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Assessment of Environmental Carcinogen Risks in Terms of Life Shortening

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An approach is presented to the assessment of carcinogen risks in which the dominant effect of carcinogen exposure is life shortening and the impact falls both on those individuals who would have gotten cancer without the carcinogen exposure as well as the new cancer cases. This analysis is based on the interaction of age-specific tumor incidence rates and population survival in terms of age-specific mortality rates without the induced risk from carcinogen exposure. The analysis yields estimates for lifetime probability of developing cancer, average lifespan lost by the entire population, the average age of cancer occurrence, and the average lifespan loss of cancer cases. The approach utilizes the animal response data to assign, to the existing human cancer occurrence, an equivalent dose of the same carcinogen which is under consideration in terms of risk evaluation. The approach has the advantages of keying the estimates of carcinogen risks to those which already exist in the environment, avoiding large extrapolations from animal data, and encompassing the variability in susceptibility and carcinogen exposure in humans.

Carcinogens can pollute the environment from technological processes that are too important to abandon, as for example, the combustion of fossil and nuclear fuels for production of electricity. Hence, it is necessary to estimate the magnitude of cancer risks from environmental contamination as an essential part of the process of weighing the costs of controlling the release of carcinogens against the consequences of deleterious health effects and thus to make a rational choice between alternative technological processes that achieve the same ends.

The assessment of cancer risks from exposure to known environmental carcinogens is an exceedingly difficult problem. Carcinogen exposures will never be tolerated unless they are expected to cause negligible increases in the existing burden of cancer; unless there is a grave miscalculation in the formulation of exposure limits, the actual risks could never be feasibly measured in humans and certainly not in experimental animals. There are additional uncertainties associated with differential sensitivity among humans and between humans and test animals.

In principle, the only feasible basis for risk extrapolations to very low levels of carcinogen exposure is to develop a sound understanding in animals of the component processes that determine the dynamics of tumor formation and thereby establish the general principles for making risk extrapolations. It is also necessary to use epidemiologic data on human cancer in response to defined levels of exposure in order to equate the relative sensitivities of human and animal for particular target organs and carcinogens. The conventional method of assessing carcinogen hazards is done by relating the level of dose to cancer incidence. This implies that the extra cancer cases bear the full effect of the carcinogen exposure and the rest of the population suffers no ill effects. No attention is paid to the age at which new cancer cases

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occur or to the possibility that additional carcinogen exposure could affect individuals who were going to get cancer from other causes. The shape of the dose–incidence curve used for extrapolations is arbitrary as for example in the case of the Mantel-Bryan approach which uses a log-normal dose–response curve with a slope of one probit per log dose (*1*). The thrust of this paper is that the temporal patterns of mortality-corrected tumor incidence should be used as the primary basis for characterizing tumor responses from chronic carcinogen exposure since they are more directly related to the time-dependent processes of neoplastic cell transformation and growth of transformed cells into tumors. The incidence and age at which tumors form depend on the interaction of the temporal tumor response patterns with population survival. This approach provides a more complete characterization of carcinogen risks since the effects are defined not only in terms of the excess cancer incidence but also in terms of life shortening. Furthermore, the approach provides a way to link the responses observed in test animals to that already occurring in the same target organ in humans and to circumvent the need for very large extrapolations.

Strong evidence exists for a simple and systematic relationship between the magnitude of chronic life-time carcinogen exposure and the temporal behavior of tumor incidence when corrected for intercurrent mortality by conventional life-table techniques. The early work by Blum on the induction of skin cancer in the mouse by ultraviolet radiation (*2*) and the later studies of Druckrey with various chemical carcinogens on a variety of target organs (*3*) gave a mathematical formulation to the common experience that the higher the level of carcinogen exposure the earlier the appearance of tumors. These investigators showed that at a given dose level, the cumulative incidence of tumors can be represented by a log-normal distribution of time to tumor occurrence. Thus, the overall response can be expressed in terms of the median time t for tumor formation. The geometric standard deviation σ_g of the cumulative incidence provides a measure of the temporal dispersion of the individual response times, i.e., the larger the geometric standard deviation the more heterogenous the response.

