Qualitative evaluation of the weight of evidence from human, animal and other studies does not make full use of this range of knowledge; it assess whether there is a hazard but no how great the risk. Many groups in society including scientists want to know more than simply whether cancer risks exist, and are pressing for information to guide them when they set priorities for the control of cancer causing agents in the environment. Consumer organizations press for full disclosure of the harmful effects of new appliances and drugs. Industrials groups want to quantify risks in order to estimate the benefits (and costs) of changing current work practices. Courts of law seek quantity estimates the benefits (and costs) of changing current work practices. Courts of law seek quantitative estimates of cancer risks to assist decisions on liability for individual cases of cancer. Quantitation of cancer risks assists the control of cancer hazards by providing policy-makers with information about the magnitude and gradient of risk. This information, coupled with population exposure profiles, enables an assessment to be made of the relative importance of each carcinogen in relation to other carcinogens and other hazards “competing” for regulatory attention and resources.

Quantitative estimates of risks may be subject to many sources of uncertainty. For example, experimental and sampling error as well as random and systematic measurement error in both exposure and response varieties all contribute to uncertainty in risk estimation. Risk can also vary appreciably among individuals in the population of
interest, even though estimates of cancer risk are subject to both uncertainty and variability, quantitative analyses can often provide a clearer basis for risk management decisions than qualitative evaluations of (known, possible or probable) carcinogens.

3.1 HISTORICAL BACKGROUND

Since the 1940s, industrialization and the proliferation of synthetic organic chemical have resulted in a myriad of actual and potential health-endangering exposures. In many industrialized countries, cancer, vascular disease and other chronic conditions have now replaced infectious diseases as the major causes of mortality. This has led to a new emphasis in public health on the risks, particularly cancer risks, posed by exposure to chemical agents (Paustenbach, 1989).

Initially, scientists and regulators used a qualitative assessment, based on toxicity testing, and invoking a binary "Yes–No" classification of agents human health hazards. However, the setting of permissible exposure limits for the workplace, systematized by industrial hygienists in the USA during the 1940s, introduced the less absolute concept of "acceptable" levels of exposure to toxic agents (Paustenbach & Linger, 1986). The rudimentary quantitative risk-assessment methods that evolved during the 1940s and 1950s included the use, for health outcomes other than cancer, of dose-response graphs to identify a "no-observed-adverse-effect level" (NOAEL), i.e. a dose below which no adverse effect was apparent (Krewski et al. 1984). Approach to risk assessment sought to identify a so-called safe level. However, for cancer risks, the notion, of a "virtually safe dose" (Mantel & Bryan 1961) soon came to be
preferred, since any exposure to carcinogens was assumed to cause some increment in cancer risk. More recently, the term “risk specific dose” has come into use in order to avoid implying the acceptability of specific levels of risks.

Mathematical models were used to estimate the dose-related excess lifetime cancer risks (including the estimated upper-bound excess risk) for humans, based on the dose-response curve obtained in animal bioassays and taking into account differences in species sensitivity to carcinogen exposure (Crump et al. 1976). Subsequent improvements in cancer modeling have come about through awareness of the process involved in carcinogen sis and improved modeling of tissue dosimetry.

3.2 DEFINITIONS OF TERMS AND CONCEPTS

The terms “hazard” refers to a potential cause of illness or injury, “risk” express the probability that some specified adverse outcome will occur in a person or a group exposed to a particular concentration of a hazardous agent over specific time intervals (Paustenbach, 1989) Quantifying that risk entails a mix of formal procedures and judgments, depending on the range of data available.

In practice the terms “exposure” and “dose” are often used interchangeably in quantitative estimation and prediction (QEP), in particular in the context of QEPs based on epidemiological studies. “Exposure” referring to the quantity of the agent in the individual’s environment: for example the amount of tobacco smoke in the immediate environment of a non-smoker. Dose “referring to the
quantity that has been taken up by the individual: for example, the amount of smoke in the bronchi of the non-smoker exposed to passive smoke.

An estimate is a value for an unknown quantity (e.g. the true risk of cancer), calculated according to sound statistical principles, and inferred from data that directly pertain to the specified exposure circumstance. The word "estimate" is used because the observations of any single study represent only a sample of all the observations that could, potentially, be made. Estimates are of varying degrees of precision and accuracy, depending on the nature of the data and on the inference methods upon which they are based. Precision will be influenced by sample size, and can be expressed in terms of standard errors or confidence intervals. Accuracy, or the degree to which the estimate is unbiased, is more difficult to evaluate, and requires consideration of potential sources of systematic as well as random error.

The term "prediction" is used here to refer to estimate of risk under conditions different from those under which the original data were obtained. It includes, in particular, extrapolation outside the range of the original data, both to different species and to different circumstances. In order to predict the risks for humans exposed at lower levels, it is essential to do one or more of the following:

- Extrapolate the high-exposure human data to lower dose levels.
- Estimate the risks for animals at high exposures, extrapolate that to low doses, and then extrapolate that prediction to humans.
• Extrapolate from low-exposure observations in animals to humans.

In regulatory applications of cancer risk assessment, risk is often expressed in a particular population under specified conditions of exposure. To make this concept precise, it is necessary to specify the expected life span over which risk accumulates. Such estimates can be adjusted for intercurrent mortality, or standardized with respect to patterns of mortality from causes other than cancer. Epidemiologists often summarize their quantitative estimates of risk in terms of age-specific cancer incidence rates, which reflect the number of new cancer cases occurring in a particular exposed population of a specified age over a specified period. Risks may also be described in terms of number of years of life lost, which may be adjusted for quality of life.

3.3 RISK PREDICTION

Risk may be expressed in relation to total "dose", or perhaps "average dose rate", variations in the temporal pattern of exposure may significantly influence the net risk. (For example, the periodicity of exposure or the peak exposure rates may be important). These include, in particular, uncertainty about how to extrapolate from high-dose to low-dose exposure and how to extrapolate from non-human species to humans. Additional difficulties, foreshadowed in the previous section, concern the handing or variability in individual response and those posed by interactive effects between two or more coexisting exposures.
Often, a no-threshold model, linearized at low dose, has been assumed. This model enables one to calculate the “lifetime unit risk”, i.e. the incremental risk of some specified health outcome associated with a lifetime of exposure to one unit of concentration (e.g. 1ug/m³ benzol [a] pyrene in air). Such an approach has been used in setting air quality criteria for Europe in relation to the risk of disease associated with a range of air pollutants (world – Health Organization, 1987).

To predict the risk of cancer at low doses, the linearized multistage procedure is commonly used. This procedure is based on the multistage model first proposed by Aromatize & Doll (1954) to explain the observation that the age-specific incidence curves of many human carcinomas are roughly proportional to a power of age. This model posits that cancer results from the accumulation, within a single susceptible cell, of a sequence of heritable and irreversible alterations. Current laboratory research leaves little doubt that cancer is the result of an accumulation of critical mutations by such a cell. Additionally, a disruption of cell division kinetics is also believed to play an important role in the carcinogenic process.

The last two decades have seen an explosion of statistical literature on relative measures of risk, which can be estimated in both case-control and cohort studies. Let \( I_e \) be the incidence rate in the exposed population and \( I_u \) be the incidence rate in the unexposed population. Then the relative incidence, i.e the relative risk (RR) is defined by \( RR = \frac{I_e}{I_u} \). A closely related measure is excess relative risk (ERR), which is defined as \( ERR = \frac{(I_e - I_u)}{I_e} = RR - 1 \). Yet another measure of risk is the attributable or etiological fraction (AF), which is defined as \( AF = \frac{(I_e - I_u)}{I} = \frac{(RR - 1)}{RR} \). AF is the fraction of incident cases in the exposed in the absence of
exposure, and "can be interpreted as the proportion of exposed cases for whom the disease is attributable to the exposure" (Rothman, 1986). In most regression analyses of epidemiological data, RR is model neither as a "multiplicative" or an "additive" function of the covariates of interest.

3.4 ERROR IN MEASUREMENT OF OUTCOME

In cancer epidemiology, the outcome of interest is the occurrence of cancer in the subjects under study. However, although easy to conceptualize, occurrence of cancer is a difficult event to measure. As a result, the event actually measured may be more closely related to it.

The most widely used outcome variables in cancer epidemiology, namely death from cancer, diagnosis of cancer, diagnosis of pre neoplastic lesions, and molecular markers of early carcinogenic effect, can be seen as consecutive steps in a process corresponding to the putative natural history of the disease.

A fundamental source of error in outcome ascertainment is incorrect specification of vital status. In particular, deaths may be missed when death record are incomplete. For example, in studies involving record linkage with mortality record, vital status may be incorrectly specified when personal identifiers are insufficient to ensure that no linkage errors occur. Linkage errors lead to bias and additional uncertainty in commonly used statistics such as standardized mortality ratios (SMRs) and relative risk regression coefficients, with an excess (deficit) of deaths leading to upward (downward) bias in the estimated SMRs.
The major difficulty in assessing diagnostic or histopathological validity is the lack of a gold standard of the characteristics being measured. In other words, there is no way to determine the absolute truth with respect to the disease at the level of organ, tissue and cell type. For this reason, measurements of diagnostic and histopathological error have usually focused on reliability rather than validity, and have measured intra-observer and inter-observer reliability. Reliable, measurements, however, are not necessarily valid, and the only certain conclusion is that an unreliable tends to be greater than the corresponding inter-observer reliability because the singing observer will repeat his or her own systematic error, whereas the often the effects of systematic errors of different systematic errors of different observer will be included in the assessment of inter-observer agreement.

Measurement of pre-neoplastic lesions, however, is also subject to random and systematic error. For example, in a study on the prevalence of melanocytic naevi in western Australia in children assessed by two nurses, it was found that 4% of the variation in numbers of naevi of all that sizes, and 8% of the variation in those of naevi of at least 2 mm in diameter was due to inter-observer variation (English & Armstrong, 1994).

Several statistical methods have been proposed for use in measuring inter-observer reliability. The simplest and most common used method is to determine the proportion of cases in which two (or more) observers agree. However, this method does not take into account the proportion of cases in agreement by chance only. It can be simply shown that this proportion varies with the prevalence of the outcome being measured, increasing as the prevalence increases to very high
or decreases to very low values. A simple statistic corrected for chance agreement is the kappa statistic (Fleiss, 1971), which is the ratio of the difference between the observed proposition in agreement (Po) and the proportion of agreement that can be expected by chance (Pe) to the proportion of agreement that cannot be attributed to chance (1 - Pe), so that:

\[
\text{Kapp} = \frac{Po - Pe}{1 - Pe}
\]

An advantage of the kappa statistic is that it can be applied to nominal scale variables, which are common in pathology and histology. It can be interpreted like a correlation coefficient, i.e. its value varies from 0.0 (no agreement beyond that expected by chance) to 1.0 (perfect agreement) and to -1.0 (complete disagreement).

A good example of the effect of outcome measurement k error deals with the risk of soft-tissue sarcomas (STS) among workers exposed to dioxin. STS are rare malignant neoplasms originating in tissues of mesodermal origin, such as fat, muscle and connective tissues. However, although most STS originate from organs primarily containing mesodermal tissue, some originate from visceral organs, such as the stomach, that also contain mesodermal tissues, but such sarcomas represent only a small fraction of all neoplasms originating in these organs. Since the International Classification of Diseases (ICD), which is used in many countries to code causes of deaths from death certificates, is based on the topography of the neoplasm's, STS arising from visceral organs are coded as neoplasm's of those organs, and are thereof not identified in a mortality study. The net
result is a 30 - 70% underestimation of the number of STS (Lynge et al., Erikson & Gezelius, 1990).

3.5 MODELING EPIDEMIOLOGICAL DATA

In epidemiological studies, modeling is carried out to estimate the risk of cancer as a function of the exposure of interest and of the host and environment factors which may modify risk. Epidemiological studies used for quantitative estimation of risk should generally encompass a range of exposure levels to permit characterization of the relationship between exposure and risk. The two main types of studies which provide data for this purpose are: (i) Cohort studies, in which a group of persons with a range of exposure levels is followed, for mortality or morbidity, from a particular disease; and (ii) case-control studies, in which the exposure history of all cases and appropriate controls is reconstructed.

