

Chapter 9

Summary of Data

Chemistry, occurrence and human exposure

Chemical and physical characteristics of constituents of sunscreens

The term 'sunscreens' is used in this volume to refer to formulated products that are ready for use to protect the skin against solar ultraviolet radiation (UVR), including those commercially available and formulations under test. 'Active' ingredients of sunscreens are the chemicals included in sunscreen formulations for the purpose of reducing the amount of UVR that reaches the viable cells of the skin. The active ingredients can be classified as organic or inorganic chemical absorbers. The seven major groups of organic chemical absorbers currently used in sunscreen formulations are derivatives of cinnamates, salicylates, *para*-aminobenzoates, camphor derivatives, anthranilates, benzophenones and dibenzoylmethanes. The inorganic chemical absorbers are titanium dioxide and zinc oxide. Approximately 42 of these major groups or their derivatives are currently used as ingredients in hundreds of branded products. Although each ingredient has several names, each is associated with a unique Chemical Abstract Services (CAS) number. Sunscreen formulations are complex mixtures of solvents, wetting and suspending agents, preservatives, fragrance materials and other additives. The active ingredients are subject to analytical evaluation and quality control.

A major characteristic of sunscreen ingredients is photostability. Decay rates have been reported under conditions of

exaggerated exposure and realistic use. In general, marketed sunscreen formulations are of acceptable stability but some ingredients have been reported to induce photoproducts, the biological and photobiological significance of which are under investigation.

Sunscreens are marketed as pharmaceuticals (drugs) in some countries (such as Australia, Canada and the USA) and as cosmetics in others (such as the countries of the European Union and Japan). The regional lists of approved ingredients are not identical but overlap broadly.

Measurement of UVR and human exposure

The solar UVR to which an individual is exposed depends on the following factors:

- intensity of ambient solar UVR,
- fraction of ambient exposure received on different anatomical sites,
- type of behaviour and time spent outdoors.

The dose of UVR absorbed by the skin is further modified by the use of photoprotective agents such as hats, clothing and sunscreens.

A number of studies indicate that adult indoor workers in northern Europe receive about 70% of their annual exposure to UVR during weekends and holidays and principally on the hands, forearms and face. Annual exposure is approximately 5% of the total ambient UVR available. As children and adoles-

cents have more opportunities for exposure to the sun, they receive about 7% of ambient UVR. Studies of children in Australia and England showed that behaviour can be as important as ambient UVR on the exposure of an individual to the sun.

Increased frequency of holidays in sunny climates and of outdoor leisure activities are resulting in increasing exposure of populations, especially those in temperate latitudes.

The sun protection factor (SPF) is popularly interpreted as a measure of how much longer skin covered with sunscreen takes to burn compared with unprotected skin. This interpretation can encourage users to prolong their exposure accordingly. Nevertheless, there is ample evidence that the numerical measure of protection indicated on a package is generally higher than that achieved in practice. Because the typical thickness applied is considerably less than that used by manufacturers (2 mg/cm²) during determination of SPF in the laboratory, consumers can expect to be protected to a degree closer to one-third of the value.

Behavioural aspects

Since 1950, an increasing number of white people have used sunscreens, principally in Australia, Europe and North America. Sunscreen use has also become common in Japan. Use of these products is one of the actions described as 'sun-related behaviour', i.e. any behaviour that increases or decreases exposure of skin or eyes to solar UVR. Other such behaviour includes wearing

protective clothing, hats or sunglasses, remaining in the shade, staying indoors around solar noon and minimizing the time spent outdoors at high altitude and low latitudes and in sunny seasons. It is often difficult to separate the protection attributable to sunscreens from that afforded by other forms of sun protection.

Two types of exposure can be distinguished during which sunscreen may be applied to uncovered parts of the skin: intentional and unintentional sun exposure. Intentional exposure is that with the primary purpose of achieving a biological response from the sun, such as acquisition of a tan. During intentional exposure, significant portions of the trunk and limbs are frequently uncovered. Sunbathing is the most typical such behaviour. In children and in adults, most sunburns occur during intentional sun exposure. Unintentional sun exposure is that which occurs during usual daily life, without the specific intention of acquiring a tan or staying in the sun for its own sake. During this type of behaviour, the parts of the body that are uncovered are generally the face, ears, neck and hands. The forearms and legs especially of women may also be uncovered, but the trunk is rarely uncovered. The randomized trials of the ability of sunscreens to prevent non-melanocytic sun-induced lesions generally addressed unintentional exposure.