The relationship between the daily dose of carcinogen d and the median time of tumor induction t was $dt^n = c$, where n and c are constants for a particular carcinogen and test system and the standard deviation σ_g was insensitive to dose rate. As shown elsewhere, the interaction of the log-normal tumor incidence curve with the population survival curve yields the cancer incidence, the average age at which cancer develops, and the average amount of life lost by the individuals developing cancer and the amount of life lost averaged over the whole population; the values of n and σ_g have important effects on the dose–response relationships (*4*).

The above formulation implies that, at a given dose level of carcinogen, every exposed individual would develop cancer if he lived long enough. The individuals that actually develop tumors are the more susceptible members of the exposed population; those that do not develop cancer are simply less susceptible and die from extraneous causes before they have a chance to develop cancer. The contrast between the effects of higher and lower carcinogen exposure levels is that the time of tumor occurrence is shortened by the higher dose level in all exposed individuals by the same proportion. Thus, the susceptibles develop cancers earlier than the less susceptibles at the lower exposure, and the additional cancer cases occur because they now die before other causes instead of afterward (in principle).

The applicability of $dt^n = c$ formulation to human cancer is illustrated by the comparison of stomach cancer in the U.S., Germany, and Japan (*5, 6*). In all three areas, the cumulative mortality-corrected incidence is log-normal with the same σ_g of 1.5. It is a reasonable supposition that dietary factors are responsible for the differences in cancer experiences in the three countries. The parallel log-normal cumulative incidence curves support the notion that incremental carcinogen exposure shortens cancer development by a constant factor in the entire population. On the assumption that $n = 2$, the equivalent carcinogen exposure is 30% higher in Germany and twice as high in Japan relative to New York State. The large value of the geometric standard deviation for stomach cancer in all three countries ($\sigma_g = 1.5$) suggests the existence of a considerable heterogeneity in the combined effects of susceptibility and carcinogen dose.

The epidemiological data on stomach cancer illustrates the generally accepted notion that much of the current cancer experience in humans is due to exposure to environmental carcinogens. It follows that the impact of additional carcinogen exposure should be described in terms of its interaction with the existing cancer experience and presumed carcinogen exposure. The biggest impact that a small additional carcinogen exposure could have on a population (that is already substantially

exposed to carcinogens) would occur when the additional and existing carcinogens were the same agents. This would shift the entire log-normal response curve to an earlier age. By contrast, if the actions were entirely independent, the small additional carcinogen exposure would have its own log-normal incidence curve occurring at a later time than that of the existing carcinogen exposure. The summated effects of the two log-normal curves would result in a deformed log-normal curve with tumor development foreshortened only at the more advanced ages.

A simple and conservative approach for estimating cancer risks could involve the use of the tumor response data in test animals (for the particular carcinogen whose risk is under consideration) to assign an equivalent carcinogen dose d_0 to the existing cancer experience in the human population to be exposed. The d_0 dose is thus one that provides in animals a comparable temporal response to that currently experienced by humans when the two species are normalized for differences in life span and under the assumption of equal average susceptibility in humans and the test animals. The impact of an additional carcinogen dose d is evaluated in humans in terms of the $(d_0+d)t^n=c$ formulation.