The most common measures of risk used in QEP are the age- and time-specific “absolute” and “relative” risk. Both of these measures can be expressed as a function of the level of the exposure of interest as described below. Absolute risk (AR) cannot be estimated from case-control studies without supplementary information on the level of risk in unexposed individuals. Relative risk (RR) can, however, be estimated from both case-control and cohort studies. Most of the developments in empirical QEP models for the analysis of epidemiological data have focused on RR models.

Data from cohort studies are often analyzed using methods developed for grouped, rather than individual, data. The parameter of interest
is the rate of mortality or morbidity from the disease under study in stratum $jk$. The observed rate is obtained as the ratio of events $o_{jk}$ (Deaths or disease occurrences) and person-years of observation $n_{jk}$ in the stratum.

The numbers of events in each cell are considered to be independent Poisson random variables with means and variances $E(o_{jk})$ and $\text{Var}(o_{jk})$. The denominators, $n_{jk}$'s are assumed to be fixed. For a technical justification for the use of the Poisson model Broslow & Day (1987). Different models for the rate can be postulated and parameters estimated using maximum likelihood. The most commonly used model in epidemiological applications is the relative risk (RR) model, in which the effect of the exposure $k$ is to multiply the background rate (the rate in stratum $j$ in the absence of the exposure) as follows:

$$\lambda_{jk} = \lambda_{jo} f(x_k)$$

Here $f$ is a function of the (Mean or median) level of exposure $x$ in category $k$. This function may depend on other factors, such as age or time since exposure, sex, and smoking history. To simplify fitting this model is often expressed as:

$$\log \lambda_{jk} = \alpha_j + \beta_k$$

where

$$\alpha_j = \log \lambda_{jo}, \quad \beta_k = \log f(x_k)$$

An often used parametrization of the RR model is the constant linear excess relative risk model:
Here, the parameter is referred to as the excess relative risk (ERR) per unit of exposure. The RR at a given exposure $x$, a more commonly used measure of risk in epidemiology, can be obtained by multiplying the ERR by the exposure $x$ and adding 1. Whereas $\beta x$ is a linear function of the exposure, $x$, non-linear functions may also be worth exploring.

Relative risk models are the most generally used models in epidemiology for several reasons. For many exposure they appear to describe the relationship between exposure and the age-specific risk of cancer better than absolute risk models. Using such models, risk estimates can be obtained without imposing any assumptions on the baseline rates of disease, $\lambda_{j0}$. They also provide a convenient framework for communicating information about radiation risks.

In Cohort studies, models may also be fitted to the original data before categorization. One of the most commonly used models for this purpose is the proportional hazards model

$$\lambda(t; Z(t)) = \lambda_0(t) \exp(X(t) \beta)$$

introduced by Cox (1972). Here, $\lambda$ denotes the hazard function for the disease of interest at time $t$ for an individual with covariate history $Z(t)$ and $(t)$ is the baseline hazard function. This is a semi-parametric relative risk model. The partial likelihood approach of Cox (1972) can be used to estimate the parameters $\beta_j$ and $(t)$. 

$$\lambda_{jk} = \lambda_{j0}(1 + \beta_{jk})$$
In case-control studies, actual rates of disease in exposed and non-exposed subjects cannot generally be estimated as the cases and controls are drawn with different sampling probabilities from the population under study. An immediate consequence is that the relative risk cannot be estimated from case-control studies when the disease is relative risk. Since specific types of cancer are relatively rare, this approximation is of considerable use in cancer risk estimation with case-control data. OR is defined as follows:

\[
\text{OR} = \frac{\text{Number of exposed cases} / \text{Number of unexposed cases}}{\text{Number of exposed cases} / \text{Number of unexposed cases}}
\]

The empirical models used for risk estimation in epidemiological studies are mostly relative risk models, fitted using logistic regression in case-control studies or Poisson or proportional hazards. The effects of factors modifying the association between exposure and disease (such as age, sex, or calendar year) can be accommodated through stratification, with different risk estimates derived within each stratum defined in terms of the effect modifiers. Another approach is to use a permanent risk model in order to describe the interactions between the exposure of interest and the modifying factors.

If a model is to be used for the estimation and prediction of cancer risks, it is important to assess whether it fits the observed data. However, the fact that a model is correct; as noted above, the BEIR V committee found that both absolute and relative risk models fitted the leukemia data equally well (US National Academy of Sciences/National Research Council, Committee on the Biological effects of...
Ionizing Radiations, 1990). While such models may provide comparable estimated risk within the observable response range, predictions of risk outside this range may differ substantially.

### 3.6 MODELING TOXICOLOGICAL DATA

Statistical models may also be used to summarize dose-response data from laboratory studies. Most long-term animal experiments encompass the greater part of the expected lifespan of the test-species, which is typically 2-3 years for rodents. In describing such models, it will be convenient to distinguish between models used to describe the lifetime probability of cancer and those which are used to describe the temporal patterns of tumor incidence. Note that the lifetime probability of cancer will be influenced by the survival rate of the animals in the experiment, early mortality reducing the opportunity for tumor occurrence.

Dose-response models used describe the relationship between the lifetime probability of cancer and dose are referred to as quintals response models since the response of interest (the presence or absence of a given tumor in a given animal during the course of the study) is a binary random variable. Krewaski & Van Ryzin (1981) have published a detailed review of quantal response models for toxicological data, including carcinogenicity data, and such models have also been discussed by Finney (1971), Govindarajarlu (1988) and Hubert (1992).

Tolerance-distribution models are based on the notion that each animal has its own tolerance to the test agent, and that a toxic
response will occur whenever the dose $d$ exceeds the tolerance $t$. $G(t)$ $(0 < t < \infty)$ denotes the cumulative distribution of tolerances in the population of interest. The probability $t$ that an individual animal selected randomly from among those exposed to dose $d$ will respond is simply

$$P(d) = \Pr(t < d) = G(d)$$

A general class of tolerance-distribution models is defined by $G(t) = F(\alpha + \beta \log t)$ where $F$ denotes any cumulative distribution function standardized so as to be free of unknown parameters to be estimated on the basis of the experimental data. Perhaps the model, for which $F$ corresponds to the standard normal distribution function:

$$F(x) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} e^{-u^2/2} du$$

In this case, the distribution of tolerances is lognormal. The logist model with

$$F(x) = \left[1 + \exp(-x)\right]^{-1}$$

And the Weibull model with

$$F(x) = 1 - \exp\{-\exp(x)\}$$

are also used to describe quintals-response toxicity data. Prentice (1976) has described a more general parametric family of dose-response models that includes the above models as special cases. The shape of the dose-response curves for both the logistic and Weibull models is determined by the value of the shape parameter $\beta$. In the low-dose region, the dose-
response curve may be linear (\( \beta = 1 \)), sublinear (\( \beta > 1 \)) or supralinear (\( \beta < 1 \)).

In contrast, the probit model exhibits a sub linear behaviour in the low-dose region regardless of the values of the model parameters. This model implies \( P(0) = 0 \), so that tumors can not spontaneously in the absence of exposure to the test agent. To allow for the occurrence of tumors in the control group, spontaneous tumors may be assumed to occur independently of those induced by the test agent or in dose wise additive fashion (Hoei, 1980). On the assumption of independence, the probability \( P'(d) \) of observing either a spontaneously occurring or an induced tumor at dose \( d \) is given by:

\[
P'(d) = \gamma + (1 - \gamma)P(d),
\]

where \( 0 < \gamma < 1 \) denotes the spontaneous response rate. For addictivity, spontaneous tumors are associated with an effective background dose \( \delta \), with

\[
P'(d) = P(d + \delta)
\]

These two methods of allowing for background response generally lead to comparable descriptions of the dose-response relationship within the observable response range. An important implication of the additive background model is that the dose-response curve will be linear at low doses for any smoothly increasing distribution function \( F \), including the probit, logit, and weibull models discussed previously (Crump et al., 1976). In contrast, the shape of the dose-response curve in the low-dose region for the independent background model corresponds to that of the function \( F \) as indicated above.
Other dose-response models have a limited biological basis, postulating the random occurrence of one or more biological events as being responsible for tumor induction. For example, Rai & Van Ryzin (1981) consider a multi-hit model based on the concept that a tumorigenic response will occur following the occurrence of k fundamental (and unspecified) biological events in the target tissue. If it is assumed that the rate of occurrence of these events follows a homogeneous Poisson process, the probability of a response at dose \( d \) is given by:

\[
P(d) = \frac{d}{[\Gamma(k)]^{-1}} \lambda^k k^{-1} \exp(-\lambda d) dt,
\]

where \( \Gamma(k) \) denotes the gamma function and \( \lambda d \) denotes the expected number of events occurring during the period of interest. Same model can also be developed by assuming a gamma tolerance distribution, thereby permitting an extension to non-integer values of \( k \). Background response can be accommodated by assuming either independence or addictivity. At low doses, the dose response curve can be linear (\( k=1 \)), sub linear (\( k>1 \)) or supralinear (\( k<1 \)). The case of \( k<1 \) however, does not seem plausible in that it would correspond to an infinite slope at the origin and could lead to unrealistic predictions of risk at very low doses.

The special case of \( k=1 \) is known as the one-hit model, with

\[ P(d) = 1 - \exp(-\lambda d) \]

In the absence of background response. With either independent or additive background tumors, the one-hit model is of the form:

\[ P(d) = 1 - \exp\{-\lambda_0 - \lambda_1 d\}, \quad \text{--------(1)} \]

Where \( P(0) = 1 - \exp\{-\lambda_0\} \) and \( \lambda_1 = \lambda \).
A widely used generalization of the one-hit model is the Armitage-Doll multistage model. A simplified version of the model that is commonly used in QEP is as follows:

\[ P(d) = 1 - \exp\{-(q_0 + q_1 d + \ldots + q_k d^k)\} \]

Where \( q_i \geq 0 \) (i=1, \ldots, k).

Any of these quantal-response models may be fitted to data derived from long-term animal carcinogen city experiments, provided that the number of dose groups is greater than or equal to the number of unknown model parameters. Suppose that a lot of \( n \) animals are used in an experiment involving \( m+1 \) dose levels \( 0 = d_0 < d_1 < \ldots < d_m \) and that \( x_i \) of the \( n_i \) animals at dose \( d_i (i=0,1,\ldots,m) \) develop the tumor of interest during study. If it is assumed that each animal responds independently of all other animals, the likelihood of the observed outcome for a given dose-response model \( P^*(d|\theta) \) depending on the vector of parameters \( \theta = (\theta_1, \ldots, \theta_t) \) is given by:

\[
L(\theta) = \prod_{i=0}^{m} (P_i^*)^{x_i} (Q^*_{i})^{n_i - x_i}
\]

Where \( P_i^* = P^*(d) \) and \( Q^* = Q^*(d) \).

Maximizing this binomial likelihood function with respect to \( \theta \) leads to the maximum likelihood estimators. Maximum likelihood estimators generally enjoy desirable statistical properties, including consistency and kl asymptotic normality. Once the estimator has been obtained, the fit of the dose-response model to the experimental data can be evaluated using a chi-square goodness-fit test.

Methods other than maximum is the method of generation estimating equations (GEFs) described by Liang & Zeger (1986). The GEE method requires specification only of the first two moments for the data rather than the complete distribution, and can easily accommodate...
extra binomial variation. GEEs have been used in modeling data on mutagenicity (Krewski et al., 1993b) and developmental toxicity (Zhu et al., 1994) where over dispersion relative to the Poisson and multinomial distributions is used to eliminate such over dispersion, thereby simplifying the analysis.

Non parametric approaches to modeling quantal dose-response data are also available (Kuo, 1988; Morris, 1988; Mullah & Schmitt, 1988). However, these methods focus on the estimation of response rates at the experimental dose levels, thereby avoiding the problem of predicting cancer risks at other dose levels.