The results of a large number of studies on sunscreen use in various populations have been published. Geographic, racial and cultural characteristics account for much of the variation in sunscreen use, but some consistent features of use are that women are more likely than men to use sunscreens; children and adults are more likely to use them than are adolescents; sunscreen use is most common on the beach or during sunbathing; white-skinned people from high latitudes, particularly in 'sunny' situations, are heavy users of sunscreens. The limited published data on

how people actually use sunscreens strongly suggest that the products are often, probably usually, not used as recommended. While behavioural studies confirm that sunscreens are used to prevent sunburn, the other underlying reasons vary considerably, from motivation to stay in the sun as long as possible without burning to deliberately seeking maximum protection against skin cancer. Educational strategies, particularly in schools and communities, can increase sun protection behaviour and increase sunscreen use, but at a population level it is probably sunscreen advertising that is most influential and most likely to promote intentional sun exposure.

Sunscreens are designed primarily to prevent sunburn. Use of sunscreens during unintentional exposure appears to reduce the occurrence of sunburn, but use of sunscreens or of higher-SPF sunscreen during intentional exposure appears to have little effect. One study of intentional exposure indicated that subjects who use high-SPF sunscreens stay in the sun longer than those who use lower-SPF products and that at least 'sun-seeking' populations use sunscreen to avoid sunburn rather than total UVR exposure; guarding against skin cancer is at best a secondary motive.

In a study of persons aged 40 or more who were randomized to apply sunscreens of SPF 15 or more or a placebo moisturizer, those given sunscreens reported a similar frequency of other sun-protection behaviour, including time spent outdoors, to those not given sunscreen. This suggests that the way in which different sun protection behaviours are 'balanced' by individuals depends on personal characteristics and motivations.

Metabolism and kinetics

The percutaneous absorption of the active ingredients of sunscreens has been assessed in human skin *in situ* and in excised skin in various animal models.

Very few studies have been done with the inorganic active ingredients of sunscreens, but there is some, limited evidence that they reach the epidermis. More extensive research has been conducted with the organic active ingredients of sunscreens. Studies in humans and animals have consistently shown percutaneous absorption of PABA and benzophenone-3. In the case of PABA, 1.6–9.6% of an applied dose was recovered in urine within 48 h, mostly in the acetylated form. In humans, 1–2% of benzophenone-3 applied at high concentrations over a 10-h period was absorbed systemically. Studies of excised skin from micro-Yucatan pigs showed percutaneous absorption of ethylhexyl methoxycinnamate. In the most extensive studies of the pharmacokinetics of sunscreens, conducted by oral administration of benzophenone-3 to rats, three metabolites were identified, and urine was found to be the main route of excretion.

Some studies have shown that the vehicle can markedly affect the percutaneous absorption of sunscreens.

Cancer-preventive effects

Humans

Cutaneous melanoma

The results of 15 case-control studies were available to evaluate the potential preventive effect of sunscreens against cutaneous melanoma. No results were available from randomized controlled trials or cohort studies.

Four case-control studies provided little evidence of an effect of sunscreen use on the risk for melanoma among all subjects.

Three case-control studies showed significantly lower risks for melanoma in users of sunscreens than in non-users. Two of these were relatively small, hospital-based studies conducted in populations in Spain with both a low prevalence of sun-sensitive subjects and a low prevalence of sunscreen use. The third was conducted among white women 25–59 years of age in California, USA.

This study was unusual in showing the highest levels of risk for melanoma among women with the least solar exposure, but all of the relative risks were close to 1.0.

Eight case-control studies, in Australia, Europe and North America, showed significantly higher risks for melanoma in users of sunscreens than in non-users, with relative risks for the highest category of use ranging up to 2.6. When adjustment was made for sun exposure and sun sensitivity variables in five studies, the relative risk fell in two studies and changed little in three studies. However, none of the adjusted relative risks fell much, if at all, below 1.0.

In two of the studies that showed significantly increased risks for melanoma among sunscreen users, analysis of subgroups suggested that use of sunscreens during heavy intentional sun exposure was associated with a particularly high risk. One of these studies provided specific evidence that sunscreen use in such a group may have led them to prolong their sun exposure. In addition, one of the studies that showed little overall effect of sunscreens found a significantly increased risk for melanoma among people who used sunscreens only during the first hours of sun exposure.

All the studies of sunscreen use and melanoma are difficult to interpret because of problems of positive confounding of sunscreen use with sun exposure, sun sensitivity and history of sun-related neoplasia and negative confounding with other sun-protective behaviour (e.g. use of protective clothing, wearing a hat or staying in the shade). None of the studies adjusted for measures of sun-related neoplasia or other sun-protective behaviour, nor was it known whether this confounding was important. Where measurement and control of sun exposure and sun sensitivity were included in the analysis, there is serious concern that they were insufficient to control confounding.

