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A Dose-response Model for Skin Cancer Induction by Chronic U.V. Exposure of a Human Population

F. R. DE GRUIJL AND J. C. VAN DER LEUN

Institute of Dermatology, State University of Utrecht, The Netherlands

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A dose-response model, based on the results of animal experiments, is presented for skin cancer induction in a human population by chronic exposure to ultraviolet radiation. The model takes into account a variety of exposure habits and susceptibilities of the individuals in the population. The required input data for the dose-response relationship are the age specific incidences of the population in question.

Calculations based on this model can be used as a step in the evaluation of the effect which a reduction of stratospheric ozone would have on the non-melanoma skin cancer incidence. As an example an evaluation for the white population of the U.S.A. is presented. The estimate resulting from this evaluation agrees fairly well with earlier estimates based on combined climatological and epidemiological data.

1. Introduction

Already in the late nineteenth century prolonged exposure to sunlight was suspected to be an important factor in the etiology of skin cancer. No hard evidence was available at first, but animal experiments showed that the short wave ultraviolet (u.v.) radiation in sunlight is carcinogenic. Over the last decades a body of experimental, epidemiologic and circumstantial information has grown which constitutes convincing evidence for the importance of u.v. radiation in the etiology of skin cancer (Urbach, 1969, 1978 and Fears, Scotto & Schneidermann, 1977).

A field study on the etiological importance of certain suspected factors was presented by Silverstone & Searle (1970). From this study the etiological importance of genetic factors was clearly established. After the factor "age", which is an important factor for most cancers, the "sunburn susceptibility" came out as a very important factor. This implies that one must be aware of genetic complications when ascribing differences in skin cancer incidences among different populations to differences in u.v. exposure only.

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The types of skin cancer for which a strong correlation with u.v. radiation has been shown to exist, are the non-melanoma skin cancers (hereafter referred to as skin cancers for short) (Fears *et al.*, 1977).

The interest in the dose-response relationship for these skin cancers was renewed by the concern about a possible reduction of the stratospheric ozone. An ozone reduction would result in an increased intensity of the u.v. radiation reaching the earth's surface, and thus one of the probable biologic effects would be an increase in the skin cancer incidence in the human population.

The first approach to the problem was made by James E. McDonald (1971). He related the latitudinal gradient in the skin cancer incidence in the white population of the U.S.A. to the amount of stratospheric ozone through which the sunlight is filtered at the different latitudes.

To express this relationship McDonald defined an amplification factor, *AF*. This amplification factor is the ratio of the fractional increment in the skin cancer incidence and the corresponding fractional decrement in the amount of ozone. In other words: if the stratospheric ozone is permanently reduced by 1%, the number of skin cancer cases per year will ultimately increase by $AF \times 1\%$. McDonald found: $AF = 6$. Van der Leun & Daniels (1975) updated McDonald's calculations and found: $AF = 2{\cdot}1$.

The latitudinal data on which these calculations are based are scanty and can reasonably well be fitted by more than one mathematical relationship.

To find a real relationship between the skin cancer incidence and the amount of stratospheric ozone one has to exclude other factors than stratospheric ozone which may be correlated with the latitude. McDonald was aware of most of the relevant factors, like cloudiness, ethnic patterns and exposure habits. The way in which he dealt with some of these factors, especially ethnic patterns and exposure habits, was of necessity crude. Even now it is practically impossible to deal with these factors more subtly if one uses McDonald's approach.

A somewhat different but essentially the same approach to the problem, i.e. correlating latitudinal data, has been made by other authors (Green & Mo, 1975 and Urbach, Davies & Berger, 1975). They used a two step procedure; in the first step they relate the amount of stratospheric ozone to the annual u.v.-dose and in the second step they relate the annual u.v.-dose to the skin cancer incidence. The annual u.v.-dose in these studies usually is an approximated annual erythemal dose.

The advantage of this approach is that one can explicitly account for dose differences which are not related to the amount of stratospheric ozone. No attempt was made, however, to account for possible genetic and behavioral differences between the various populations.

A fundamentally different approach is to evaluate the effect of an ozone reduction indirectly by using a dose-response theory to describe the effect of an increment in the annual u.v.-dose (Rundel & Nachtwey, 1978). We will call this the indirect approach.

This approach resembles the forementioned "two step approach". It also uses the same two steps. The difference is that the step in which the annual u.v.-dose is related to the incidence is not based on latitudinal data but on a dose-response model. The advantage of this approach is that one deals with one population, and does not have the problem of genetic, environmental and behavioral differences at different locations.