3.7 MODEL OF TIME TO RESPONSE

Tumor incidence data from long-term animal experiments, quantal dose-response models do not take into account the age at which tumors were observed. A more complete description of the data derived from such experiments may be achieved using time-to-tumor models.

Let $T$ be a random variable denoting the tumor onset time. Although $T$ could be precisely defined as the time at which the first cancer cell appears. Consequently, a more practical definition, such as the earliest possible time that a cancerous lesion could be detected clinically or histologically, is usually adopted. The probability of a tumor occurring by time $t$ at dose $d$ is then given by $p(t;d) = \Pr$. The complement of the tumor onset distribution $Q(t;d) = 1 - p(t;d) = 1 - q$ is known as the survivor function.

The hazard function:

$$\lambda(t;d) = \lim_{\Delta t \to 0} \frac{\Pr\{T \in (t, t+\Delta t) \mid T > t\}}{\Delta t}$$

denotes the instantaneous probability of a tumor developing at time $t$ in a tumor-free individual and is used to describe the age specific tumor incidence rate. The survivor and hazard functions are related by:

$$Q(t;d) = \exp\{-\int_0^t \lambda(u;d) du\}.$$

Where $\Lambda(t) = \int_0^t \lambda(u;d) du$, is the cumulative hazard function.
Thus, we may model the distribution of tumor-onset times either in terms of \( p(t;d) \) or \( \Lambda(t) \). Note that at a fixed time \( t=t_0 \), \( P(t_0;d) \) considered as a function of \( d \) alone represents the dose-response relationship in the absence of intercurrent mortality.

The Cox regression model, originally proposed by Cox (1972), is widely used in the analysis of failure time data, including time to tumor or death. The hazard function for the Cox regression model is given by:

\[
\lambda(t;d) = \lambda_0(t) \exp\{Z(t)^\top \beta\}
\]

Where \( \lambda_0(t) \) is an unspecified baseline hazard function independent of dose \( d \) is a vector of regression parameters and \( Z \) is a vector of covariates that may depend on both time \( t \) and dose \( d \). When \( Z \) is independent of time \( T \), the hazard at different doses are proportional. With time-dependent covariates, however, the hazard ratios in different doses groups can vary with time. For example, \( z = (d, d \log(t))^\top \) corresponds to:

\[
\lambda(t;d) = \lambda_0(t)e^{d_1 t + d_2}
\]

In general form, the Cox regression model is sufficiently flexible to describe a wide variety of dose-response relationships (Prentice et al., 1982).

Time-to-tumor models depend on the amount of information available on tumor-onset times, whether or not cause of death can be determined, and relationship between tumor mortality and competing causes of death (Krewski et al. 1983).
The general process of tumor onset and development over time can be conveniently described within the general framework. An animal may develop a tumor at some time during the study period; such animals may then survive until the termination of the study, or die either as a consequence of the tumor or of some other competing cause prior to the end of the study. It is also possible that an animal may die during the course of the study from competing risks without developing a tumor. Finally, an animal may survive tumor-free until the end of the study period. By examining the tumor status and survival times of animals dying during the course of the study, it is possible to make certain inference about the distribution of tumor-onset times in relation to dose.

The compartmental model may be characterized in terms of the hazard function for tumor onset $\lambda_T(t)$. Given the occurrence of tumor at time $u$, the hazard function for death due to the tumor or due to other causes are denoted by $\lambda_{TD}(t|u)$ and $\lambda_{D|T}(t|u)$ respectively. (Note that the cause of death must be determined in order to distinguish between $\lambda_{TD}$ and $\lambda_{TID}$.) The hazard function for deaths due to competing risks prior to tumor occurrence is denoted by $\lambda_D(t)$. This compartmental model also
provides a convenient basis for the development of statistical tools for the
effects of the test agent.

Maximum likelihood estimation with time-to-tumor data is more
complex than with quantal response data. As an illustration, suppose that
observations \((T_i, J_i, d_i)\) are available for each animal, \(i=1,\ldots,n\). Here
\(J_i=1\) if the \(i^{th}\) individual is observed to have a tumor present at the \(t_i\)
of death or termination of the study; otherwise \(J_i=0\). Exposure of the
\(i^{th}\) individual is at a constant level \(d_i\). Consider first the case of rapidly
lethal tumors, in which \(T_i\) will be approximately the time of tumor
occurrence. If it is assumed that the time of tumor occurrence and
the time of death due to competing risks are stochastically independent,
the likelihood function is given by

\[
L = \prod_{i=1}^{n} \left[ \exp\{-\Lambda(T_i, d_i)\} \right] \left[ \lambda(T_i, d_i) \right]^h
\]

Terms of the form \(-\Lambda(T_i, d_i)\) \(\lambda(T_i, d_i)\) represent the contribution to the
likelihood of animals developing tumors at time \(T_i\); terms of the form \(\exp\{-\Lambda(T_i, d_i)\} = Q(T_i, d_i)\) correspond to animals not competing risks.

With incidental tumors that are not life threatening the likelihood
function is of the form:

\[
L = \prod_{i=1}^{n} \left[ 1 - \exp\{-\Lambda(T_i, d_i)\} \right] \left[ \lambda(T_i, d_i) \right]^h \left[ \exp\{-\Omega(T_i, d_i)\} \right]^h
\]

Assuming that the presence of a tumor does not affect the death rate from
competing causes. Here, the terms \(1 - \exp\{-\Lambda(T_i, d_i)\}\) and \(\exp\{-\Lambda(T_i, d_i)\} = Q(T_i, d_i)\) correspond to the probability of observing or not observing a
tumor at the study termination.
One assumption that greatly simplifies the form of the likelihood and avoids certain identifiability issues is $A_D|T(t|u) = \lambda_T(t)$. This is a strong assumption that asserts that the presence of a tumor does not affect the death rate due to competing risks.

Non-parametric models for time-to-tumor data have proposed by Dinse (1986) and Dewanji & Kalbfleisch (1986). These non-parametric models once again cannot be used to predict strike at doses other those used in the original experimental protocol. Non-parametric models are most useful with serial sacrifices, a design feature not included in most experimental protocols for long-term laboratory studies. This limitation may be circumvented by using the semi parametric models proposed by Rai et al. (1999).

CARCINOGENIC POTENCY

The strength of agent with carcinogenic potential may be expressed in terms of quantitative measures of carcinogenic potency, first mentioned in the scientific literature in the 1930s. Twort & Twort (1930, 1933) examined the times at which tumors appeared during the course of animal experiments, and used the time at which 25% of the animals developed tumors as a measure of carcinogenic potency. Related measures of carcinogenic potency that took into account both the time of tumor appearance and inter current mortality in laboratory studies of carcinogen city were later proposed by Iball (1939) and Irwin and Goodman (1946). Reviews of other measures of carcinogenic potency have been published by Barr (1985) and Godderd et al. (1993).
More recent developments in measuring carcinogenic potency are related to the TD50 index introduced by Peto et al. (1984) and Sawyer et al. (1984). Formally, TD50 is defined as the dose that will have the proportion of tumor-free animals at a specified point in time. If \( P(d) \) denotes the probability of a tumor occurring at dose \( d \), TD50 is that dose \( d \) that satisfies the equation:

\[
R(d) = \frac{[P(d) - P(0)]}{1 - P(0)} = 0.5,
\]

where \( R(d) \) is the extra risk over background at dose \( d \). Thus, once the dose-response relationship \( P(d) \) has been determined, TD50 may be estimated from equation.

\[
R(u) = \frac{k! u^{r-1}(1-u)^{k-r}}{t^r(r-1)(k-r)} \leq k
\]

\( k = \) number of stages with \( r \) dose dependent

Sawyer et al. (1984) used a hazard function of the form:

\[
\lambda(t;d) = (1+bd)\lambda_0(t)
\]

where \( \lambda \) denotes the baseline hazard at time in the absence of exposure. This leads to an essentially linear dose-response relationship.

\[
P(d;T) = 1 - \exp\{-(1+bd)\Lambda_0(T)\}
\]

at a fixed time \( T \), in the absence of mortality from causes other than tumor occurrence.
Ideally, the time of tumor occurrence would be used as the basis for tumor induction. Unfortunately, since most tumors in live animals are unobservable, the tumor-onset time is generally unknown. Sawyer et al. (1984) avoided this problem by using the time of death of those animals with tumors as a proxy for the time of tumor onset.

Finkelstein & Ryan (1987) addressed this problem by using the methods of Peto et al. (1980) for combining tumor and prevalence data to estimate TD$_{50}$. Bailar & Portier (1993) used survival-adjusted quantal-response data, as described by Bailar & Portier (1988), to estimate TD$_{50}$.

Dewanji et al. (1993) used Weibull models for the time of tumor onset, time to death due to tumor occurrence, and the time to death from competing risks to estimate TD$_{50}$. Specifically, the survivor functions for the time to tumor onset ($X$), the time to death from tumor ($Y$), and the time to death from competing risks are given by:

$$S_x(t,d) = \exp\{-\left(\alpha + \beta d^p\right)t\}$$
$$S_y(t,d) = \exp\{-\left(\alpha + \beta d^p\right)pt\}$$
$$S_z(t,d) = \exp\{-\left(\mu + Vd^p\right)t\}$$

respectively, where, for example $S_x(t,d)=\Pr(X>t|d)$ denotes the probability that the time to tumor onset $X$ exceeds $t$ at dose $d$, and $p$ is the tumor lethality parameter with $p=0$ (and hence $S_x=1$) corresponding to non-lethal or incidental tumor and $p=1$ ($S_y=S_x$) rapidly lethal tumors. Intermediate values for $p$ between zero and one represent tumors of intermediate lethality.

This Weibull model can be fitted to the data without direct information on the tumor-onset time $X$. Different forms of the model can be fitted.
depending on the availability of cause-of-death information, or the assumptions concerning tumor lethality. These include the following special cases: (i) cause of death and tumor lethality unknown; (ii) rapidly fatal tumors (iii) incidental tumors; and (iv) cause of death known, death from tumor, death from competing risks with tumor and death from competing risks without tumor.

3.8 ARMITAGE-DOLL MULTISTAGE MODEL

The Armitage—doll model, which has been used extensively in the last four decades, was first proposed to explain the observation that in many human carcinomas, age-specific incidence rates increase roughly with a power of age. The age-specific incidence rate is a measure of the rate of appearance of tumors in a previously tumor-free tissue. The appropriate statistical concept is that of the hazard function.

For the tissue of interest, let $T$ be a random variable representing time to appearance of a malignant tumor, and let

$$P(t) = \text{Prob}\{T \leq t\}.$$

Then the hazard function $h(t)$ is defined by

$$h(t) = \lim_{\Delta t \to 0} \frac{\text{Prob}\{t < T \leq t + \Delta t \mid > t\}}{\Delta t} = P'(t)/(1-P(t)),$$

Where $P'(t)$ denotes the derivative of $P(t)$. Suppose that there are $N$ cells susceptible to malignant transformation in the tissue of interest and that $T_1, T_2, \ldots, T_n$ are independent identically distributed random variables representing the time to transformation of the individual cells. Then, $T = \min \{T_1, T_2, \ldots, T_n\}$, i.e. $T$ is a minimum order statistic. For a given susceptible cell; let $p(t)$ be the probability of malignant transformation by
time $t$. An easy computation shows that the hazard function for the tissue is given by the expression:

$$h(t) = \frac{Np'(t)}{1 - p(t)}.$$  

The Armitage–Doll model postulates that a malignant tumor in a tissue when a single susceptible cell in that tissue undergoes malignant transformation via a finite sequence of intermediate stages, the waiting time between any stage and the subsequent one being exponentially distributed. Schematically, the model may be represented as follows:

$$
\begin{array}{cccc}
\lambda_0 & \lambda_1 & \lambda_2 & \ldots & \lambda_{n-1} \\
E_0 & E_1 & E_2 & \ldots & E_n
\end{array}
$$

Here $E_0$ represents normal cell, $E_n$ represents the malignant cell, and the $\lambda_i$ represents the parameters of the (exponential) waiting time distributions.