Acquired melanocytic naevi are considered to be precursors of some cutaneous melanomas. One randomized trial of the ability of sunscreens to inhibit the formation of melanocytic naevi has been published and suggests a protective effect. Other evidence on this issue comes from four cross-sectional or cohort studies among children carried out in Australia and Europe. Two of these studies reported no reduction in naevus counts among children who used sunscreens when compared with children not using them. The two other studies reported higher naevus counts on children who used sunscreens, but the first presented no data to support this contention. In the other, the relationship persisted after attempts to control for sun sensitivity and sun exposure.

Two cross-sectional studies of melanocytic naevi have been conducted among adults. One report did not provide quantitative information on sunscreen use or the number of naevi. The other study showed a modest elevation in the prevalence of naevi among subjects who used ordinary sunscreens and a greater elevation among subjects who used psoralen-containing sunscreens. The studies in adults are difficult to interpret as it is not clear whether the naevi appeared before or after use of sunscreens.

The studies of melanocytic naevi, like those of cutaneous melanoma, suffer from possible confounding of sunscreen use with sun exposure, sun sensitivity and use of other sun-protective measures and from problems of accuracy of measurement.

Basal-cell carcinoma

One randomized trial of the effectiveness of sunscreens in reducing the risk for basal-cell carcinoma was conducted in an appropriate population with appropriate measures. No protective effect on sun-exposed body sites was seen in the 4–5 years of follow-up. A single cohort study conducted among female nurses in the USA showed a small but non-sig-

nificant increased risk for basal-cell carcinoma. Two case-control studies gave contrasting results. An Australian study showed a modest increase in risk among subjects using sunscreens in the 10 years prior to diagnosis. The other case-control study, conducted in a Spanish population, showed a lower risk among subjects using sunscreens, but data on basal- and squamous-cell carcinomas were combined in the analysis. These studies faced the same difficulties in control of confounding of sun-sensitivity factors and sun exposure as the case-control studies of melanoma.

Squamous-cell carcinoma

A single randomized trial has been conducted to evaluate use of sunscreens in preventing squamous-cell carcinoma. Fewer participants in the sunscreen group developed new squamous-cell carcinomas than those in the comparison group, and the total number of squamous-cell carcinomas among participants given sunscreen was lower than that in the comparison group. Only the latter difference was statistically significant.

The single cohort study showed no decrease in risk for squamous-cell carcinomas with use of sunscreens. Two case-control studies have been conducted of sunscreen use and squamous-cell carcinoma. The Australian study showed no consistent pattern of decreased risk among subjects of three different age groups using sunscreens. The Spanish study showed a decrease in risk among sunscreen users, but data on basal- and squamous-cell carcinomas were combined in the analysis. One case-control study of lip cancer appeared to show a reduced risk with use of lip coverings; however, it is unclear whether the lip coverings were sunscreen preparations. Control for sun sensitivity and sun exposure was probably not complete in either the cohort or case-control studies.

Actinic keratoses are a recognized precursor lesion for squamous-cell

carcinomas. Two randomized trials showed a significant protective effect of use of sunscreens against actinic keratoses. A cross-sectional study conducted in the United Kingdom was uninformative.

Experimental systems

Of the 20 reported studies of protection against photocarcinogenesis by sunscreens in experimental animals, 18 were performed in hairless mouse strains and two in haired mice. In most of the studies, suboptimal UVR sources were used. Solar-simulated UVR was used in only seven of 17 studies on the induction of skin carcinogenesis, and in two of three studies of co-carcinogenesis with 7,12-dimethylbenz[*a*]anthracene. Furthermore, in 10/20 studies, UVR was administered in various incremental regimens, in contrast to the constant daily exposure used in the other studies. The resulting tumours ranged from benign papillomas to malignant squamous-cell carcinomas. The carcinogenic effect was measured either as the median increase in latency for skin tumour development or as the tumour load per mouse. Sunscreens were shown to prevent UVR-induced carcinogenesis in all studies.

Inorganic sunscreens were tested in mice exposed only to solar-simulated UVR in two of the 20 reported studies, but not adequately. In one study of the co-carcinogenicity of solar-simulated UVR and 7,12-dimethylbenz[*a*]anthracene, a titanium dioxide-containing sunscreen was protective.

Formulations containing multiple UVR absorbers were tested with solar-simulated UVR in only three studies and with non-solar UVR in six of 20 studies. Single agents were tested in all other studies. Dose-response relationships were not established for UVR in any of the studies, and different sunscreen formulations could not be compared.