In this paper we will develop such a dose-response model, based on animal experiments. Using this model we derive a formula which gives us the relationship between a fractional increment in the annual U.V.-dose and the corresponding fractional increment in the skin cancer incidence.

So far, the approaches made in this line consisted of extensive computations (Beadle, 1978 and Rundel & Nachtwey, 1978); in the other approaches mentioned (Green & Mo, 1975 and Urbach *et al.*, 1975) numerical correlations were sought between epidemiological and climatological data. Both of these methods make it hard to gain insight in how changes in certain factors may affect the outcome. In our analytical approach the relatively simple mathematical derivations facilitate this aspect of gaining insight and quantifying the importance of the factors involved.

In the discussion at the end of this paper we will make an estimation of the amplification factor for the white population of the U.S.A. via the indirect approach.

2. Some Conceptions

Before we go into the development of the dose-response model we will first introduce some conceptions.

For the indirect approach one needs to have spectral information on u.v.-carcinogenesis in order to link-up the amount of ozone with the annual "carcinogenic u.v.-dose" (this is less relevant in the two step approach, Van der Leun & Daniels, 1975). The influence of the amount of ozone on the u.v.-irradiance is highly wavelength dependent, the intensity at shorter wavelengths being affected more strongly than at longer wavelengths.

To account for this effect the concept of an annually available effective dose for carcinogenesis, D, (in analogy to the erythemal dose) can be used:

$$D = \int_0^\infty A(\lambda) S(\lambda, 0_3)\, d\lambda \tag{1}$$

where λ is the wavelength (in nm), 0_3 the amount of ozone (in atm cm, i.e.

the equivalent ozone layer thickness in cm at 20°C and 1 atm), $A(\lambda)$ the carcinogenic action spectrum (dimensionless) and $S(\lambda, O_3)$ the spectrum of the annual dose of solar radiation (in J m^{-2} nm^{-1} yr^{-1}) as a function of O_3. $A(\lambda)$ weights the radiant energy at each wavelength according to its carcinogenic effectiveness. Usually $A(\lambda)$ is chosen to be 1 at a certain wavelength, λ_0. This means that D (in J m^{-2} yr^{-1}) is defined as an equivalent dose at λ_0. In this conception it is assumed that the effective doses of different wavelengths can be added up to a total effective dose.

As mentioned earlier, the action spectrum mostly used for u.v.-carcinogenesis is the erythemal action spectrum, which makes D the annually available erythemal dose. The correct action spectrum for carcinogenesis in human skin, however, is unknown. So far, only estimates of the spectral sensitivity have been produced.

McDonald's amplification factor can be written as follows:

$$AF = -\frac{O_3}{I} \cdot \frac{dI}{dO_3} \tag{2}$$

where I is the incidence of skin cancers.

One must be careful when using the AF. In principal the AF may well be dependent on I and O_3. This means that it can only be used for limited changes in O_3, given a certain I.

If the AF is considered to be a constant, then one imposes a power law relation between I and O_3, and one certainly has to be aware of doing so. A direct consequence of the power law relation would be that all the skin cancers are ozone (i.e. u.v.) related, because if O_3 tends to infinity I becomes 0. In our model we do not impose the power law relation between I and O_3. However, we will assume that all the skin cancers are u.v.-induced. This is disputable, but the distribution of skin cancers over the body regions gives the impression that the great majority is related to sunlight exposure (unfortunately it is impossible to select the u.v.-induced skin cancers).

The indirect as well as the two step approach can concisely be expressed by the following equations (Van der Leun & Daniels, 1975):

$$AF = AF_o\, AF_b \tag{3}$$

where

$$AF_o = -\frac{O_3}{D}\frac{dD}{dO_3} \tag{3a}$$

and

$$AF_b = \frac{D}{I}\frac{dI}{dD}. \tag{3b}$$

AF_o is called the optical amplification factor; if the amount of ozone decreases by 1% the annually available effective dose will increase by $AF_o \times 1\%$. AF_b is called the biologic amplification factor; if the annually available effective dose increases by 1% the incidence will increase by $AF_b \times 1\%$. AF_o and AF_b represent the two steps from an ozone decrement to a skin cancer increment.

The influence of the only vaguely known spectral response of the skin is included in the optical amplification factor AF_o; the biologic amplification factor AF_b does not explicitly depend on it.

In this paper we will primarily be concerned with the biologic amplification factor, which represents the dose-incidence relationship.