Let $p_i(t)$ represents the probability that a given cell is in stage $E_i$ by the time $t$. Then $p_n(t) = p(t)$ is the probability that the cell is malignantly transformed by the $t_i$ and the expression for the hazard $h(t)$ can be rewritten as:

$$h(t) = \frac{Np'_n(t)}{1 - p_n(t)}.$$  

In the usual treatment of the multistage model, two approximations are usually made at this point. First at the level of the single cell, malignancy is a very rare phenomenon. Thus, for any cell, $p_n(t)$ is very close to zero during the life span of an individual and $h(t)$ is approximately equal to $Np_n(t)$

An explicit expression of $Np'_n(t)$ in terms of the transition rates $\lambda_i$ is presented in the Appendix (See also Mulgavkar 1978, 1991) it is shown that:
involves second and higher order moments of the transition rates, Retention of only the first non-zero term (this is the second approximation) in this series expansion leads to the Armitage-Doll expression, namely:

\[ h(t) = \frac{N \sum \lambda_i t^{i-1}}{(n-1)!} \]

Thus, with the two approximations made, this model predicts an age-specific incidence curve that increases with a power of age that is one less than the number of distinct stages involved in malignant transformation.

It is immediately obvious from the model that, given sufficient time, any susceptible cell eventually becomes malignant. Furthermore, since the waiting time distribution to malignant transformation is the sum of n exponential waiting time distributions, it follows that h(t) is a monotone increasing function.

A simple example serves to show that the Armitage-Doll approximation can be inadequate if the transition rates are not small enough. The hazard function can be viewed as follows. Let X_i(t), I = 1,2,..., n be a sequence of random variables associated with each cell, with X_i(t) = 1 if the cell is in stage i at time t and 0 otherwise. The kolmogorov equations in the Appendix imply that
\[ h(t) = \frac{Np_n(t)}{(1-p_{n-1}(t))} = N\lambda_{n-1} E[X_{n-1}(t) | X_n(t) = 0] \]

where \( E \) denotes the expectation. In other words, the hazard or incidence is proportional to the expected (or mean) number of cells in the penultimate stage, conditional on there being no cells that are malignant. When \( p_n(t) \) is close to zero, or equivalently the transition rates are small enough, the conditional expectation may be approximated by the unconditional expectation,

\[ h(t) = Np_n(t) = N_{n-1}E[X_{n-1}; E[X_{n-1}(t)]. \]

Thus the Armitage-Doll approximation consists of replacing the conditional expectation of \( X_{n-1} \) by the unconditional expectation and then retaining only the first non-zero term in the Taylor series expansion of the unconditional expectation.

### 3.9 POPULATION MODELS

The main aim of a registry is to collect, insofar as this is possible, the total number of cases in a defined area. Information on the number of persons at risk in the total population covered by a registration area is generally obtained from official demographic sources such as the institute of statistics, regional, national or international. Such data derived normally from population censuses and are carried out at varying intervals of time and on a regular or irregular basis according to county. Problems arise when estimating a population between census years and for the post projecting a population for post central years. We represent following models for the population growth.
SINGLE - SPECIES NON-AGE-STRUCTURED POPULATION MODELS

Simple Logistic Models

Let \( x(t) \) be the population at time \( t \); also let \( b \) and \( d \) be the intrinsic or specific birth and death rates i.e. let \( b \) and \( d \) be the number of births and deaths per individual per unit time. Thus gives the equation due to Malthus (1978):

\[
\frac{dx}{dt} = bx - dx = (b-d)x = ax 
\]

\[ 
...........(1) 
\]

when \( b, d, a \) are constants we get on integration

\[
x(t) = x(0)\exp(at) 
\]

\[ 
...........(2) 
\]

so that the population grows exponentially if \( a > 0 \), decay exponentially if \( a < 0 \) and remains constants if \( a = 0 \). In general \( b \) is a monotonic decreasing function of \( x \) and \( d \) is a monotonic increasing function of \( x \) so that \( a \) is a monotonic decreasing function of \( x \). Hence,

\[
\frac{dx}{dt} = x[b(x) - d(x)] = x a(x) 
\]

\[ 
...........(3) 
\]

\[
bx = b_1 - b_2 x, \ dx = d_1 + d_2 x, \ a(x) = a - cx 
\]

\[
a = b_1 - d_1, \ c = b_2 + d_2 
\]

\[
\ \ \ b_1, b_2, d_1, d_2, a, c > 0 
\]

where we assume for the present that

\[
x <= \frac{b_1}{b_2} 
\]

\[ 
...........(5) 
\]

If however \( x > \frac{b_1}{b_2} \) the birth rate is taken as zero.

\[
\frac{dx}{dt} = x(a - cx) \text{ or } \frac{1}{x} + \frac{c}{a-cx} \ dx = adt 
\]

\[ 
...........(6) 
\]

Integrating (6) we obtain

\[
\ln \left[ \frac{x(t)}{a-cx(t)} \right] = at + \ln \left[ \frac{x(0)}{a-cx(0)} \right] 
\]

\[ 
...........(7) 
\]

OR

\[
x(t) = \frac{a/c}{1 + \left( \frac{(a/c)}{x(0)} - 1 \right) \times \exp(-at)} 
\]

\[ 
...........(8) 
\]
So that as $t \to \infty$ $x(t) \to a/c$. If $x(0) < a/c$ then $dx / dt$ is always positive and $x(t)$ increases to a limiting population size $a/c$. If $x(0) > a/c$, then $dx / dt$ is always negative and $x(t)$ decreases to $a/c$. The final population size in any case is $a/c$. and since

$$a/c = [(b_1-d_1)/(b_2+d_2)] < b_1/b_2 \quad \ldots \quad (9)$$

when $x(0) < a/c$ condition (5) is always true and birth rate always remains positive.

Differentiating (6) we obtain

$$d^2x / dt^2 = a - 2cx = 2c[(a/2c) - x] \quad \ldots \quad (10)$$

If $x(0) < a/(2c)$ then $dx/dt$ increases as $x$ varies from $x(0)$ to $a/(2c)$ and decreases as $x$ varies from $a/(2c)$ to $a/c$. $dx / dt$ changes from an increasing to a decreasing function at $x = a / (2c)$ and $d^2x / dt^2$ vanishes when $x = a/(2c)$, so that there is a point of inflexion in the population growth curve when half the final population size is reached.

From (8), the point of inflexion accrues at time

$$t_1 = 1/a \{ \ln[(a/c)/x(0)] - 1 \}$$

if $x(0) > a/(2c)$, there is no point of inflexion
STOCHASTIC MODELS

In the above deterministic model we tried to find out the population size \( x(t) \) as a uniquely determined function of \( t \), no uncertainty or probability being associated with \( x(t) \). In actual experimental or field situations, even when we start with some fixed initial population size, we may find that population sizes \( x(t) \) at time \( t \) differ for each experiment for each field survey. If we conduct a large number of experiments or carry out a large number of field surveys under identical initial conditions, we find that the population size at time \( t \) is not unique and tends to fluctuate in a random manner about some mean size with some variance. It is therefore preferable to have models that give us \( p(x,t) \) or \( p(n,t) \) which are the probabilities having \( x \) of \( n \) persons in the population at time \( t \). At any fixed time \( t \), we require a probability distribution defined by the set of probabilities

\[
p(0,t), p(1,t), p(2,t), \ldots, p(n,t), \quad \text{-------------------------}(1)
\]

From this probability distribution we can find at time \( t \), the mean size, variance and other moments of the population distribution defined as follows:

\[
\bar{n}(t) = E(n) = \sum_{n=0}^{\infty} np(n, t),
\]

\[
\sigma^2(t) = E(n - \bar{n})^2 = \sum_{n=0}^{\infty} (n - \bar{n})^2 p(n, t) = \text{variance}(t),
\]

\[
\mu'_r(t) = \sum_{n=0}^{\infty} n^r p(n, t), \quad \text{------------------------}(2)
\]

\[
\mu'_r(t) = \sum_{n=0}^{\infty} n(n-1) \ldots \ldots (n-r+1)p(n,t),
\]

\[
\mu_r(t) = \sum_{n=0}^{\infty} (n^r - \bar{n}^r) p(n, t),
\]
Where \( r=0,1,2,3, \ldots \). To find these, it is sometimes convenient to define the probability generating function (pgf) given by:

\[
\phi(s, t) = \sum_{n=0}^{\infty} p(n, t) s^n
\]

All the probabilities can be obtained or 'generated' by expanding \( \phi(s, t) \) in powers of \( s \). It is easily verified that:

\[
\{ \phi(s, t) \}_{s=1}^{\infty} = \sum_{n=0}^{\infty} p(n, t) = 1
\]

\[
\frac{\partial \phi}{\partial s} \bigg|_{s=1} = \sum_{n=0}^{\infty} n p(n, t) s^{n-1} \bigg|_{s=1} = \sum_{n=0}^{\infty} n p(n, t) = n(t)
\]

\[
\frac{\partial^2 \phi}{\partial s^2} \bigg|_{s=1} = \sum_{n=0}^{\infty} n(n-1) p(n, t) s^{n-2} \bigg|_{s=1} = \sum_{n=0}^{\infty} n(n-1) p(n, t) = \mu_2(t)
\]

\[
= \text{Variance}(t) = \sigma^2(t)
\]

Here we determine chance factors arise from random fluctuations in the environments. There are two approaches to take these chance factors into account: (i) to talk in terms of probabilities of birth or death in a small time interval \( (t, t+\delta t) \) rather then talk in terms of birth or death rates and (ii) to incorporate random elements in the difference of differential equations of the deterministic model. The deterministic and stochastic models thus obtained by using method (ii) are

\[
\frac{dx}{dt} = xa(x), \quad \frac{dx}{dt} = x \{a(x) + y(t)\}
\]
Where y(t) is a random variable with known probability distribution. In general we take y(t) to be normally distributed with zero mean and variance $\sigma^2(t)$, So that

$$dP = \left[ \frac{1}{\sqrt{2\pi}\sigma(t)} \right] \exp[-1/2\{y^2/\sigma^2(t)\}]dy$$

-------------------------(7)

Equation (7) corresponds to white Gaussian noise.

Linear Birth - death - immigration - emigration processes

Let $p(n,t)$ be the probability of two or more of these events taking place in this interval is $0(t)$. Now there can be n persons in the system at time $t+\delta t$ in the following six mutually exclusive cases when there are

(i) n-1 persons at time t, and one person is born in the interval (t, t+\delta t)
(ii) n+1 persons at time t, and one person dies in the interval (t, t+\delta t)
(iii) n-1 persons at time t, and one person immigrates in the interval (t, t+\delta t)
(iv) n+1 persons at time t, and one persons emigrates in the interval (t, t+\delta t)
(v) n persons at time t and nobody is born or dies or immigrates or emigrates in the interval (t, t+\delta t)
(vi) two or more events in the interval (t, t+\delta t) and the final population size n

By using the theorem of compound probability the probabilities of (i) to (vi) are respectively given by
Since these six cases are mutually exclusive, on using the theorem of total probability we get

\[ P(n,t+\Delta t) = P(n,t) + \left[ ((n-1)\lambda + \gamma) P(n-1,t) + ((n+1)\mu + \alpha) P(n+1,t) - (n^2 + \lambda + \alpha) P(n,t) - (n\lambda + \mu + \alpha) P(n,t) \right] \Delta t + O(\Delta t) \quad \text{-------(9)} \]

Transferring \( P(n,t) \) to the left hand side, dividing it by \( \Delta t \) and proceeding to the limit as \( \Delta t \to 0 \), we obtain,

\[ \frac{d}{dt} P(n,t) = ((n-1)\lambda + \gamma) P(n-1,t) + ((n+1)\mu + \alpha) P(n+1,t) - (n^2 + \lambda + \alpha) P(n,t) \quad \text{-------(10)} \]

This equation is valid for \( n=1,2,3,\ldots \). For \( n=0 \), proceeding in a similar manner we get from first principles

\[ \frac{d}{dt} P(0,t) = (\mu + \alpha) P(1,t) - \gamma P(0,t) \quad \text{-------(11)} \]

Each of the equations (10) and (11) is a differential difference equation because there is differentiation w. r. to the continuous variable \( t \) and differencing w. r. to the discrete variable \( n \). We thus get an infinite set of differential difference equations to solve for the infinite set of probabilities \( P(n,t) \) for \( n=0,1,2,\ldots \).

