

RISK ASSESSMENT AND REGULATORY DECISION MAKING

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Summary—An overview of the regulatory decision-making process is presented, with special reference to the regulation of chemical carcinogens. Current procedures for assessing human risk on the basis of toxicological investigations in animal models are reviewed and a critical appraisal of the available techniques for quantitative risk assessment is provided. The integration of factors other than risk into the regulatory process, including information on health, economic and other benefits, is discussed.

Introduction

Although the nature of the risks confronting mankind has changed dramatically over the years, the concept that risk is an integral component of life has not. Man has always had to contend not only with natural catastrophes and infectious diseases, but also with nutritional deficiencies, toxic moulds, environmental contaminants and extreme climatic conditions. Tannahill (1973) notes that the mean life expectancy of Neanderthal man was twenty years and that less than 10% of the population survived to the ripe old age of forty. Since the beginning of the twentieth century, however, there has been a remarkable improvement in the health status of the Canadian population. Life-span has been steadily increasing, and many infectious diseases as well as certain degenerative diseases, such as cardiovascular disease and some forms of cancer, are slowly coming under control. These improvements in the overall quality of life may be attributed to a variety of technological developments in the medical sciences and in agricultural and food-marketing practices, although it must be recognized that technological progress is not without its own hazards.

Our transition from a largely rural to a predominantly urban society, coupled with substantial advances in the biological sciences in recent years, has dramatically shifted the public's perception of risk acceptability. Voluntary risks, which our forefathers accepted as an integral part of existence, have become involuntary risks, which the public expects, indeed demands, to have stringently controlled if not eliminated. Much of this public concern stems from a perceived failure of government authorities and industry to deal effectively with risks associated with chemicals in foods, occupational settings and the environment generally.

The use of chemicals in food production and processing has increased dramatically since the turn of the century (Jukes, 1977; Oller, Cairns, Bowman & Fishbein, 1980). Some of these substances are added to food to protect against bacterial deterioration or oxidative changes, while others are used to improve the flavour and texture of food. Pesticides are used to control insects and fungi in agriculture, and certain

drugs are used to stimulate growth in food-producing animals. Many of these uses are necessary to sustain the food supply of our ever-burgeoning world population. Thus, it is essential that risk associated with these chemicals be carefully balanced against the health, economic and other benefits that accrue from their use. This is not to say that undue health risks should be tolerated. On the contrary, they should be minimized to the extent technologically feasible, but they must not be eliminated at the cost of compromising the food supply, facilitating the spread of disease, or lowering the overall quality of the environment.

In Canada, as in most nations, the government's intentions with regard to the control of risks are clearly defined. With respect to toxic substances in food, Section 4 of the Canadian Food and Drugs Act (Food and Drug Regulations 1979, Ottawa) provides the Department of Health and Welfare with the legislative power to curtail or eliminate exposure to "poisonous or harmful" substances. A major problem confronting all countries with similar legislation relates to the definition of the terms 'poisonous' and 'harmful'. If we hold the view as toxicologists that these qualities are not inherent vices of a compound but rather a function of dose-dependent toxicity, we have some leeway for permitting the use of chemicals in food. Indeed, it is only by application of such principles that food as we know it can be sold at all. Thus many substances known to produce toxic effects at high doses in laboratory animals are permitted for use in food production or processing. The procedural rules for deciding upon acceptable human exposure levels have been entrenched in regulatory circles for many years, are endorsed by the World Health Organization, and have involved the use of uncertainty factors for translating animal data to man (Vettorazzi, 1980). This procedure is not hard and fixed but is subject to considerable discretion on the part of the regulator, depending upon the nature and degree of hazard involved.

In this paper the role of government in avoiding or reducing exposure to cancer-causing and other harmful agents will be discussed. While problems related to microbiology and nutrition are still very high on our priority list, the pendulum of scientific activity as well

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as public concern and debate over food-safety issues has swung over in favour of programmes to detect and eliminate carcinogenic substances. The rapid rate at which we are detecting carcinogens in our environment, coupled with increased consumer awareness, indeed a fear of cancer, has led those of us in government to re-examine critically food-safety policies pertaining to carcinogens as we look towards the future.