3. A Transformation of the Experimental Results

In the 1940s Blum, Grady & Kirby-Smith carried out extensive experiments on albino Swiss mice (Blum, 1959). In these experiments groups of mice were regularly exposed to a certain dose of u.v.-radiation. As a result it was found that the prevalence curve of tumor bearing animals as a function of time was shaped like an integrated log-normal distribution. The standard deviation was constant and for the median development time of the first tumor, t_m, the following dose-dependence was established:

$$dt_m^2 = k_1 \tag{4}$$

where d is the total dose per unit time (for example: in mJ cm^{-2} per day) and k_1 is a constant which depends on the time-interval between successive exposures.

Blum used equation (4) as a basic relationship between dose and development time for his model of u.v.-carcinogenesis, based on the idea of an accelerated fractional growth of a tumor instead of a constant fractional growth as usually is assumed.

Forbes, Blum & Davies (1979) performed similar experiments on albino hairless mice and the results are comparable to those found earlier by Blum. From the results of Forbes *et al.* [Fig. 1(a)] a slightly different relationship between dose and median development time is found:

$$dt_m^p = k_2 \tag{5}$$

where $p = 1{\cdot}6 \pm 0{\cdot}1$ and k_2 is a constant.

Forbes *et al.* also measured the tumor yield (i.e. the number of tumors in the surviving group divided by the number of survivors) as a function of time. If one looks at the time which elapses till a certain tumor yield is reached in relation to the applied daily dose, then again one finds a relationship like

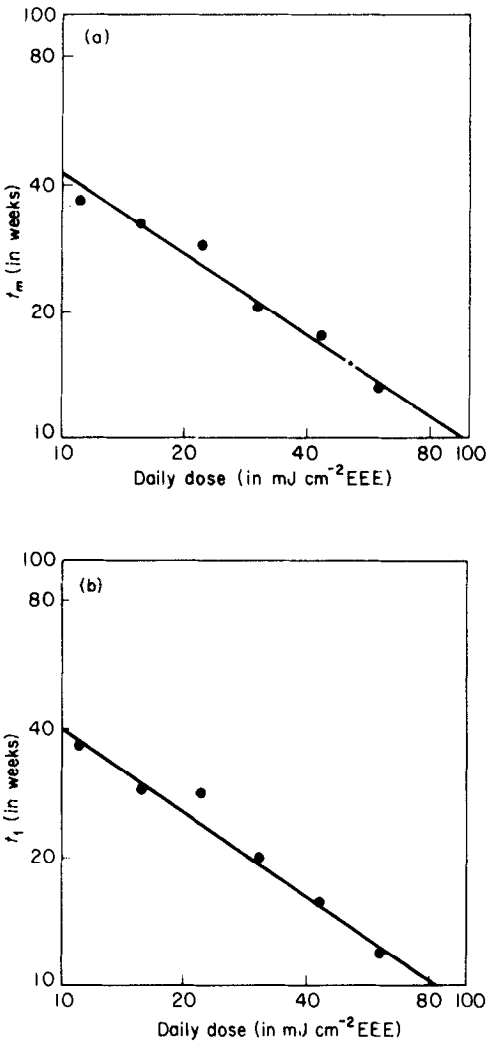

FIG 1. (a) The median development time, t_m, vs. the daily dose (Forbes *et al.*, 1979). (b) The time which elapses till a tumor yield of 1 is reached, t_1, vs. the daily dose (Forbes *et al.*, 1979).

equation (5). As an example we give here the relationship between the dose and the time which elapses till a tumor yield of one tumor per survivor, t_1, is reached [Fig. 1(b)]:

$$dt_1^q = k_3 \tag{6}$$

where $q = 1{\cdot}5 \pm 0{\cdot}1$ and k_3 is a constant.

Blum's data only dealt with first skin tumors, but the data of Forbes *et al.* also include the following skin tumors. This is a valuable addition to the experimental results, because in the human epidemiological data no distinction is made between first and following skin tumors.

Taking into account all these experimental results, we construct the hypothesis that for every skin cancer—not only a first—which is induced by chronic u.v.-exposure we can write:

$$dt^p = k \tag{7}$$

where p is a constant ($p = 1{\cdot}8 \pm 0{\cdot}2$, averaged from the experimental data), k is a constant and t is the development time. This is a deterministic interpretation of the results which facilitates the description of the response to dose changes.

By making the assumption that the mechanism of u.v.-carcinogenesis is basically the same for mice and men, we apply the hypothesis to the problem of u.v.-carcinogenesis in men. To use this hypothesis for a human population we otherwise follow the same procedure as Beadle (1978) for his numerical approach to the problem:

(1) We introduce the concept of a skin cancer site as being simply a part of the skin of an individual in which a skin cancer can be induced.