To solve (10) and (11) we shall use the p. g. f. defined in (3). Multiplying (10) by \( S^n \), (11) by \( S^0 \) and adding for all values of \( n \), we get
Using (3) we obtain

\[
\frac{d\Phi}{ds} = \sum nP(n,0)S^{n-1} = \sum nP(n,t)S^{n-1}
\]

\[
\text{(13)}
\]

Using (3), (12) and (13) we get

\[
\frac{d\Phi}{ds} = \lambda \left( S^2 - S - \right) + \mu \left( -S - \right) + \gamma (S\Phi - \Phi)
\]

\[
+ \alpha \left( S \left( \Phi - P(0,t) \right) \right) - \alpha (\Phi - P(0,t))
\]

\[
\text{(14)}
\]

OR

\[
\frac{d\Phi}{ds} = \frac{d\Phi}{ds} + \alpha \left( S - P(0,t) \right)
\]

\[
\frac{d\Phi}{ds} \frac{\alpha}{S} \left( S - 1 \right)
\]

\[
\text{(15)}
\]

If we can solve (15) to get \( \Phi(S,t) \) then by using relations (4), we can easily obtain the mean and variance of the probability distribution for all persons at time \( t \).

- Linear Birth - Death Process
- Linear Birth - Death Immigration Process
- Linear Birth - Death Emigration Process
AGE STRUCTURED POPULATION MODEL

BENARDELI (1941), LEWIS (1942) AND LESLIC (1945) OR BLL MODEL:

Let the population be divided into n age groups and let the populations of the n age group at time be $x_1(t)$, $x_2(t)$, $x_3(t)$, .......... $x_n(t)$. The basic model we discuss is discrete age scale in the sense that we consider district age groups and assume birth rates to be constant within each age group, and it is discrete time because we consider the changes in population in stages i.e. knowing the population at time t, we shall try to determine the population at time t+1. The model is also one-sex model since we take into account only the changes in female populations and assume that male populations conform to these changes. Besides, the model is deterministic because we do not consider any chance element and therefore, we shall try to determine $x_1(t)$, $x_2(t)$, $x_3(t)$, .......... $x_n(t)$. Finally the model is linear, since all changes are assumed to be proportional to the population sizes.

Let $f_i$ ($i=1,2,...,n$; $f_i \geq 0$) represent the average number of daughters who will be alive at time t+1, born in the time interval t to t+1, to each female who was in age group i at time t. Now the number of females in the age group i at time t is $x_i(t)$ each of whom gives birth, on an average, to a certain number of daughters in the interval t to t+1, of whom $f_i$ will be alive at time t+1, so that the number of daughters in the age group 0 to 1, alive at time t+1, born of these $x_i(t)$ females is $f_i x_i(t)$. Thus the number of females in the first age group at time t+1 is given by

$$X_1(t+1) = f_1 x_1(t) + f_2 x_2(t) + \ldots + f_n x_n(t) \quad (1)$$
Now let $p_i$ (i=1,2,3......n-1; 0<p_i<1) be the proportion of females of the $i^{th}$ age group at time $t$, who are surviving to become females of the $(i+1)^{th}$ age group at time $t+1$ so that

$$X_{i+1}(t+1) = p_i X_i(t), \quad i = 2,3,\ldots,n \quad \text{(2)}$$

Thus the complete system of equations is

$$X_1(t+1) = f_1 x_1(t) + f_2 x_2(t) + \ldots + f_n x_n(t)$$
$$X_2(t+1) = p_1 x_1(t)$$
$$X_3(t+1) = p_2 x_2(t) \quad \text{(3)}$$
$$\ldots$$
$$X_n(t+1) = p_{n-1} x_{n-1}(t)$$

Knowing the populations at time $t$, we can use (3) to find the populations at time $t+1$ so that, knowing the populations $x_1(0), x_2(0), x_3(0), x_4(0), \ldots, x_n(0)$ we can find $x_1(t), x_2(t), x_3(t), x_4(t), \ldots, x_n(t)$ for any positive integer $t$.

The model is in terms of a system of recurrence relations or linear difference equations (3) which can be written in the matrix form

$$
\begin{bmatrix}
X_1(t+1) \\
X_2(t+1) \\
X_3(t+1) \\
\vdots \\
X_n(t+1)
\end{bmatrix} =
\begin{bmatrix}
f_1 & f_2 & f_{n-1} & f_n \\
p_1 & 0 & 0 & 0 \\
0 & p_2 & 0 & 0 \\
\vdots & \vdots & \vdots & \vdots \\
0 & 0 & \ldots & p_{n-1}
\end{bmatrix}
\begin{bmatrix}
x_1(t) \\
x_2(t) \\
x_3(t) \\
\vdots \\
x_n(t)
\end{bmatrix}
\quad \text{(4)}
$$
Or

\[ X(t+1) = AX(t) \]

Where

\[
A = \begin{bmatrix}
  f_1 & f_{n-1} & f_n \\
p_1 & 0 & 0 \\
0 & p_2 & 0 \\
\vdots & \vdots & \vdots \\
0 & 0 & p_{n-1}
\end{bmatrix}, \quad X(t) = \begin{bmatrix}
x_1(t) \\
x_2(t) \\
x_3(t) \\
\vdots \\
x_n(t)
\end{bmatrix}
\]

The elements of the square matrix A are non-negative, the elements of its first row are greater than or equal to zero, the elements of its main subdiagonal are positive and less than unity, and the remaining elements are zero. A matrix of this type is called Leslie Matrix.

We can easily solve (5) to get

\[ X(t) = A^tX(0) \]

If A has distinct eigen values \( \lambda_1, \lambda_2, \lambda_3, \ldots, \lambda_n \), we can write

\[ A = Y \Lambda Y^{-1} \]

Where \( \Lambda \) is the diagonal matrix with its diagonal elements \( \lambda_1, \lambda_2, \lambda_3, \ldots, \lambda_n \). Y is the matrix whose columns are the right eigen vectors of A and \( Y^{-1} \) is the inverse of Y, so that

\[ A^t = Y \Lambda^t Y^{-1} \]

Thus we get,

\[ X(t) = Y \Lambda^t Y^{-1}X(0) \]

As \( t \rightarrow \infty \), the behaviour of \( x_i(t) \) will be determined more and more by that eigen value which has the largest absolute value. If the absolute value
of $\lambda_0$ is greater than unity, the populations of all age groups will grow; if it is less than unity, the populations will tend to extinction and if it is to unity, the populations of all age groups will be asymptotically stationary.

It is therefore obvious that the eigen values of $A$ and in particular, its dominant eigen value have an important role to play in our discussion.

**Stable Age structure**

A population is said to have a stable age structure if the ratios of the populations of the various age groups viz.

\[
\frac{x_1(t)}{x_2(t)} : \ldots : \frac{x_n(t)}{x_n(t)}
\]

do not change with time. In fact, the ratios define the age structure of the population at time $t$ and the age structure is stable if it does not change with time. The population age structure is said to be asymptotically stable if these ratios approach steady-state values as $t \to \infty$.

When a population has a stable age structure, the population of different age groups increase in the same ratio so that, if the population vector at time $t$ is $x$, then at time $t+1$, it is given by $\lambda x$. From (5), it follows that

\[
\lambda x = \lambda x
\]

So that $\lambda$ must be an eigen value of $A$. But the only eigen value of $A$ which is positive and for which $X$ is positive is $\lambda_0$, so that
\[ \lambda = \lambda_0 , \quad X = X_0 \]  

Thus if we start with a population structure \( X_0 \) given by

\[
X_0 = \begin{bmatrix}
1 \\
p_1 / \lambda_0 \\
p_1 p_2 / \lambda_0^2 \\
p_1 p_2 p_3 / \lambda_0^3 \\
& \ddots \\
p_1 p_2 \cdots p_{n-1} / \lambda_0^{n-1}
\end{bmatrix}
\]

then the structure will always remain the same, though in magnitude the population of each age group increases (or decreases) in a geometrical progression according as \( \lambda_0 > (\text{or} <) \) unity. If we start with a population structure different from \( X_0 \), the population approaches a steady state structure as \( t \to \infty \), then in the limit, since \( X(t) \) and \( X(t+1) \) have the same structure and \( X(t+1) \) is a multiple of \( X(t) \), (5) gives (14). Thus, \( X_0 \) denotes the multiple steady state structure or the asymptotic stable structure and \( \lambda_0 \) denotes the rate at which the population of each group will ultimately increase (or decrease) per unit time.

A TWO-SEX MODEL

Let \( x_i(t) \) and \( y_i(t) \) be the population of males and females in the \( i^{th} \) age group, \( f_i \) and \( f'_i \) be the birth rates of males to females and females to females and let \( p_j \) and \( p'_j \) be the proportions of survivors of males and females, respectively, where \( i \) goes from 1 to \( n \) and \( j \) goes from 1 to \( n-1 \).
This is female dominated model in which all births are attributable mothers. It is essentially a one-sex model since the eigen values of this matrix are given by

\[ \lambda^n (\lambda^n - f_1 \lambda^{n-1} - f_2 \lambda^{n-2} - \ldots - f_n p_1 p_2 \ldots p_{n-1}) = 0 \]  

So that the non-zero eigen values are the eigen values of the n x n sub matrices corresponding to females only.

Continuous Time Discrete Age Scale Population Models

In the Bernardelli – Lewis – Leslie (BLL) models, each age group extends over the same length of time and this interval of time is the same as the interval of differencing for forming the system of difference equations. This is a serious restriction on the model. Even when the ages can be determined and equal time lengths for age groups are meaningful for the sake of greater precision, we can use a smaller interval for differencing than the time spanned by each age group. This is not permitted in BLL.
model. As shown by Oster (1976), there can also be a possibility of an apparent stochastic behavior in a deterministic model. Yet another possibility is that of a population size jumping from a positive value to a negative value in one step, though we can overcome this by using difference equation models, which allow transition from positive values to positive values only.

Linear Continuous time Model
Let \( x_1(t), x_2(t), \ldots, x_n(t) \) be the populations of the \( n \) age groups at time \( t \). Let \( p \) of these age groups be pre-reproductive, \( q \) be reproductive and \( r \) be post reproductive so that \( p + q + r = n \). Let \( b_{p+1}, b_{p+2}, \ldots, b_{p+q} \) be the birth rates in the \( q \) reproductive age groups and \( d_1, d_2, \ldots, d_n \) be the death rates in the \( n \) age groups. Also, let \( m_i \) be the rate of migration, on maturity and survival from the \( i^{th} \) age group to \( (i+1)^{th} \) \( (i = 1,2,\ldots,n-1; m_n = 0) \).

The rate of change of the populations of the first age group is determined by (i) births in the \( q \) reproductive groups (ii) deaths in the first group, and (iii) migration from the first group to the second.

The rate of change of any other group is determined by (i) migration into the group from the preceding group (ii) deaths in the group and (iii) migration from this group into the next group.