To illustrate the application of animal data to the assignment of an equivalent carcinogen dose d_0 to human cancer and the subsequent estimation of risks, let us suppose that we are concerned about the risks from the carcinogen diethylnitrosamine (DENA) which is assumed to produce only primary liver cancer in humans. A log-normal temporal response for liver tumors over a wide range of dose rates of DENA with $n=2.2$ has been reported by Druckrey for an inbred strain of rats (*3*). The cumulative incidence of primary liver cancer reported by the Connecticut State Tumor Registry for males in 1962–1964 (*6*) is log-normal with a σ_g of 1.7 and an extrapolated median time t of 350 yr. For purposes of illustration, it is assumed that 1 yr of human life span is equal to 1.52 weeks of life-span in rats. The median time t of 350 yr corresponds to 535 weeks in rats. The plot of $\log d$ versus $\log t$ for the DENA response of rats is linear and extrapolates to a dose of about 2 μg/kg-day at 535 weeks which is taken to be the equivalent dose d_0 for the background primary liver cancer experience in men. Computer calculations have been done for normalized tumor responses covering a range of values of n and σ_g to obtain values for incidence, average age of cancer occurrence and the average amount of life span lost by cancer cases (*4*). In these calculations, d was normalized to unity for t equal to the 62-yr mean life span of humans. It is assumed that humans exposed to DENA will show the same n value as that observed in rats, i.e., n = 2.2, but σ_g, which is a measure of heterogeneity of response, is taken to be that for the observed primary liver cancer occurrence in humans, namely, σ_g = 1.7. Table 1 presents, for various percent increments in the DENA equivalent dose d_0 for background liver cancer occurrence, the calculated values of t (median age), p (lifetime probability of developing cancer), Δ (average life-span lost by the entire population). x (the average age of cancer occurrence) and δ (the average life-span loss of cancer cases).

Table 1. Effect on various response parameters of the indicated percentage increments in equivalent carcinogen dose for liver cancer occurrence in Connecticut males, 1962–64.

Increment in equivalent carcinogen dose for current liver cancer experience %	Median time of cancer t, yr	Probability of cancer $p \times 10^{-4}$	Avg. age of cancer occurrence $\bar{x}$, yr	Avg. life span loss in entire population $\Delta \times 10^{-2}$, yr	Avg. life span loss in cancer cases δ, yr
0	350	18.9	71.27	2.12	11.21
2	347	20.0	71.20	2.25	11.24
5	342	21.7	71.07	2.51	11.32
10	334	24.6	70.87	2.92	11.43

To understand the significance of these figures let us examine, for example, the effects of the 10% increase in the equivalent carcinogen dose, i.e., 0.2 μg/kg-day. This carcinogen exposure reduces the time of tumor occurrence by 4.8%. The effects in the average age of cancer occurrence and the corresponding losses in life span are summarized in Table 2. The average age of the $18.9/10^4$ cases

Table 2. Effect of 0.2 μg/kg-day of DENA on the incidence, average age of tumor occurrence and life-span loss of spontaneous and new hepatic cancer cases.

	Incidence per 10^4	Average age, yr	Loss in life span, yr
"Spontaneous" cases (no DENA)	18.9	71.27	—
"Spontaneous" cases (with DENA)	18.9	67.85	3.42
Extra cases	5.7	80.75	1.99
Total cases	24.6	70.87	—

which occur at background exposure will be reduced by 4.8% from 71.27 yr to 67.85 yr. These spontaneous cancer cases would therefore lose 3.42 yr of life due to the carcinogen exposure. Furthermore, the incidence rises from $18.9/10^4$ to $24.6/10^4$ with the carcinogen exposure so that there are an extra $5.7/10^4$ cancer cases. However, the average age of cancer development for all the cancer cases which occur in association with the carcinogen exposure ($24.6/10^4$) decreases only slightly from 71.27 yr at background exposure to 70.87 yr with the carcinogen exposure. Since the carcinogen exposure reduces the average age of the original $18.9/10^4$ cancer cases to 67.85 yr, the $5.7/10^4$ extra cancer cases must have developed at an average age of 80.75 yr since the overall average age of cancer development in association with the carcinogen exposure is 70.87 yr.

As a result of the carcinogen exposure and the consequent foreshortening of the cancer time, the extra cancer cases die somewhat before other causes of death instead of somewhat later (in principle) so that the actual life shortening is roughly half the full 4.8% loss in life span of the original cancer cases. Hence, the average age of death at 80.75 yr represents a 2.4% reduction from what it would have been without the carcinogen exposure, i.e., 82.74 yr, and, consequently, the extra cancer cases suffer a 1.99 yr loss of life due to the carcinogen exposure. This is substantially less than the 3.42 yr lost by the original cancer cases and it also occurs later in life, so that the major brunt of the life-shortening is borne by those cancer cases who would have gotten their disease without the additional carcinogen exposure.

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