A derivation of the Weibull distribution and its relevance to dose response relationships, initiation and promotion and stopping experiments

Assume that for a cell to start a tumour it must undergo a certain number of cellular changes. Under the further assumption that the risk of any cell being transformed at any instant is extremely small we will show that the probability g(t) of an animal getting cancer by time t is given by the Weibull distribution

$$g(t) = 1 - \exp(-b(t-w)^k) \qquad (1)$$

where w and k are constants and b depends on the dose applied.

Firstly consider a two stage process where event 1 has probability $\alpha_1 c_1 t^{(\alpha_1-1)}dt$ of occurring in the period (t, t+dt) and event 2 has a similar probability $\alpha_2 c_2 t^{(\alpha_2-1)}dt$. These probabilities are commonly known as incidence rates. Assume that event 1 must occur before event 2 and that the c's are so small that we can neglect any power of these above the second. We wish to find the probability h(T) that the cell will not have succumbed to both stages by time T.

It is well known that the probability of survival from event 1 alone to time T is given by $\exp(-c_1 T^{\alpha 1})$ and therefore using the fact that the probability of survival from both is equal to the chance it survived 1 throughout plus the sum of the chances that it got 1 at time t and survived 2 from t to T we get:

$$h(t) = \exp(-c_1 T^{\alpha 1}) + \int_0^T \exp(-c_1 t^{\alpha 1}) \exp -c_2 (T^{\alpha 2} - t^{\alpha 2}) \alpha_1 c_1 t^{(\alpha 1-1)} dt$$

$$\simeq 1 - c_1 T^{\alpha 1} + \frac{c_1^2 T^{2\alpha 1}}{2} + \int_0^T \alpha_1 c_1 t^{(\alpha 1-1)} (1 - c_1 t^{\alpha 1} - c_2 T^{\alpha 2} + c_2 t^{\alpha 2}) dt$$

$$= 1 - c_1 T^{\alpha 1} + \frac{c_1^2 T^{2\alpha 1}}{2} + \left[c_1 t^{\alpha 1} - \frac{c_1^2 t^{2\alpha 1}}{2} - c_1 c_2 t^{\alpha 1} T^{\alpha 2} + \frac{\alpha_1 c_1 c_2 t^{(\alpha 1+\alpha 2)}}{\alpha_1 + \alpha_2} \right]_0^T$$

$$\therefore h(t) = 1 - \left(\frac{\alpha_2}{\alpha_1 + \alpha_2} \right) c_1 c_2 T^{\alpha 1 + \alpha 2}$$

$$\simeq \exp\left(-\frac{\alpha 2}{\alpha_1+\alpha_2}\ c_1c_2T^{\alpha_1+\alpha_2}\right)$$

hence the incidence rate from both events at time ti is given by $\alpha_2c_1c_2t^{(\alpha_1+\alpha_2-1)}$ or rewriting it $(\alpha_1+\alpha_2)\left(\frac{\alpha_2c_1c_2}{\alpha_1+\alpha_2}\right)t^{(\alpha_1+\alpha_2-1)}$

which is of the same form as the original incidence rates. Call this result Theorem 1.

Suppose the incidence rate for the ith stage is a constant bi. We will show that the incidence rate for k successive stages is given by

$$\frac{b_1b_2\ldots\ldots\ldots\ldots b_k}{(k-1)!}\ t^{k-1} \qquad (2)$$

Assume the result is true for k=r and consider the probability of survival from event 1 (the first r stages) and event 2 (the (r+1) th stage). Now in the notation of Theorem 1

$$a_1=k \quad a_2=1 \quad c_1=\frac{b_1b_2\ldots b_k}{k!} \qquad c_2=b_{k+1}$$

Hence from Theorem 1 we see that the incidence rate for (r+1) stages is given by

$$\frac{b_1b_2\ldots\ldots\ldots b_{r+1}}{r!}\ t^r$$

Since this is known to be true for r=1 the result (2) follows at once.

Hence the probability of a cell surviving the k stages to time t is given by

$$\exp\left(\frac{-b_1b_2\ldots.b_k}{k!}\ t^k\right)$$

(Note: if we assume the changes can occur in any order the effect is simply to remove the k! from the denominator.)