Hence the basic system of differential equations for the linear continuous time model as
\[
\frac{dx_1}{dt} = b_{p+1} x_{p+1} + \ldots + b_{p+q} x_{p+q} - (d_1 + m_1) x_1,
\]

\[
\frac{dx_i}{dt} = m_{i-1} x_{i-1} - \ldots - (d_i + m_i) x_i, \quad (i = 2, 3, \ldots, n).
\]

System (1) can be written in the matrix form

\[
\frac{dx}{dt} = BX
\]

where \( B \) is an \( n \times n \) square matrix with its diagonal elements as \(-(d_1 + m_1), -(d_2 + m_2), \ldots, -(d_n + m_n)\) with its main sub diagonal elements as \( m_1, m_2, \ldots, m_{n-1} \), the \((p+1)\)th to \((p+q)\)th elements of the first row as \( b_{p+1}, b_{p+2}, \ldots, b_{p+q} \), and with the remaining elements as zero. Now in general (2) can be rewritten as

\[
\frac{dx}{dt} = Y A Y^{-1} X
\]

where \( A \) is the diagonal matrix with its diagonal elements as the eigen values of the matrix \( B \) and \( Y \) is the matrix whose columns are the eight eigen factors of this matrix. The solution of (3) is

\[
X(t) = Y e^{At} Y^{-1} X(0)
\]

Thus the nature of the solution of the matrix differential equation depends on the nature of the eigen values and eigen factors of \( B \). In particular the eigen value with the largest real part has an important role to play in determining the asymptotic growth of the population, as \( t \to \infty \). The last \( r \) eigen values of \( B \) are given by

\[
-(d_j + m_j), \; j = p + q + 1, \; p + q + 2, \ldots, p + q + r = n
\]
and the remaining $p+q$ eigen values are the roots of 

$$
\phi(\lambda) = (d_1 + m_1 + \lambda) (d_2 + m_2 + \lambda) \cdots (d_{p+q} + m_{p+q} + \lambda) - m_1 m_2 \cdots m_p \left\{ b_{p+1} (d_{p+2} + m_{p+2} + \lambda) \cdots (d_{p+q} + m_{p+q} + \lambda) + b_{p+2} m_{p+1} (d_{p+3} + m_{p+3} + \lambda) \cdots (d_{p+q} + m_{p+q} + \lambda) + b_{p+3} m_{p+2} m_{p+1} \cdots (d_{p+q} + m_{p+q} + \lambda) \right\} = 0
$$

If $d+m$ is the smallest of $d_i + m_i$ for $i = 1, 2, \ldots, p+q$, then 

$$
\phi(-(d+m)) < 0, \quad \phi(\infty) > 0
$$

So that there is at least one real eigen value greater then $-(d+m)$. We can now write (6) as 

$$
\psi(\lambda) = \frac{b_{p+1}}{(d_1+m_1+\lambda) \cdots (d_{p+1}+m_{p+1}+\lambda)} + \frac{b_{p+2} m_{p+1}}{(d_1+m_1+\lambda) \cdots (d_{p+2}+m_{p+2}+\lambda)} + \cdots + \frac{1}{m_1 m_2 \cdots m_p}
$$

It is easily seen that $\psi(\lambda)$ is a monotonic decreasing function of $\lambda$ decreasing from $\infty$ to 0 as $\lambda$ increases from $-(d+m)$ to $\infty$, then hence, 

$$
\psi(\lambda) = \frac{1}{m_1 m_2 \cdots m_p}
$$

has one and only one real root greater than $-(d+m)$
We shall denote this root by $\lambda_1$. All other roots are either complex or real negative and less than $-(d+m)$. The root $\lambda_1$ is positive if $\phi(0) < 0$ i.e. if

$$
(d_1+m_1)\cdots(d_{p+q}+m_{p+q}) < m_1m_2\cdots m_p \{b_{p+1}(d_{p+2}+m_{p+2})\cdots(d_{p+r}+m_{p+r})
+b_{p+2}(d_{p+3}+m_{p+3})\cdots(d_{p+q}+m_{p+q})\cdots b_{p+r}m_{p+r-1}\}
$$

We shall assume that

$$
d+m < d_j+m_j \text{ for } j = p+q+1, \ldots, p+q+r
$$

if (10) is satisfied, the population of all age groups will ultimately grow exponentially. Now let $u_1, u_2, \ldots, u_n$ be the eigen vector corresponding to an eigen value $\lambda$ of $B$. Then we get

$$
b_{p+1}u_{p+1} + \cdots + b_{p+r}u_{p+r} = (d_1 + m_1 + \lambda) u_1
$$

$$
m_{p+1}u_{p+1} = (d_1 + m_1 + \lambda) u_1 \quad (l = 2, 3, \ldots, n)
$$

So that

$$
u_1 = \frac{u_2}{(d_2+m_2+\lambda)\cdots(d_n+m_n+\lambda)} = \frac{u_n}{m_1(d_3+m_3+\lambda)\cdots(d_n+m_n+\lambda) m_1m_2\cdots m_n;}
$$

Since,

$$
d_i+m_i+\lambda > 0 \text{ for } i = 1, 2, \ldots, n
$$

the eigen vector $X_1$ corresponding to $\lambda_1$ has all ith component positive

In fact

$$
X_1 = \begin{bmatrix}
(d_2+m_2+\lambda)\cdots(d_n+m_n+\lambda) \\
m_1(d_3+m_3+\lambda)\cdots(d_n+m_n+\lambda) \\
\vdots \\
m_1m_2\cdots m_{n-1}
\end{bmatrix}
$$

---------(15)
If we take any other complex (negative real) eigen value of B, it gives an eigen vector with complex (negative real) components. Thus the only eigen value which gives an eigen vector with all its components positive is $\lambda_1$.

Stable Age Structure

The population is said to have a stable age structure if

\[
x_1(t) : x_2(t) : \ldots : x_n(t) = x_1(0) : x_2(0) : \ldots : x_n(0) \quad \text{------------------(16)}
\]

\[
x_n(t) = f(t) x_1(0) \quad \text{Or} \quad x(t) = f(t) x(0) \quad \text{------------------(17)}
\]

Or

\[
\frac{dx}{dt} = f(t) x(0) \quad \text{Or} \quad \frac{dx}{dt} = f(t) x(t) \quad \text{------------------(18)}
\]

Or

\[
B x(t) = f(t) x(0) \quad \text{Or} \quad B x(0) = f(t) x(0) \quad \text{------------------(19)}
\]

So that $f(t) / f(t)$ must be a constant and be equal to that eigen value of B which gives a positive eigen vector so that

\[
\frac{f(t)}{f(t)} = \lambda_1 \quad , \quad x(0) = x_1 \quad \text{------------------(20)}
\]

Integrating the first equation of (20) and using $f(0) = 1$ we get

\[
f(t) = e^{\lambda_1 t} \quad \text{------------------(21)}
\]

Therefore, the only stable age structure is given by $x_1$ and if the population has initially this stable age structure, it will continue to have this structure for all times. Moreover, the population of each age group grows exponentially if $\lambda_1 > 0$ and decays exponentially if $\lambda_1 < 0$. 

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Effect of Changes in Parameters

(i) If all death rates decreases by $K$, then it is obvious from (6) that $\lambda_1$ increases by $K$ so that populations of all age groups in the stable age structure increase by a factor $\exp(kt)$. Similarly if all death rates increase by $K$, then $\lambda_1$ decreases by $K$ and the rate of growth of populations is slowed down by a factor $\exp(-Kt)$.

(ii) If death rates decreases by $K_1$, $K_2$, $K_n$ then $\lambda_1$ increases by an amount that lies between the smallest and largest of $K_1$, $K_2$, $K_n$.

(iii) If all birth rates increases, then from (8) the new $\psi(\lambda)$ is greater than the original $\psi(\lambda)$ for all $\lambda$ such that from the fig 4.10 $\lambda_1 > \lambda_1$ so that as expected the rate of growth of each age group increases.
(v) If birth rates increase \( \lambda_1 \) increases from (15) the age structure changes in favor of the earlier age groups. Similarly if birth rates decline, then the age structure changes in favor of the earlier age groups.

(vi) Suppose only the migration rates from the first \( p \) groups increase. Then from (8) we have

\[
g(\lambda) = \frac{d_1 + \lambda}{m_1} \quad \frac{1}{\frac{(d_{p+1} + m_{p+1} + \lambda)}{m_p}} + \frac{d_{p+2} + m_{p+2}}{(d_{p+1} + m_{p+1} + \lambda)(d_{p+2} + m_{p+2} + \lambda)}
\]

\[+ \ldots + \frac{d_{p+1} + m_{p+1}}{(d_{p+1} + m_{p+1} + \lambda) \ldots (d_{pq} + m_{pq} + \lambda)} = 1 \]

(23)

g(\lambda) > g(\lambda) \text{ for all } \lambda \text{ and so, using a figure similar to Fig 4.10 we can increase } \lambda_1.

Two Sex Continuous Time – Model
Let \( x_i(t) \), \( y_i(t) \) be the population of males and females in the \( i^{th} \) age group at time \( t \). Let \( d_i \), \( d_i' \) be the respective death rates and \( m_i \), \( m_i' \) be the rates of
migration of males and females from the \(i^{th}\) group to the next \(i=1,2,...,n\); \(m_n=m'_n=0\). Let \(b_{p+j}, b'_{p+j}\) be the birth rates to females for male and female children in the \((p+j)\)th group \((j=1,2,...,q)\). Then our model gives

\[
\begin{align*}
\frac{dx_i}{dt} &= b_{p+1}y_{p+1} + \ldots + b_{p+q}y_{p+q} - (b_1 + m_1)x_i \\
\frac{dx_i}{dt} &= m_{i-1}x_{i-1} - (d_i + m_i)x_i \quad (i = 2,3,...,n) \\
\frac{dy_i}{dt} &= b'_{p+1}y'_{p+1} + \ldots + b'_{p+q}y'_{p+q} - (d'_1 + m'_1)y_i \\
\frac{dy_i}{dt} &= m_{i-1}y_{i-1} - (d'_1 + m'_1)y_i \quad (i = 2,3,...,n)
\end{align*}
\]

If \(U(t)\) denotes the combined populations vectors for males and females then (1) and (2) give

\[
\frac{du}{dt} = DU = \begin{bmatrix} D_1 & D_2 \\ D_3 & D_4 \end{bmatrix} U, \quad \text{-------------------}(3)
\]

Where

(i) \(D_1\) is an \(n \times n\) sub matrix with diagonal elements as \((d_i + m_i), i = 1,2,...,n\) the principal sub diagonal elements as \(m_1, m_2, m_3, ..., m_{n-1}\), and the remaining elements as zero,

(ii) \(D_2\) is an \(n \times n\) sub matrix with \((p+1)^{th}\) to \((p+i)^{th}\) elements of its first row as \(b_{p+1}, b_{p+2}, ..., b_{p+q}\) and the remaining elements as zero.

(iii) \(D_3\) is an \(n \times n\) sub matrix with all its elements as zero and
(iv) $D_4$ is an $n \times n$ sub matrix, which is the matrix for the female group only.

The eigen values of $D$ are the eigen values of the sub matrix $D_4$ for the female group together with $-(d_1 + m_1), -(d_2 + m_2),.. -(d_n + m_n)$. In general the growth of the combined population is determined by the female groups and thus the two-sex model we have discussed is essentially a female – dominant models.

INTERCENSAL ESTIMATES

The evaluation of a population is determined by one constant, ageing and by three demographic components, births, deaths and migration. If these components are not available, either or in part, estimates can be made according to different hypotheses suited to the population studied. Such estimates are often published by different demographic services. Nevertheless, these hypotheses lead to inaccuracies, the full extent of which is not easily measured until the results of the following census are known.

When the total population by age group of two successive censuses is known, it is necessary to estimate the figures for each of the years between the two census years. It is natural to assume that, for particular age-group, evolution takes place in a linear fashion over the period. This procedure has the advantage of simplicity and can be done by hand. However this approach does not take into account the evolutionary nature of an age pyramid. Following demographic methods have been proposed for intercensal years.
(a) Simple Diagonal Method:

This is applicable when the only information available comprises the two census populations (e.g. in 1980 and in 1990.). It is based on calculating the difference in population size between subjects aged \( i \) in 1980 and \( i + 10 \) in 1990, and assuming that this difference (due to deaths and migrations) is distributed equally in the years between the two censuses. Thus:

\[
N(80+a)_{i+a} = N80_i + a[N90_{i+10} - N80_i] / 10, \quad 1 < a < 9
\]

Where, \( N80_i \) is the population aged \( i \) in 1980.

\( N90_{i+10} \) is the population aged \( i +10 \) in 1990.

\( N(80+a)_{i+a} \) is the population aged \( i + a \) in year 1980+a.