Quantitative risk assessment

Safety factors and thresholds

Traditional toxicological procedures define a safe level of exposure for man as some arbitrary fraction of that dose level at which no effects are observed in a group of test animals. For food additives and pesticides inducing toxic effects other than cancer, for example, an acceptable daily intake has often been established through the application of a 100-fold safety factor. This uncertainty factor admits the possibility that man may be up to ten times more sensitive than the animal species tested and allows for a ten-fold variation in sensitivity within the human population (Lehman & Fitzhugh, 1954). The magnitude of the safety factor may be modified depending on the chemical and kinetic properties of the test compound and the effects induced, as well as on the quality of the available toxicological data (Committee on Food Protection, 1980; Safe Drinking Water Committee, 1980).

The use of safety factors in arriving at acceptable human exposure levels would appear to rest at least tacitly on the assumption of the existence of a threshold dose below which no adverse effects will occur. However, it is precisely because the threshold concept may not be universally applicable to carcinogenesis that the regulation of carcinogens is regarded as a unique issue in food safety. This uncertainty as to the low-dose effects of carcinogenic agents has resulted in the proposed use of safety factors as high as 5000-fold (Truhaut, 1979; Weil, 1972).

In mathematical terms, the absence of a threshold precludes the possibility that a sufficiently low level of exposure will be free of any attendant degree of hazard. Biological arguments in favour of the no-threshold concept for carcinogenesis are generally based on the fact that irreversible self-replicating lesions may result from a mutation in a single somatic cell, often following the administration of only a single dose. Arguments against this position draw on the existence of metabolic detoxification, DNA repair, immunological surveillance and other mechanisms that may operate to nullify effects at low doses. Even admitting their existence, thresholds are likely to vary among individuals. The determination of a population threshold thus presents the difficult statistical problem of determining the minimum of the individual thresholds, a minimum which may well be effectively zero in some cases (Brown, 1976).

The safety factor approach has also been criticized on the grounds that the observed no-effect level will depend on the sample size, with response rates of 0/10 and 0/1000 obviously having different interpretations. Moreover, there is always the possibility of observing no effects even though the test compound may affect an appreciable proportion of the population at risk.

For example, with fifty animals on test, there is a better than even chance of observing no effects with a compound for which the population risk is actually as high as 1% (Cornfield, Carlborg & Van Ryzin, 1978).

Less generally recognized is the fact that the application of a standard safety factor does not take into account the slope of the dose-response curve for the particular response of interest (Cornfield, Rai & Van Ryzin, 1980). Clearly, a moderate safety factor may provide an adequate margin of safety if the dose-response relationship is relatively steep but may not be sufficiently conservative if the dose-response curve is relatively shallow. Conversely, the universal application of a very large safety factor will result in tolerances that will often be unduly low.

This brings us to the hub of a debate that rages among toxicologists and statisticians alike. This discussion concerns the use of mathematical models to evaluate risks at low doses—doses to which humans may be exposed. The use of point estimates of risk as a major decision criterion in the regulatory control of carcinogens would permit an assessment of the relative risks due to various compounds. Although this perhaps represents the ultimate application of mathematical modelling techniques, knowledge deficiencies in the science base at present preclude the possibility of realizing the full potential of the procedures currently available. However, it is instructive to review briefly where we now stand on the application of procedures for quantitative risk assessment for purposes of regulatory decision making.

Mathematical models and virtual safety

Statistical procedures for quantitative risk assessment involve a mathematical model relating the probability of an induced response to the dose rate. Because of the statistical problems inherent in the determination of no-effect levels, most mathematical models have dispensed with the threshold concept. [Cornfield (1977) has discussed a kinetic model which leads to the existence of thresholds under steady-state conditions. As noted by Brown, Fears, Gail, Schneiderman, Tarone & Mantel (1978), however, the possibility of a response being induced by the reactive metabolite formed during the approach to steady state results in some degree of risk no matter how small the dose.] While absolute safety may be guaranteed in the absence of a threshold only when the level of exposure is zero, a virtually safe level of exposure associated with some suitably low level of risk may still be estimated (Fig. 1). It is important to recognize that since direct estimates of risk at low levels of exposure would require the testing or prohibitively large numbers of animals, the determination of a virtually safe dose will generally involve extrapolation of the experimental results well outside the observable response range.