Mechanisms of cancer prevention

In studies of DNA damage induced by UVB and solar-simulated UVR in human

skin, sunscreens reduced the number of adducts. The degree of protection against DNA damage provided by sunscreens varied among individuals. The relationship between DNA damage and the erythral response remains uncertain. DNA damage is considered to be a transient early biomarker of photocarcinogenesis. Several additional studies in animals showed that sunscreens prevented DNA damage.

The protein TP53 plays an important role in the cellular response to DNA damage. Four experimental studies in humans have shown that topical sunscreen application decreases the accumulation of wild-type TP53 in epidermal keratinocytes, which represents the physiological response to UVR-induced DNA damage. Mutation of the *p53* gene is considered to be a biomarker for the development of squamous-cell carcinoma of the skin. One study in mice showed that sunscreens protect against *p53* mutations induced by solar-simulated UVR, and another showed protection against *p53* mutations induced by a filtered FS40 sunlamp (UVB/UVA). In humans, UVR-induced DNA damage and *p53* mutations appear to be involved in the development of squamous-cell carcinoma and basal-cell carcinoma. Use of sunscreens reduced the level of UVR-induced DNA damage, but only a single, small study showed a reduction in *p53* mutations in basal-cell carcinoma.

Thirty-three studies in experimental animals have been published on protection by sunscreens against immune suppression, 18 of which were conducted with solar-simulated UVR. Ten of the latter showed a dose-related effect, and five of these were conducted with hairless mice. From these results, it was concluded that sunscreens provide some protection against various end-points in UVR-induced immune suppression.

In humans, sunscreens have been shown to provide at least some protection against several immunological end-points, including the induction of primary

immune suppression, the suppression of elicitation of recall responses and suppression of allostimulation of T cells with epidermal dendritic cells. Most of these studies were defective with respect to the source of UVR used or the experimental design, and it is still not known whether these immunological end-points are predictive of skin cancer prevention.

There are no adequate experimental data to establish quantitative relationships between biomarkers and the risk for skin cancer.

Other beneficial effects

Sunscreens can prevent sunburn and have proven effectiveness in the prevention of UVR-induced provocation of certain cutaneous diseases. They may reduce the development of photoageing. Photosensitive cutaneous disorders consist of the idiopathic photodermatoses, which do not develop in the absence of light, and the photoaggravated dermatoses, which are sometimes provoked by exposure to light.

Carcinogenic effects

Humans

Eight case-control studies on cutaneous melanoma showed significantly higher risks among sunscreen users. While these studies could be taken to suggest an increase in the risk for melanoma due to use of sunscreens, they are difficult to interpret because of problems of positive confounding; that is, people who have fair, sun-sensitive skin, heavy sun exposure or a history of skin cancer are also the most likely to use sunscreens and the most likely to develop melanoma. Negative confounding with protective behaviour, such as use of clothing and hats, can also occur.

Two of the case-control studies showed significantly increased risks for melanoma in relation to intentional sun exposure among sunscreen users, suggesting that use of these products to extend time in the sun may increase the risk for melanoma.

One cohort and one case-control study showed increased risks for basal-cell carcinomas among sunscreen users. None of the studies of squamous-cell carcinoma indicated an increased risk among sunscreen users. The results of these studies are difficult to interpret because of the probable confounding noted above.

Experimental animals

No studies were available in which the carcinogenicity of sunscreens was adequately tested. However, numerous studies of the protective effect of sunscreens have not raised suspicion of a carcinogenic effect.

Other toxic effects

Humans

Few published reports are available of contact or photocontact sensitization to

sunscreening agents. Case reports suggest a greater frequency of photocontact dermatitis among patients with photodermatoses such as polymorphic light eruption, who frequently use sunscreens.

Although there is evidence that sunscreen use reduces vitamin D production, the levels of vitamin D in sunscreen users appear to be within the normal range, and there have been no reports of biological responses suggesting reduced vitamin D levels.

Experimental systems

Topical application of sunscreen ingredients has not been shown to cause adverse effects on reproduction or fetal development, although some effects have been observed with high oral doses of sunscreen ingredients. Topically applied sunscreen preparations (in the absence of UVR) can have deleterious

effects on the immune system under some experimental conditions. Most of the studies of the toxicity of the active ingredients of sunscreens have shown them to be relatively safe when applied topically at the concentrations normally found in sunscreens, and there have been no reports of gross or anatomical effects.

The active ingredients of sunscreens, with and without UVR, can cause cellular toxicity, including DNA damage, inhibition of normal cellular function and cell death. In one study, ethylhexyl dimethyl PABA was genotoxic in the presence of UVR or visible light, and phenylbenzimidazole sulfonic acid in the presence of UVR or visible light caused DNA damage.