reactions related to skin cancer risk due to UVR exposure are the reactions with the main chromophores of the skin's outer layer—urocanic acid, DNA, tryptophan, tyrosine, and the melanins. The products resulting from UVR's reaction with DNA (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 various DNA photoproducts differ in their mutagenic potential (IARC 1992).

UVR-induced DNA photoproducts cause 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 (IARC 1992, Yarosh and Kripke 1996).

UVB is considered to be the major cause of skin cancer, despite the fact that it does not penetrate the skin as deeply as UVA or react with the outer skin layer as vigorously as UVC. Its high reactivity with macromolecules, coupled with the depth to which it penetrates skin, makes UVB the most potent portion of the UV spectrum for both short-term and long-term biological effects. UVA, while possibly not as dangerous, also causes biological damage (Farmer and Naylor 1996).

Use

Broad-spectrum UVR has many uses as a natural source of energy and is important in various biological processes. Solar radiation is required for life. Plants must have sunlight to grow and to produce carbohydrates and oxygen. Broad-spectrum UVR from solar radiation helps produce vitamin D in human skin cells. Vitamin D metabolites promote the absorption of calcium by the intestinal tract; therefore, it is essential for the growth and development of healthy bones. Brief exposure to sunlight on a regular basis is sufficient to produce all of the vitamin D most people need. This vitamin also can be obtained from dietary sources. Artificial sources of broad-spectrum UVR have many uses, including tanning, medical diagnosis and treatment, and promotion of polymerization reactions (e.g., curing of protective coatings). Sunbeds use artificially produced UVR to enable individuals to develop a suntan for cosmetic reasons. Originally, sunbeds were built with mercury arc lamps, which emitted large quantities of UVB and UVC. Now, sunbeds and solaria emit mostly UVA (IARC 1992).

Broad-spectrum UVR has both diagnostic and therapeutic uses in medicine and dentistry. More than 30 disorders now can be treated through UVA exposure combined with compounds called psoralens (PUVA therapy). Psoriasis and eczema are the skin diseases most frequently treated with PUVA therapy. PUVA can also be used with UVB exposure to treat psoriasis patients who are not good candidates for systemic therapy with methotrexate or etretinate (Morrison 1992). In addition, broad-spectrum UVR and, more commonly, UVB are used with coal-tar creams to treat psoriasis (Reid 1996). UVB also may be used to convert 7-dehydrocholesterol (provitamin D) to vitamin D in the skin of vitamin D-deficient patients.

UVA may be a component of the phototherapy to treat neonatal jaundice or hyperbilirubinemia. Typically an infant is irradiated with visible light for several hours a day, for up to one week; however, the lamps also may emit UVR, and one commercial neonatal phototherapy unit was found to emit UVA and shorter wavelengths of UVR (IARC 1992). UVA has been found to react with melatonin, a hormone that helps to regulate sleep-wake cycles. Although the photoproducts of melatonin have not been identified, melatonin has been predicted to be moderately phototoxic (Kim *et al.* 1999).

Broad-spectrum UVR has many industrial applications. One of its major industrial uses is in photopolymerization, including curing of protective coatings and inks. Broad-spectrum UVR is used to simulate weathering of various materials, such as polymers. UVR (usually UVC at 260 to 265 nm) is used to sterilize and disinfect tools and materials. Other uses include UV photography, UV lasers, and in dental examinations to detect early dental caries, dental plaque, and calculus (IARC 1992).

Sources

In the broadest sense, broad-spectrum UVR is formed when something is heated or when electrons that have been raised to an excited state return to a lower energy level. Broad-spectrum UVR is naturally emitted by the sun. An estimated two-thirds of the energy emitted by the sun penetrates the atmosphere. Broad-spectrum UVR constitutes approximately 5% of the solar radiation that reaches the earth's surface (IARC 1992).

Six artificial sources of broad-spectrum UVR have been identified: incandescent lights, gas discharge lamps, arc lamps, fluorescent lamps, metal halide lamps, and electrodeless lamps. Incandescent sources provide visible radiation in a continuous spectrum. Gas discharge lamps produce visible radiation when an electrical current is passed through a gas. The type of gas present in the lamp determines the emission wavelengths; low gas pressures produce narrow bands, whereas higher pressures produce broad bands. Arc lamps are intense sources of broad-spectrum UVR and often are used to simulate solar radiation. Fluorescent lamps emit radiation from a low-pressure mercury discharge, which produces a strong emission at 254 nm; this radiation excites the phosphor-coated lamp to produce fluorescence. Various emission spectra can be obtained by altering the makeup and thickness of the phosphor and the glass envelope. In metal halide lamps, metal halide salts are added to a mercury-vapor discharge lamp, thus creating extra emission lines. Electrodeless lamps use magnetrons to generate microwave energy, which then is absorbed by the discharge tube (IARC 1992).

Low-pressure mercury vapor lamps, sunlamps, and black-light lamps are considered to be low-intensity UVR sources. High-intensity UVR sources include high-pressure mercury vapor lamps, high-pressure xenon arc lamps, xenon-mercury arc lamps, plasma torches, and welding arcs.