(2) We state a basic dose-time relationship for the development of a skin cancer, which in our case is equation (7) (Beadle used a special case of equation (7), with $p = 1$). Every skin cancer site has its own value of k, which represents its resistance to cancer induction.

(3) To make equation (7) operational for a human population we make the assumption that we may use the annual effective dose for d and the age of an individual at the time he gets his skin cancer for t.

(4) The problem which needs to be solved next is the fact that different cancer sites are exposed to different annual effective doses, even if the skin cancer sites are located on the same person. To account for this we introduce an exposure factor, E_i, for every skin cancer site (exposure factors are also used by other authors, but they all use it as being an "overall exposure factor" of a population and never as being an exposure factor of an individual cancer site; the exception to this is of course Beadle from whom we adopted the idea). If a skin cancer appears at the age a we write for the total dose its site has received until then:

$$da = E_i Da. \tag{8}$$

Substituting a for t in equation (7) and using equation (8) gives:

$$Da^p = k_i \tag{9}$$

where $k_i = k/E_i$. Again each skin cancer site has its own value of k_i, but all skin cancer sites in a population, living in one location, have the same annually available effective dose, D.

Equation (9) forms the basis of our model for skin cancer induction in a human population by chronic u.v.-exposure.

4. Model for a Human Population

In a human population we have skin cancer sites each with its own value of k_i. The age, a, at which the skin cancer will manifest itself at site i may, according to equation (9), be written as:

$$a = (k_i/D)^{1/p}. \tag{10}$$

The number of skin cancer sites is proportional to the number of people and there is a certain distribution of k_i-values, $f(k_i)$, over the skin cancer sites.

Generally speaking, $f(k_i)$, will be a function of the age, because exposure habits can change with time. For simplicity, however, we treat $f(k_i)$ as being age-independent (this simplification is justified if only small changes in D are considered and if $f(k_i)$ changes gradually with age).

In principle the $f(k_i)$-distribution can be found for the skin cancer sites that manifest themselves during the life-span of man from the age specific incidence data [which Beadle (1978) has done]. We could call the so-found $f(k_i)$-distribution the "age-independent approximation of $f(k_i)$". In our approach it is not necessary to explicitly calculate the age-independent approximation of $f(k_i)$.

5. Dose-dependence of U.V.-induced Skin Cancer Incidence

In order to derive an expression for the biologic amplification factor we will first derive a formula which gives us the dose-dependence of the age specific incidence.

The model states that there is an age-independent distribution of k_i-values for which we can write:

$f(k)\mathrm{d}k$ = the number of skin cancer sites per person with k_i between the values k and $k + \mathrm{d}k$, where $\mathrm{d}k$ is an infinitesimal interval of k_i-values.

With a certain annually available dose D the development time of the cancer is determined by k_i according to equation (9) or (10). If we pick an age a and look at the skin cancers that will develop per person of this age as they reach the age $a + da$, where da is an infinitesimal age-interval, then this number equals the number of skin cancer sites per person for which equation

(10) is satisfied over the age-interval between a and $a+\mathrm{d}a$. This number is given by:

$$\mu(a, D)\mathrm{d}a = f(Da^p) \cdot \frac{\partial Da^p}{\partial a}\,\mathrm{d}a \tag{11}$$

where $\mu(a, D)$ is the age specific incidence.

From this it follows that

$$\mu(a, D) = pDa^{p-1}f(Da^p). \tag{12}$$

In order to gain insight in the dose-dependence of μ we will rewrite equation (12). To this end we substitute a "reference annually available effective dose" D_0 into equation (12), which gives:

$$\mu_0(a) = \mu(a, D_0) = pD_0a^{p-1}f(D_0a^p). \tag{13}$$

Rewriting equation (12) by substituting $D = (D/D_0)D_0$ and using equation (13) gives:

$$\mu(a, D) = \left(\frac{D}{D_0}\right)^{1/p} pD_0\left[a\left(\frac{D}{D_0}\right)^{1/p}\right]^{p-1} f\left\{D_0\left[a\left(\frac{D}{D_0}\right)^{1/p}\right]^p\right\}$$

$$= \left(\frac{D}{D_0}\right)^{1/p} \mu_0\left[a\left(\frac{D}{D_0}\right)^{1/p}\right]. \tag{14}$$

Now we have come from a dose-time relationship to a dose-dependence of the age specific incidence. This enables us to derive a biologic amplification factor for the overall incidences of u.v.-induced skin cancers in a human population. For the number of newly developed skin cancer cases per year in one age-group with ages between a and $a+\mathrm{d}a$ we can write:

$$N(a, D)\,\mathrm{d}a = \mu(a, D)n(a)\,\mathrm{d}a \tag{15}$$

where $n(a)$ is the age distribution of the population in question. Integrating equation (15) with respect to a and differentiating it with respect to D yields:

$$\frac{\mathrm{d}N}{\mathrm{d}D} = \int_0^\infty n(a)\frac{\partial \mu(a, D)}{\partial D}\,\mathrm{d}a \tag{16}$$

where $N = N(D) = \int_0^\infty \mu(a, D)n(a)\,\mathrm{d}a$. In words: N is the number of new skin cancer cases per year, which is a function of D.