A number of existing models that have been discussed in the literature are given in Table 1 (Krewski & Brown, 1981). Statistical models are based on the notion that each individual in the population has his own tolerance to the test compound. Any level of exposure below this tolerance will have no effect on the individual, while any level of exposure exceeding the tolerance will result in a positive response. These tolerances are presumed to vary among individuals in

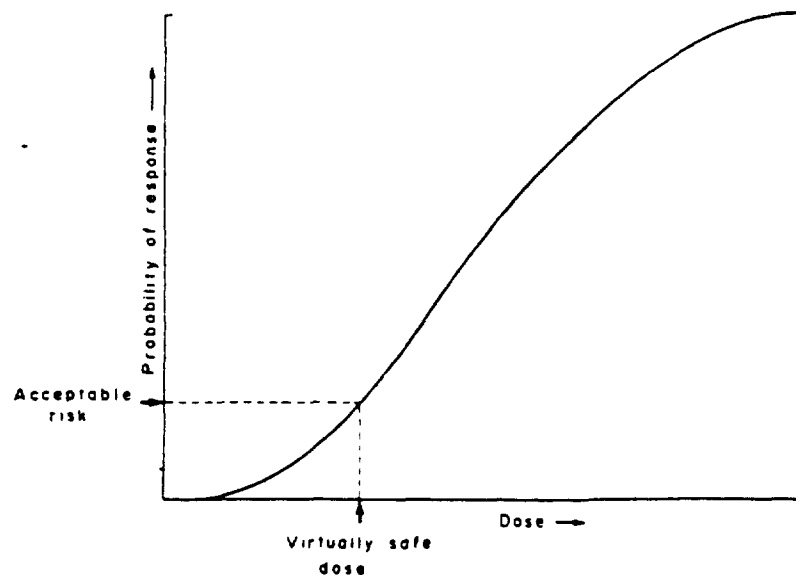


Fig. 1. Determination of a virtually safe dose.

the population, with the lack of a population threshold reflected in the fact that the minimum tolerance is allowed to be zero. Specification of a functional form for the distribution of tolerances determines the shape of the dose-response curve and thus defines a particular statistical model. Although the choice of the tolerance distribution is to a large extent arbitrary, three commonly encountered models of this type are the probit, logit and Weibull. [Certain statistical models may also be formulated in terms of time to response considerations. Chand & Hoel (1974) have shown that the probit model rises when the time to response follows a lognormal distribution, with the median time to response satisfying the Druckrey equation.]

Stochastic models are based on the premise that a positive response is the result of the random occur-

rence of one or more biological events. The one-hit model (Hoel, Gaylor, Kirschstein, Saffioti & Schneiderman, 1975) is based on the concept that a response will occur after the target site has been hit by a single biologically effective unit of dose. The multi-hit model (Rai & Van Ryzin, 1981) is a direct extension of the one-hit model, assuming that more than one hit is required in order to induce a response. [This model may also be viewed as a tolerance distribution model, where the tolerance distribution is gamma. This formulation allows the 'hit' parameter k to assume non-integral values.] The multi-stage model, on the other hand, is based on the assumption that the induction of irreversible self-replicating toxic effects such as carcinogenesis is the result of the occurrence of a number of different random biological events, the time rate of

Table 1. Mathematical models and their low-dose behaviour in the case of zero background

Model	Probability $P(d)$ of a response at dose d †	Low-dose behaviour‡		
		Linear	Sublinear	Supralinear
Probit	$(2\pi)^{-1/2} \int_{-\infty}^{d/\beta} \exp(-u^2/2) du$ ($\beta > 0$)	—	$\beta > 0$	—
Logit	$[1 + \exp(-\alpha - \beta \log d)]^{-1}$ ($\beta > 0$)	$\beta = 1$	$\beta > 1$	$\beta < 1$
Weibull	$1 - \exp(-\lambda d^m)$ ($\lambda, m > 0$)	$m = 1$	$m > 1$	$m < 1$
One-hit	$1 - \exp(-\lambda d)$ ($\lambda > 0$)	$\lambda > 0$	—	—
Multi-hit	$[F(k)]^{-1} \int_0^d u^{k-1} \exp(-u) du$ ($\lambda, k > 0$)	$k = 1$	$k > 1$	$k < 1$
Multi-stage	$1 - \exp\left(-\sum_{i=1}^k \beta_i d^i\right)$ ($\beta_i \geq 0$)	$\beta_1 > 0$	$\beta_1 = 0$	—

†With independent background, the probability of a response at dose d is given by $P^*(d) = \gamma + (1 - \gamma)P(d)$, where γ ($0 < \gamma < 1$) denotes the spontaneous response rate. Under additive background, $P^*(d) = P(d + \delta)$ where $\delta > 0$ denotes the effective 'background' dose.

‡Low-dose behaviour for independent background also. (All models are linear at low doses under additive background.)

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