The population aged less than 10 in 1990 (born since the 1980 census) is obtained by applying the same method to the number of births in the years 1980-1990 the precise calculation depends on the date of the census and the less than one year. For the final age category (open-ended) a simple linear interpolation must be made between age ‘\( i \)’ in 1980 and the same age \( i \), in 1990.

(b) The Diagonal Method With Deaths

This can be used if the numbers of death are known, by year, sex and age distributing the deaths gives an estimate of net migration (immigration – minus emigration).
If $D_{80i} = \text{the number of deaths in 1980 of subjects aged } i$ and $N_{80i} = \text{the number of subjects aged } i \text{ in 1980}$ then in the absence of migration the number ($n_{81i+1}$) of subjects aged $i+1$

$$n_{81i+1} = N_{80i} - D_{80i},$$

The number ($n_{82i+2}$) of subjects aged $i+2$ in 1982 will be

$$n_{82i+2} = n_{81i+1} - D_{81i+1},$$

and so on: $n_{83i+3} \ldots \ldots n_{90i+10}$

The difference between the population aged $i+10$ in 1990 thus calculated (assuming no migration), i.e. $n_{90i+10}$ and the name be given by the census, $N_{90i+10}$, provides an estimate of the net migration between 1980 and 1990 for the cohort aged $i$ in 1980. This net migration is divided between the years (1981, 1982, ....1990) assuming that the number of migrations is constant each year (assuming a constant rate of migration yields similar results ). The annual average net migration of the cohort aged $i$ in 1980 is thus:

$$S_i = \frac{(N_{90i+10} - n_{90i+10})}{10}$$

and hence

$$N_{82i+2} = n_{82i+2} + 2S_i,$$

$$N_{89i+9} = n_{89i+9} + 9S_i,$$

### 3.10 MODELS OF DISEASE ASSOCIATION

The simplest types of risk factors are binary of “all or none “ variety, as exemplified by the presence or absence of a particular genetic marker. Environmental variables are usually more difficult to quantify since individual histories vary widely with respect to the onset, duration and intensity of exposure, and whether it was continuous or intermittent. Nevertheless it is often possible to make crude classifications into an exposed versus non-exposed groups for example by comparing confirmed cigarette smokers with non-smokers, or life long urban with life long rural residents. In order to introduce the concept of risk factor disease
association, we suppose here that the population has been divided into two such subgroups one exposed to the risk factor in question and the other not exposed.

Incidence rates may vary widely within the population according to factors such as age, sex and calendar year of observation. What is clearly desired in this situation is a measure of association, which is as stable as possible over the various subdivisions of the population. The greater is the necessity to describe how the effect of exposure is modified by demographic or other relevant factors on which information is available.

Suppose that the population has been divided into 'i' strata on the basis of age sex, calendar period of observation, or combinations of these and other features. Denote by $\lambda_i$, the incidence rate of disease in the $i^{th}$ stratum for exposed subgroup and by $\lambda_0$, the rate for non-exposed subgroup in that stratum. The first measure of association we consider is the excess risk of disease defined as difference between the stratum specific incidences

$$b_i = \lambda_i - \lambda_0$$

Since the measure is defined in terms of incidence rates, rather than risk, it would perhaps be more accurate to refer to it as the excess rate of disease.

The intuitive idea underlying this approach is that cases contributing to the "natural" or background disease incidence rate in the $i^{th}$ stratum are due to the presence of general factors, which operate on exposed and non-exposed individuals alike. The excess risk would be relatively constant from stratum to stratum, apart from random statistical fluctuations. The idea of a constant excess risk due to the particular exposure may be
formally expressed by hypothesizing an additive model for the two dimensional sets of rates. With \( b \) representing the additive effect of exposure, the model states

\[
\lambda_{1i} = \lambda_{0i} + b
\]

In technical statistical terms this model states that there are no interactions between the additive effects of exposure and strata on incidence rates; exposure to the risk factor has the same effect on disease incidence rates in each of the population strata.

Another measure is the relative risk of disease, defined as the ratio of the stratum specific incidences

\[
r_i = \frac{\lambda_{1i}}{\lambda_{0i}}
\]

The assumed effect of exposure is to multiply the background rate \( \lambda_{0i} \) by the quantity \( r_i \). Absence of interactions here leads to multiplicative model for the rates such that, within the limits of statistical errors, these may be expressed as the product of two terms, one representing the underlying, natural disease incidence in the stratum and other representing the relative risk \( r \) More precisely, the model states

\[
\lambda_{1i} = \exp(\beta)\lambda_{0i}
\]

where \( \beta = \log(r) \). Alternatively, if the incidence rates are expressed on a logarithmic scale it takes the form

\[
\log \lambda_{1i} = \log \lambda_{0i} + \beta
\]

In other words the multiplicative model (4) is identical to an additive model in log rates. Such models are called log linear.
While excess and relative risk are defined here in terms of differences and ratios of stratum specific incidence rates analogous measures for the comparison of cumulative rates and risks may be deduced directly from equations

\[
\lambda(t) = \int_0^t \lambda(u) \, du \quad \text{and} \quad \lambda_j(t) = \frac{d_j}{n_j} + \frac{d_2}{n_2} + \ldots + \frac{d_j}{n_j}
\]

Let \( P_0(t) \) denote the net probability that a non-exposed person develops the disease during the time period 0 to \( t \) years and let \( P_1(t) \) denote the analogous quantity for the exposed population. If the corresponding incidence rates satisfy the multiplicative equation

\[
\lambda_j(u) = r \lambda_0(u) \quad \text{for all} \ u \ \text{between} \ 0 \ \text{and} \ t \ \text{then}
\]

\[
P_1(t) = 1 - \left[ 1 - P_0(t) \right]^r
\]

This relationship is well approximated by that for the cumulative rates

\[
P_1(t) = r P_0(t)
\]

**EMPIRICAL BEHAVIOR OF THE RELATIVE RISK**

Several examples from the literature of cancer epidemiology will illustrate that the relative risk provides a stable measure of association in a wide variety of human populations. When there are difference in the (multiplicative ) effect of exposure for different populations, it is often true that the levels of exposure are not the same of that there are define biological in reasons for the discrepancies the response to the same exposure
This figure gives a plot of incidence rates against age for stomach cancer occurring in males in the countries. (Waterhouse et al, 1976). In calculating these rates six 5 years age intervals were used: 35-39, 40-44, 45-49, 50-54, 55-59, 60-64. Since a logarithmic scale is used for both axes, the plotted points appear to lie roughly on three parallel straight lines each with a slope of about 5 or 6. This quantitative relationship, which is common for many epithelia tumors, may be expressed symbolically as follows. Denote by $\lambda_i(t)$ the average annual incidence rate for the $i^{th}$ area at age $t$, where $t$ is taken to be the midpoint of the respective age interval: $t = 37.5, 42.5$, etc. The fact that the log plots are parallel and linear means that approximately

\[
\log \lambda_i(t) = \alpha + \beta_i + \gamma \log(t)
\]  

---

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Where we arbitrarily set $\beta_i = 0$, thus using country 1 as a baseline for comparison. Raising each side of this equation to the power $e$, the relationship may also be expressed as

$$\lambda(t) = e^{\alpha r_i t^r}$$

where $r_i = \exp(\beta_i)$

The values of the parameters in (1) which give the best ‘fit’ to the observed data points using a statistical technique known as ‘Weighted least squares regression’ are $\alpha = -18.79$, $\beta_1 = 0$, $\beta_2 = 0.67$, $\beta_3 = 1.99$ and $\Gamma = 5.49$. Although the deviations of the plotted points about the fitted regression lines are slightly larger than would be expected from purely random fluctuations, the equations well describe the important features of the data.

The parameters $r_i (= \exp \beta_i)$ describes the relative positions of the age incidence curves for the three countries. By considering ratios of incidence rates, the relatives risk of stomach cancer in males in Japan versus those in Connecticut is

$$\frac{\lambda_3(t)}{\lambda_1(t)} = \frac{r_3 t^r}{r_1 t^r} = \exp(\beta_3 - \beta_1) = 7.3$$

While the relative risk in Birmingham Versus that in Connecticut is $\exp(\beta_2 - \beta_1) = 1.9$

The most important feature of the above relationships is that to the extent that equations (1) or (2) hold, the relative risks between different areas do not vary with age. The chance that a Birmingham male of a given age contract stomach cancer during the next year is roughly twice that of his
New England counterpart and the same applies whether he is 45, 55 or 65 years old. On the other hand the absolute differences in the age specific rates, $\lambda_2(t) - \lambda_1(t)$, vary markedly with age. The percentage increase in incidence associated with each 10% increase in age is related to the parameter $Y$ through the equation and varies neither with age nor with area.

$$\frac{\lambda_n(1.1t)}{\lambda_n(t)} - 1 \times 100\% = ((1.1)^Y - 1) \times 100\% = ((1.1)^{49} - 1) \times 100\% = 69\%$$

**EFFECT OF COMBINED EXPOSURE**

It is equally important to examine the extent to which the relative risk associated with one risk factor varies with changing exposure to a second risk factor and in this situation one also frequently observes relative uniformity. Consider the simplest situation with two dichotomous variables A and B. There are four incidence rates denoted by $\lambda_{AB}^*$, $\lambda_A^*$, $\lambda_B^*$ and $\lambda_0^*$ according to whether an individual is exposed to both one or neither of the factors. The there relative risks expressed using $\lambda_0$ as the baseline incidence are respectively.

$$r_{AB} = \frac{\lambda_{AB}}{\lambda_0}, \quad r_A = \frac{\lambda_A}{\lambda_0}, \quad r_B = \frac{\lambda_B}{\lambda_0},$$

Among those exposed to B, the relative increase in risk incurred by also being exposed to A is given by $\lambda_{AB} / \lambda_B = r_{AB} / r_B$.

If the relative risk associated with exposure to A is same, whether or not there is exposure to B, we say that the effects of the two factors are independent or do not interact.

In this case $r_{AB} / r_B = r_A$ from which $r_{AB} = r_A \cdot r_B$.
Thus the independence of relative risks for two or more exposures implies a multiplicative combination for the joint effect. But if the two risk factors each have additive rather than multiplicative effects on incidence then similar calculations show that the relative risk for the joint exposure under the no interaction assumption is

$$r_{AB} = r_A + r_B - 1$$

Women in the United States have an incidence of breast cancer about six times higher than that of Japanese women. The joint action of the factor responsible for the elevated risk among United States women, whatever it may be and age at first birth is clearly multiplicative. The great majority of cases of esophagus cancer in Europe and the United States arise from the combined multiplicative effect of alcohol and tobacco.

### 3.11 PHARMACOKINETIC MODELING

Pharmacokinetics is the study of the absorption, distribution, metabolism and elimination of xenobiotics in biological systems. By studying the fate of chemicals entering the body, it is possible to obtain information on the amount of either the parent compound or its metabolites reaching tissues that may be targets for the induction of cancerous lesions. Pharmacokinetics thus affords an opportunity to incorporate information on tissue dose in cancer risk assessment. Pharmacokinetic models permit an evaluation of the relationship between tissue dose and toxic response under different conditions of exposure. They also offer considerable insight into non-linear relationships that may exist between the level of exposure to environmental carcinogens and the dose of toxic metabolites.
reaching target tissues. In such cases, the use of tissue doses rather than environmental exposure levels will lead to more accurate estimates of potential cancer risk.

The development of physiologically based Pharmacokinetic (PBPK) models has provided a powerful tool for tissue dosimetry. Such models attempt to describe the processes that regulate chemical disposition, taking into account the physiological characteristics of the biological system under study. In PBPK modeling, a biological system is envisaged as consisting of a small number of physiologically relevant compartments. The model is characterized by actual physiological parameters such as body weight, cardiac output, breathing rates, blood flow rates, and tissue volumes. Biochemical parameters are used to describe the partitioning of the parent chemical or its metabolites among target tissues. Pharmacokinetic constants are also used to describe removal processes such as hepatic metabolism.