Differentiating equation (14) with respect to D and rewriting the so-obtained equation in terms of $\mu(a, D)$ and $\partial\mu(a, D)/\partial a$ we get:

$$\frac{\partial \mu(a, D)}{\partial D} = \frac{1}{pD}\left\{\mu(a, D) + a\frac{\partial \mu(a, D)}{\partial a}\right\}. \tag{17}$$

Equation (17) can also be derived directly from equation (12) without rewriting $\mu(a, D)$ like we have done in equation (14).

Substitution of equation (17) into equation (16) gives:

$$\frac{dN}{dD} = \frac{1}{pD}\left\{N + \int_0^\infty a \frac{\partial \mu(a, D)}{\partial a} n(a)\, da\right\}. \tag{18}$$

For practical reasons we will transform equation (18) in such a way that we get $dn(a)/da$ instead of $\partial\mu(a, D)/\partial a$; the former is often more accurately determinable. We do this by partial integration of equation (18) under the conditions that $\mu(0, D) = 0$ and $\lim_{a\to\infty} n(a)\mu(a, D) = 0$, which yields:

$$\frac{dN}{dD} = \frac{-1}{pD}\left\{\int_0^\infty a\mu(a, D) \frac{dn(a)}{da} da\right\}. \tag{19}$$

By substituting equation (19) into the definition of the biologic amplification factor [i.e. equation 3(b)], using the relation $I = N/P$ (where $P = \int_0^\infty n(a)\, da$, i.e. P is the total number of people in the population), we find:

$$AF_b = \frac{-1}{pN}\left\{\int_0^\infty a\mu(a, D) \frac{dn(a)}{da} da\right\}. \tag{20}$$

We can approximate the integration in equation (20) by a summation over finite age groups:

$$\begin{aligned} AF_b &\simeq \frac{-1}{pN}\left\{\sum_i a_i\mu_i \frac{\Delta n_i}{\Delta a_i}\Delta a_i\right\} \\ &\simeq \frac{-1}{pN}\left\{\sum_i a_i\mu_i\, \Delta n_i\right\} \end{aligned} \tag{21}$$

where a_i is the mean age of age group i, $\Delta a_i = a_{i2} - a_{i1}$, where a_{i1} and a_{i2} are the boundary ages of age group i ($a_{i1} < a_{i2}$), $\Delta n_i = n(a_{i2}) - n(a_{i1})$ and μ_i is the skin cancer incidence in age group i. N and μ_i can be obtained from epidemiological data and Δn_i from population statistics.

6. A Biologic Amplification Factor Independent of the Age Distribution

By using some idealized linear age distributions and the incidence data on non-melanoma skin cancers from the Third National Cancer Survey (Scotto, Kopf & Urbach, 1974 and Rundel & Nachtwey, 1978; the latter paper states the results in a more detailed form), it appeared that the age distribution had very little influence on the biologic amplification factor (substitution of linear age distributions yields very simple expressions for the AF_b).

These calculations suggest that the biologic amplification factor is rather independent of the age distribution of the population. It can be shown why this holds fairly generally; the age specific incidences as found in the Third National Cancer Survey can reasonably well be approximated by the formula (Fears, Scotto & Scheidermann, 1977):

$$\mu(a) = \gamma a^x \tag{22}$$

where

$$\gamma = bD^c \tag{22a}$$

and b, c and x are constants.

The value of x they found is somewhat greater for the male subpopulations ($3{\cdot}7 \pm 0{\cdot}5$) than for the female subpopulations ($3{\cdot}1 \pm 0{\cdot}5$). For c they found $3{\cdot}0 \pm 0{\cdot}6$ for the male subpopulations and $2{\cdot}5 \pm 0{\cdot}6$ for the female subpopulations.

Like with McDonald's amplification factor one should be careful with an equation like (22a), because again one imposes a power law and with extrapolation it follows that all skin cancers are u.v.-induced (if $D \to 0$ then $I \to 0$).