Now assume there are N cells at risk. The chance of an animal surviving to time t is therefore

$$1-g = \exp\left(\frac{-Nb_1b_2\ldots b_k\ t^k}{k!}\right)$$

$$\text{Set} \qquad b = \frac{Nb_1b_2\ldots b_k}{k!} \tag{3}$$

and assume that it takes a constant time w from succumbing to the kth stage to producing a detectable tumour we can write

$$g(t) = 1 - \exp(-b(t-w)^k)$$

which is result (1).

By maximum likelihood methods we can from the recorded weeks of death or first tumour for a group of animals estimate values of the parameters b, w and k.

Dose response relationships

Consider the expression (3). For untreated controls we have a small value of b as some tumours do occur so this implies that each of the b_i have non-zero values.

When we apply a carcinogen it is reasonable to assume that some of the stages are affected and that this extra probability will be proportional to dose for each stage. Thus if the carcinogen affected 2 of 3 stages and dose levels d, 2d, 4d, 8d.... were applied we would expect (in suitable units)

b(untreated controls) = 1 x 1 x 1

b(level 1) = $(1+\alpha_1 d)(1+\alpha_2 d)$ x 1

b(level 2) = $(1+2\alpha_1 d)(1+2\alpha_2 d)$ x 1

etc

If the dose were high enough so that $\alpha_1 d$ and $\alpha_2 d$ were fairly large compared with 1, then clearly doubling the dose level would very nearly multiply the b's by a factor of 4.

We have found for benzpyrene tested at 6, 12, 24 and 48 µg this 4:1 relationship of b's between dose levels almost exactly and so we would deduce that benzpyrene affects two stages of cancer strongly which ties in with the theory that it is both a strong initiator and promotor.

We can state more specifically that if a carcinogen affects s stages of cancer strongly then multiplying the dose by m will multiply b by m^s. But it is of course possible that some stages are affected weakly and others strongly. Take for an example one weak effect $\alpha_1 = 0.5$ say and one strong effect $\alpha_2 = 20$. Then we have the following dose response relationship

Dose	b
1	31.5
2	82
4	243

This relationship will go from linear at low doses to quadratic at high doses and could explain why we find that for smoke condensate over a certain range doubling the dose multiplies the response b by about 3.

However it is difficult to come to exact conclusions for smoke as one is never sure of the "effective" dose at high levels which may explain why the dose-response curves flatten off against the prediction of this model.

Initiation and Promotion

Classical experiments have always put a large dose of initiator on at the beginning of the experiment to be followed by continuous dosing of promotor.

In this case assuming the initiator affects the first stage we

will have after it is dosed effectively a k-1 stage process on a reduced number of cells N^1 which have passed this first stage. However in this case the probability of a cell being initiated may well not be small at all and changing the dose of initiator at constant promotor would not necessarily lead to a response relationship of the same type as for continuous dosing.

There seems no reason why initiator and promotor in smaller doses should not both be painted continuously and this could very likely simulate human conditions better that the classical method. In this case if each one affected a different stage strongly one would expect a linear dose response of b against dose for each applied individually but in combination doubling the dose of each should multiply the response b by four.

One can see here a means of testing between initiators and promotors. Suppose one has a known initiator A and an unknown substance either initiator or promotor B. Test at various dose levels combinations of A and B. If the response is linear then B is an initiator, if quadratic then B is a promotor. Of course for this to be effective dose levels of each must be high enough for the expected values of the b_i's to be much higher than those of untreated controls.

I feel experiments of this type would be useful in serving to strengthen or refute the basic hypotheses my derivation is based on.

Stopping painting experiments

If the multi-stage hypothesis as put forward were true then one could use stopping painting experiments to get a much clearer picture.

For if w weeks after painting ceased virtually no more tumours were recorded this would suggest that the last stage was affected by the carcinogen. If however the incidence rateremained constant as seemed to occur in British Doctor's stopping smoking the suggestion

would surely be that this stage was not affected by the carcinogen at all but that previous experience had passed a number of cells through all the stages but one and that whether cancer subsequently occurred was due to some other constant factor.

If the incidence rate decreased continuously after stopping this would suggest reversibility of one or more of the stages and could imply that the Weibull derivation is rather too simple.

Conclusion

Considerable insight into cancer mechanisms can be gained by investigating dose response curves for single carcinogens applied continuously. But more still could be obtained by designing experiments with a) combinations of carcinogens applied continuously and b) carcinogens applied for a given period and then stopped.

P.N.L.

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