Sunlamps and sunbeds emit broad-spectrum UVR. Sunbeds now chiefly emit UVA; however, before the mid 1970s, they more commonly emitted UVB and UVC (IARC 1992). Three different UVA phosphors have been used in sunlamps sold in the United States since the late 1970s, producing emission spectra that peak at 340, 350, or 366 nm. Two modern sunlamps evaluated by the U.S. Food and Drug Administration emitted 99.0% and 95.7% UVA; the remaining radiation was UVB. A new high-pressure UVA sunbed with eighteen 1600-watt filtered arc lamps emitted 99.9% UVA. An older type of sunlamp, used prior to the late 1970s (UVB/FS type), emitted 48.7% UVA (Miller *et al.* 1998).

Exposure

The greatest source of human exposure to broad-spectrum UVR is solar radiation; however, the exposure varies with geographical location. Information on global broad-spectrum UVR levels has been compiled from data gathered for epidemiological studies of skin cancer

and other health effects, such as premature aging of the skin, cataracts, and suppression of the immune response. Despite the large number of measurements, estimating human exposure is complex. The UVR wavelengths to which an individual is exposed vary considerably with latitude, altitude, time of day, and season. People also vary in their length of outdoor exposure, the parts of the body they expose, and the shapes of their bodies. Nevertheless, many studies have estimated exposure to broad-spectrum UVR. Few studies, however, were able to distinguish between UVA, UVB, and UVC exposure (IARC 1992).

Various factors influence terrestrial levels of UVA (i.e., levels found at the earth's surface). UVA levels decrease with increasing distance from the equator and increase with increasing altitude. Terrestrial UVA levels also are decreased by stratospheric ozone, which varies with latitude and season. When there is less ozone, more UVA reaches the earth's surface. Time of day also influences UVA levels. Clouds reduce the amount of UVA reaching ground level. Air pollution, including tropospheric ozone, can decrease UVA exposure, especially in urban areas. Surface reflection also contributes to personal exposures to UVA and can result in exposure to body parts that otherwise would be shaded from the sun (IARC 1992).

Terrestrial UVB levels are affected by the same factors as terrestrial UVA levels; however, since UVB is absorbed more by stratospheric ozone than is UVA, differences in latitude and altitude affect UVB exposure more than UVA exposure. Seasonal changes affect UVB levels, mostly in temperate regions. Generally, cloud cover scatters less than 10% of the UVB under a clear sky; however, very heavy cloud cover virtually eliminates UVB, even in the summer. Surface reflection also contributes to human UVB exposure (IARC 1992).

Commonly used fluorescent sunlamps deliver 0.3 to 1.2 times the annual UVA dose from the sun to a typical tanner exposed for 20 sessions at 2 minimal erythemal doses (MED) per session (Miller *et al.* 1998). (The MED is the lowest UVR exposure sufficient to produce well-defined reddening of the skin within 24 hours of exposure.) A frequent tanner (100 sessions at 4 MED/session) receives 1.2 to 4.7 times the annual solar UVA dose, while the newer high-pressure sunlamps deliver 12 times the annual solar UVA dose to the frequent tanner.

Approximately 25 million people in the United States use sunbeds each year, and one to two million people visit tanning facilities as often as 100 times per year (Sikes 1998, Swerdlow and Weinstock 1998). Teenagers and young adults are prominent among users. A 1995 U.S. survey found that of commercial tanning salon patrons, 8% were 16 to 19 years old, 42% were 20 to 29 years old, and 71% were female (Swerdlow and Weinstock 1998).

Anyone working outside (such as agricultural, construction, and road work laborers) is exposed to solar radiation on the job. For a group of more than 800 outdoor workers in the United States at 39° N latitude (the latitude of Philadelphia), personal annual exposure of the face was estimated at 30 to 200 MED (Rosenthal *et al.* 1991). However, this estimate may be low because Rosenthal and colleagues assumed facial exposure to be only 5% to 10% of ambient exposure, whereas other data suggested that it could be as high as 20%. Based on this higher estimate, the annual facial exposure doses for these outdoor workers would be 80 to 500 MED (IARC 1992).

Occupational exposure to artificial broad-spectrum 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 (IARC 1992). UV lasers, such as those used in cornea shaping and coronary angioplasty, are another potential source of occupational exposure, with relative risks that could be comparable to risks for individuals in outdoor professions (Sterenborg *et al.* 1991). Electric arc welders are the largest occupational group with exposure to artificial broad-spectrum UVR. It is estimated that more than 500,000 welders in the United States have been occupationally exposed to broad-spectrum UVR. Occupational exposure to artificial broad-spectrum UVR depends on both the source of exposure and the protective methods used to decrease exposure. Some artificial broad-spectrum UVR sources (such as germicidal lamps in some uses) are self-contained and present no risk to workers. Other occupational uses, such as use of UVR in laboratories, UV photography, and UV lasers, inevitably lead to broad-spectrum UVR exposure, which may include intense short-term exposures (IARC 1992).

Regulations

FDA

Performance standards for sunlamps and other devices that emit ultraviolet radiation have been developed

User instructions and warning labels must accompany sunlamps and other devices that emit ultraviolet radiation

Guidelines

ACGIH

Threshold limit values (TLVs) have been developed for over 60 different wavelengths (ranging from 180 to 400 nm) in the ultraviolet spectrum. In addition to these TLVs, specific protections for the eye to exposures from UV radiation in the 315 to 400 nm spectral range also have been developed[1]

NIOSH

Comprehensive recommendations for standards have been developed that include various exposure limits, labeling and warning sign requirements, and numerous work practice requirements[1]

[1]See *Introduction* for information on where to obtain additional detail on regulations and recommendations.

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