This kind of age-dependence of the incidence has also been found for other types of cancer and forms the basis of some mathematical multi-stage models for carcinogenesis (Nordling, 1953, Armitage & Doll, 1954 and Fisher, 1958). According to the multi-stage models x and c in the equations (22) and (22a) should be integers, but they can be truncated if the dose or the number of people exposed changes with time.

By substituting equation (22) into equation (18) it can be easily derived that:

$$\frac{dN}{dD} = \frac{N}{pD}(x+1) \tag{23}$$

and with equation [3(b)] it follows that:

$$AF_b = \frac{x+1}{p}. \tag{24}$$

This means that if the age specific incidence can be described by a power-function [equation (22)], the biologic amplification factor is totally independent of the age distribution.

By using equation (24) we can make an overall estimate of the biologic amplification factor for all the non-melanoma skin cancer data of the Third National Cancer Survey. To this end we substitute the mean of the values for x, $x = 3{\cdot}4$, into equation (24). As a result we get:

$$AF_b = 2{\cdot}4 \pm 0{\cdot}6.$$

7. Applicability

To evaluate the effect of an increase in the annual u.v.-dose we could ask the question: "What would have been the skin cancer incidence for this population at this particular moment if the annually available effective dose would have been greater and all the other factors involved (like exposure habits) would have been the same?" This question bears direct relevance to a real human population and can be answered by using the approach we have put forward.

An evaluation like this is, strictly speaking, not a prognosis of the increase in the future incidence of skin cancer caused by a possible increase in the annual u.v.-dose. In order to give a correct prognosis one should have information on factors like possible changes in exposure habits and the development of the age distribution [if equation (22) does not hold]. Both of these are hard to predict, especially changes in the exposure habits which may be caused by fashion. Our model at least gives some idea of how these factors may influence the prognosis.

In the presentation of our model we have not mentioned migration. It should be realized that, strictly speaking, the model is only applicable if the aspect of immigration can be ignored.

The biologic amplification factor expresses the difference in the skin cancer incidence of two identical populations due to a small difference in the annually available effective dose. For greater differences the amplification factor can only be used to give a first and rough estimate of the difference in the skin cancer incidences.

In order to give a more accurate approximation for a drastic increase in the annual u.v.-dose, one could extrapolate the age specific incidence for ages greater than the maximum age. Then one can calculate the new age specific incidence by using equation (14). This, of course [as Beadle (1978) has already pointed out], introduces the uncertainty of the validity of the extrapolation. Also one assumes the $f(k)$-distribution to be age independent, which is a doubtful approximation if the change in the age of appearance of the skin cancers becomes too great. In case of a drastic decrease in the annual u.v.-dose we do not have the problem of the extrapolation, but we still have to make the assumption that the $f(k)$-distribution is age independent.

It is interesting to mention here that, if we make the assumption of an age independent $f(k)$-distribution and assume equation (22) to be valid for ages greater than the maximum age, we can write (Appendix A):

$$\mu(a, D) = bD^{(x+1)/p}a^x \tag{25}$$

and

$$\log (I_1/I_0) = \frac{x+1}{p} \log (D_1/D_0) \tag{26}$$

where I_i is the incidence if $D = D_i$.

Under the aforementioned assumptions the equations (25) and (26) can be used no matter how great the change in the annually available effective dose. Notice the resemblance between equation (25) and the equations (22) and [22(a)] which Fears *et al.* (1977) used to describe the age specific incidence. By comparing these equations we find:

$$c = \frac{x+1}{p}. \tag{27}$$

Substituting the x-values of Fears *et al.*, we get $c = 2{\cdot}6 \pm 0{\cdot}4$ for the male subpopulations and $c = 2{\cdot}3 \pm 0{\cdot}4$ for the female subpopulations. These values are very close to the values Fears *et al.* actually found for c (the agreement would be even better if we use $p = 1{\cdot}6$).

8. Discussion

It may be useful to summarize the fundamental premises here on which our model is based in order to appreciate its advantages and its limitations:

(1) There is a certain class of skin cancers which are induced by chronic u.v.-exposure. We take the non-melanoma skin cancers to be identical with this class.

(2) A deterministic dose-time relationship, inferred from animal experiments, is also applicable to men.

(3) The variation in a parameter (k_i) of this dose-time relationship is due to genetic, environmental and behavioral differences.

A point which needs to be mentioned is that it is assumed that various skin cancer sites receive different fractions of the annually available effective dose, and that if the dose is increased by a certain factor, the annual effective dose for every skin cancer site is increased by the same factor.

This is, strictly speaking, a simplification where a reduction in the amount of stratospheric ozone is concerned. If the ozone diminishes, the fractional increase in the effective intensity depends on the time of day and on the season. Therefore, the fractional increase in the effective dose on a person's skin will depend on his exposure habits.

In spite of this observation, the assumption can be made plausible by noticing that most skin cancer candidates must be exposed under optimal conditions in order to get their skin cancers. In conclusion we can say that the

model allows for a vast variety of exposure habits as long as the effective exposures take place at high solar elevation.

From the formulae for the biologic amplification factor we can directly see that it is proportional to $1/p$. This means that the biologic amplification factors based on a dose-time relationship with $p = 1$ (i.e. based on the reciprocity concept) will be 1·8 times greater than if $p = 1{\cdot}8$.

This probably explains why the biologic amplification factors found by Green, Findley *et al.* (1976), using the incidence data of a single population and a dose-time relationship with $p = 1$, are markedly greater than the factors they found by combining the dose and incidence data of several populations.

Van der Leun & Daniels (1975) used a biologic amplification factor of 0·5. They derived this value from an intuitive reasoning, which also started with the dose-time relationship found by Blum (1959) [equation (4)]; the reasoning proceeded on the assumption that the incidence of skin cancer in a population would vary inversely proportional to the time required for tumors to develop. This latter assumption cannot be generally validated; it would only hold in case the incidence would be independent of the age, which is not realistic. Expressed in terms of our present equations, we then have $\partial\mu(a, D)/\partial a = 0$ and AF_b would be equal to $1/p$, as can best be seen from equation (18); thus AF_b would indeed equal 0·5 if $p = 2$.

Rundel & Nachtwey (1978) calculated biologic amplification factors from the data of the Third National Cancer Survey. They started out by fitting the human data to the relationships found by Blum (1959). Their calculations of the biologic amplification factors, however, are based on the concept of reciprocity. They did this to get a worst case estimate: strictly speaking it is only one out of many possible cases which are worse than if $p = 1{\cdot}8$. We have chosen to incorporate the experimental results as much as possible, and therefore used $p = 1{\cdot}8$.

By using a formula (Appendix B) we can transform the biologic amplification factors found by Rundel & Nachtwey (denoted by A_c) to values, which our theory would have yielded (denoted by AF_b). In Table 1 we give the AF_b's calculated in this way from the original A_c's as Rundel & Nachtwey found them.

Beadle (1978) made the same assumption of reciprocity and worked out two models to which we shall refer as the simple and the more sophisticated model.

The same argumentation we used in Appendix B for the A_c's found by Rundel & Nachtwey applies to the biologic amplification factor which Beadle found by using his simple model. In Table 1 (column "Beadle 1") we give the transformed value for Beadle's simple model.

TABLE 1

Adjusted biologic amplification factors, for further explanation see text

Authors	Population	A_c ♂	A_c ♀	AF_b ♂	AF_b ♀
Rundel & Nachtwey	Dallas–Ft. Worth	3·7	3·4	2·7	2·5
	Iowa	4·3	4·4	3·1	3·1
	Minneapolis–St. Paul	4·2	4·0	3·0	2·9
	San Francisco–Oakland	3·9	3·5	2·8	2·6
		(1)	(2)	(1)	(2)
Beadle	England–Wales	4·0	5·1	2·9	2·8

Beadle's more sophisticated model, which he worked out numerically, is equivalent to our model with $p = 1$. This means that the biologic amplification factor from this model is 1·8 times greater than if $p = 1{\cdot}8$. In Table 1 (column "Beadle 2") we also give the transformed value for Beadle's more sophisticated model.

Notice that the two transformed values for the biologic amplification factor from the results of Beadle are very close, like they should be.

Fears *et al.* (1977) also studied the data of the Third National Cancer Survey and found a dose-incidence relationship which is represented by the equations (22) and (22a). If we would make the assumption that all the subpopulations studied in the Third National Cancer Survey are identical except for sex and annual u.v.-dose, then c in equation (22a) would equal the biologic amplification factor. The mean value of c can be considered as an overall estimate of the biologic amplification factor and is equal to $2{\cdot}8 \pm 0{\cdot}6$. This value for the biologic amplification factor is very close to the value of $2{\cdot}4 \pm 0{\cdot}6$ we found from the same data.

To evaluate the effect of a reduction in the amount of stratospheric ozone, using the model presented in this paper, we have to know the optical amplification factor, AF_o. In order to find the optical amplification factor we should have detailed spectral information on u.v.-carcinogenesis in human skin, which unfortunately we have not.

Green & Mo (1975) have calculated optical amplification factors using two different action spectra: the human erythemal action spectrum and the absorption spectrum of DNA. They found that the two optical amplification factors did not differ much: respectively 1·53 and 1·83.

If we assume that the action spectrum for u.v.-carcinogenesis in the human skin is somewhat like these spectra, we could use $AF_o = 1{\cdot}7$ as an estimate till we have more spectral information.

Combining this estimate of the optical amplification factor (1·7) with the overall estimate of the biologic amplification factor (2·4) from the data of the Third National Cancer Survey, yields a value of about 4 for the estimate of McDonald's amplification factor [equation (3)]. Thus our estimate is that, if the amount of stratospheric ozone would have been continuously reduced by 1% over the last century, we would have had a 4% higher incidence of non-melanoma skin cancers in the U.S.A. (i.e. about 12 000 extra non-melanoma skin cancer cases per year). This strongly indicates how sensitive the incidence is to changes in the amount of ozone.

Our estimate does not differ much from the estimates which have been made so far, especially if one considers the uncertainties involved. But we hope to have made a contribution to a fundamental approach to the problem, which includes genetic differences, human autonomic behavior and experimental information on u.v.-carcinogenesis.

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APPENDIX A

Derivation of the equations (25) and (26)

If we substitute $\mu(a) = \mu(a, D_0)$ into equation (22) and combine this with equation (14) we get:

$$\mu(a, D) = \left(\frac{D}{D_0}\right)^{(x-1)/p} \mu(a, D_0) \tag{A1}$$

or

$$\mu(a, D) = \gamma \left(\frac{D}{D_0}\right)^{(x+1)/p} a^x. \tag{A2}$$

Equation (A2) is identical to equation (25), where

$$b = \gamma D_0^{-(x+1)/p}. \tag{A3}$$

Combining the equations (15) and (A1) we find:

$$\begin{aligned} N(D) &= \int_0^\infty \mu(a, D) n(a)\, da \\ &= \left(\frac{D}{D_0}\right)^{(x+1)/p} \int_0^\infty \mu(a, D_0) n(a)\, da \\ &= \left(\frac{D}{D_0}\right)^{(x+1)/p} N(D_0). \end{aligned} \tag{A4}$$

Rewriting equation (A4) we get:

$$\frac{I_1}{I_0} = \left(\frac{D_1}{D_0}\right)^{(x+1)/p} \tag{A5}$$

where $I_1 = N(D_1)/P$ and $I_0 = N(D_0)/P$.

A logarithmic transformation of equation (A5) yields equation (26).

APPENDIX B

The transformation of A_c

Rundel & Nachtwey used the formula:

$$A_c = \frac{1}{f} \frac{\sum_a (I'_a - I_a) W_a}{\sum_a I_a W_a} \tag{B1}$$

where I_a is the original incidence in age group a, I'_a the altered incidence in

age group a, W_a the number of people in age group a and $f = (D - D_0)/D_0 (= 0{\cdot}05$ for Rundel & Nachtwey); f is the fractional change in the annual u.v.-dose.

They used the concept of an effective age; if the annual u.v.-dose would have been $(1+f)$ times greater than it actually was, the effective age for u.v.-carcinogenesis would be

$$a' = (1-f)a \tag{B2}$$

where a is the actual age. From this they concluded that

$$I'_a = I_{a'} \tag{B3}$$

which is not in agreement with our equation (14), even if reciprocity holds.

To adjust their results to our model we will start out by also using the concept of the effective age. If this is given by equation (B2), then according to our model the annual u.v.-dose must have been changed by a factor of $(1+pf)$ (if $pf \ll 1$), which means that

$$(D - D_0)/D_0 = pf. \tag{B4}$$

And, according to equation (14), equation (B3) should be:

$$I'_a = (1+f)I_{a'}. \tag{B5}$$

If $\sum_a I_a W_a = N_0$ and $\sum_a I_{a'} W_a = N_r$, we can rewrite equation (B1) for the theory of Rundel & Nachtwey as:

$$A_c = \frac{1}{f}\left(\frac{N_r}{N_0} - 1\right). \tag{B6}$$

According to our theory we can rewrite equation (B1) as:

$$AF_b = \frac{1}{pf}\left(\frac{(1+f)N_r}{N_0} - 1\right). \tag{B7}$$

Combining the equations (B6) and (B7) yields:

$$AF_b = \frac{1}{p}[(1+f)A_c + 1]. \tag{B8}$$

Equation (B8) is the formula by which we have transformed the values of A_c.