PBPK models offer a number of advantages over the compartmental models used previously in classical Pharmacokinetic analyses. A physiologically based model can be interpreted in biological terms, and lead to an understanding of the actual Pharmacokinetic processes governing chemical disposition in the body. Lack of fit of a particular model may suggest alternative hypotheses about Pharmacokinetic processes involved in the distribution and metabolism of xenobiotics. PBPK models also offer a powerful tool for predicting target tissue dose from one route of exposure to another and between species. Once a PBPK model has been established for inhalation exposure, the same model can be used to predict doses in internal tissues following dermal exposure after modifying only those model parameters governing uptake by the body into
the circulatory system. Similarly, a PBPK model established on the basis of studies in non-human mammalian species can be applied to humans after substituting the appropriate algometric, biochemical, and Pharmacokinetic parameters for humans. Finally, by providing a means of estimating the dose of reactive metabolites reaching target tissues, PBPK models may lead to more accurate predictions of risk than can be obtained using environmental exposure levels, particularly when saturation effects lead to a nonlinear relationship between environmental exposures and tissue doses.

DEVELOPMENT OF A PBPK MODEL
A PBPK model envisages the body, as consisting of a small number of physiological compartments. Each compartment represents a relatively homogeneous group of organs or tissues, linked to the central blood compartment by arterial and venous blood flow. The model is characterized by physiological parameters such as tissue volumes and blood flow rates, biochemical parameters such as partition coefficients, and kinetic parameters for metabolism and removal.

MATHEMATICAL DESCRIPTION OF A PBPK MODEL
A PBPK model is described mathematically by a system of non-linear partial differential equations that consist of a mass balance equation describing the entry and exit of xenobiotics in each compartment in the model. This system of equations can be solved simultaneously to predict the concentration of metabolites in each compartment as a function of time.

As an illustration, consider a single physiological compartment. Here, \( X(t) \) denotes the mass of the parent compound or its metabolites in the
compartment at time $t$. The concentration of the substance is then $C(t) = \frac{X(t)}{U}$, where $U$ denotes the volume of the tissue in that compartment. The arterial and venous blood concentrations, denoted by $A(t)$ and $V(t)$ respectively, reflect the entry of the substance to the compartment and its exit from it via the circulatory system. (To maintain continuity of blood flow, the rates of arterial and venous blood flow are assumed to be equal.) In some cases, the compound of interest may enter or leave the compartment by pathways other than blood. The rates of the substance entering and leaving the compartment by non-circulatory pathways are denoted by $Y(t)$ and $Z(t)$, respectively.

With this notation, the mass balance equation for the compartment is given by:

$$\frac{dX(t)}{dt} = Q[A(t) - V(t)] + Y(t) - Z(t)$$

where $Q$ denotes the rate of blood flow. If the solubility of the substance in the compartment is simply:

$$C(t) = V(t)$$

In the case of differential solubility in tissue and blood, we may write:

$$C(t) = V(t)P,$$

Where $P$ is the tissue-to-blood partition coefficient. Measurement of the partition coefficient $P$, which is greater than unity if the compound is more soluble in tissue than in blood and less than unity otherwise, is discussed later in this section.

More complex processes can also be described using extensions of the simple mass balance equation (14) above. Tissue solubility may change with dose if protein binding is saturable. Leung et al. (1990a) found it
necessary to include a complex secondary binding mechanism to describe the metabolism 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in liver. Separate mass balance equations are needed for the blood compartment of possibly a combined lung-blood compartment (Ramsay & Andersen, 1984).

Separate equations are needed to describe direct input to, and removal from the body. In the case of intravenous injection of a dose \( d \) of a particular compound at time \( t_k \) directly into the blood compartment,

\[
Y_b(t) = d\delta(t-t_k),
\]

Where \( \delta(t) \) denotes the Dirac delta function and \( Y_b(t) \) denotes the amount of the compound entering the blood supply at time \( t \). Oral and dermal uptake can be described using first order kinetics, or Michaelis-Menten kinetics (Michaelis & Menten, 1913; Gibaldi & Perrier, 1975) when uptake is saturable.

Removal can be accommodated in a similar manner. For water-soluble substances eliminated in urine, we have:

\[
Z_k(t) = K_k U_k V_k(t),
\]

Where \( Z_k(t) \) denotes the rate at which the substance is removed from the kidney, \( K_k \) is the removal coefficient, \( U_k \) is the volume of the kidney, and \( V_k(t) \) is the venous concentration in the kidney. Implementation of this particular removal process is accomplished by isolating the kidney as a separate compartment attached to the liver (cf. Paustenbach et al., 1988).

Krewski et al. (1991) discuss the development of the mass balance equations to describe a general PBPK model in more detail. If all of the
differential mass balance equations used to characterize the dynamics of individual compartments are linear, then a closed form solution of this system can be obtained by analytical means. In most cases, however, one or more processes involved in the system will be saturable, leading to a system of non-linear partial differential equations that must be solved using numerical methods. This can be done using computer software specifically designed for use in solving PBPK models (Mitchell & Gaugheir, 1992; Steiner et al. 1989).

**SELECTION OF MODEL COMPARTMENTS**

Physiological compartments should ideally be as homogeneous as possible. At the same time, the number of compartments should be kept small to simplify the analysis and interpretation of the results.

Fiserova-Bergerova (1983) suggests that tissues in which chemical concentrations increase or decrease at the same rate may be included in the same physiological compartment. Based on this criterion, richly perfused tissues such as skin and fat amalgamated to form another class. Since metabolism in the liver represents a function of particular importance in Pharmacokinetic, the liver is usually treated as a special compartment. Furthermore, since fat will demonstrate a high partition coefficient for lipophilic compounds, fatty tissue is often considered as a separate compartment, particularly when studying fat-soluble substances. Blood is also considered as a single compartment because it provides chemical transport to all compartments in the body.

These considerations suggest the use of a PBPK model with the following five compartments: blood, liver, richly perfused tissue, poorly perfused
tissue, and fat. With some variations, this basic five-compartment model has been widely used in PBPK modeling. With volatile compounds, for example, the blood compartment may be replaced by a blood/lung compartment. In other cases, unique target tissues such as mammary or fontal tissue may be explicitly defined as separate compartments (Fisher et al, 1988, 1989; O’Flasherty et al., 1992).
DETERMINATION OF PHYSIOLOGICAL, BIOCHEMICAL AND METABOLIC PARAMETERS

As was seen previously, the behavior of a PBPK model is characterized by a system of differential equations that describe the flow, tissue binding, and metabolism of a chemical entering the body. These mass balance equations for the influx, efflux and removal of the chemical in each compartment are defined using relevant physiological, physiochemical, and biochemical parameters. Depending on the specific features incorporated, even a relatively simple five-compartment model such as that illustrated in Figure can involve more than 20 different parameters. Estimates of the values of all of these parameters are required before the model can be solved.

PHYSIOLOGICAL PARAMETERS

Physiological parameters of interest include tissue volumes, blood flow rates, cardiac output, and alveolar ventilation. Arms & Travis (1988) have compiled reference values for these and other physiological parameters for a generic 25-g mouse, a 250-g rat and a 70-kg man.

When such parameters are unavailable for an untested species, or parameter values are desired for individuals of different body weights, values can be estimated by scaling methods. Many of the physiological parameters required in PBPK models vary with body weight according to the power function

\[ Y = aW^b \]

Here, \( Y \) is the physiological parameter of interest, \( W \) denotes body weight, and \( a \) and \( b \) are constants (Fiserova-Bergerova & Hughes, 1983). If \( b = 1 \), the parameter \( Y \) scales in direct proportion to body weight; if \( b = 2/3 \), \( Y \) is
roughly proportional to body surface area. Tissue volume scales across species based on equation (15) with $0.70 < b < 0.99$, depending on the tissue considered (Aldolph, 1949). In interspecies scaling of cardiac output, a value of $b=3/4$ appears to be more appropriate (Takezawa et al., 1980).

PARTITION COEFFICIENTS

Partition coefficients are used to measure the affinity of a compound to tissues in the different compartments of PBPK model. The partition coefficient $P$ of a chemical between two media is defined as the ratio of the chemical concentration in the first medium to that in the second medium. A commonly used method for determining partition coefficients is the vial equilibration technique described by Sato & Nakajima (1979). With this approach, a known amount of the chemical in air, tissue and blood is then measured. The inverse ratios of the concentration in air to the concentration in blood and the concentration in tissue are called the blood-to-air and tissue-to-blood partition coefficients, respectively. The tissue-to-blood partition coefficient is then obtained by taking the ratio of the tissue-to-air and blood to air partition coefficients. Other approaches for measuring partition coefficients for non-volatile chemicals include in vitro equilibrium dialysis (Lin et al., 1982) and in vivo constant infusion methods (Chen & Gros, 1979).

METABOLIC PARAMETERS

Biochemical constants governing metabolism have been estimated using different techniques, including measurement of the total amount of metabolites formed as a function of dose (Ghering et al., 1978); examination of whole body clearance (Andersen et al., 1984); or the use of
noninvasive inhalation techniques (Gargas et al., 1986; Gargas & Andersen, 1989).

If metabolism is mediated by an enzyme whose supply is limited with respect to the time of reaction, the rate of metabolism will saturate as function of time. This saturation effect is described by the Michaelis-Menten equation:

\[
\frac{dM_m(t)}{dt} = \frac{V_{\text{max}} V(t)}{K_m + V(t)},
\]

where \( M_m \) is the amount of the metabolite formed, \( V(t) \) is the concentration of the substrate in venous blood at time \( t \), \( V_{\text{max}} \) is the maximum metabolic rate possible for the reaction, and \( K_m \) is the Michaelis constant defined as the venous blood concentration at which the metabolic rate is half \( V_{\text{max}} \). When the rate of metabolism is not saturable, the rate of formation of the metabolite follows first-order kinetics with:

\[
\frac{dM_m(t)}{dt} = K U V(t)
\]

Here, \( U \) is the volume of the tissue compartment (usually the liver) in which metabolism occurs, and \( k \) is the linear metabolic rate constant.

TISSUE DOSIMETRY

In the past, some measure of the exposure of the whole body has been used as a dose metamer for predicting carcinogenic risk. More accurate estimates of risk may be possible if some measure is used of the dose of reactive metabolites reaching target tissues. Moving closer to the site of pharmacodynamic action leads to more direct measures of exposure, transcending saturation effects that can occur during metabolic activation. Although PBPK models provide a means of predicting tissue doses,
consideration needs to be given to the most appropriate measure of dose to the target tissue.

Andersen (1981) suggested the use of an integrated measure of tissue dose-based on the area under the concentration-time curve (AUC) for either the parent compound or its reactive metabolites in the tissue of interest. Specifically, the AUC for the parent compound in blood is defined by:

\[
\text{AUC}_b = \int_0^\infty C_b(t) \, dt,
\]

where \(C_b(t)\) denotes the concentration in blood at time \(t\). The AUC for serum can be determined by measuring the concentration of the parent compound in blood samples taken at frequent intervals. This cannot be done in most other compartments, however, since most tissue samples require destructive sampling. Once a PBPK model has been developed, however, it can be used to predict the concentration of metabolites in any of the tissue compartments included in the model.

For a linear PBPK model, the AUC of the parent compound in blood following intravenous administration of single-dose \(d\) can be expressed as:

\[
\text{AUC}_b = d(1/Q_i + 1/k_i),
\]

Which involves only blood flow \(Q_i\) to the liver and the rate of metabolism \(k_i\) in the liver. If the PBPK model has been well validated, this relationship can be used to estimate the AUC in blood without direct measurement of blood concentrations over time. The AUCs of the parent compound in other compartments are related to those in serum, For example, if can be shown that in liver:
Further data on the relationship between the AUC in target tissues and the AUC in blood are given by Pelekis et al., (1997).

### 3.12 APPLICATIONS

Considerable experience with the development and application of PBPK models for toxic chemicals now exists. While PBPK models for volatile anesthetics date back to Haggard (1924), these models were not widely applied to toxic chemicals until the 1970s. One of the earliest applications in toxicology was the development of PBPK mode 1 for styrene by Ramsay & Andersen (1984). By analyzing existing Pharmacokinetic data, they deduced the partition coefficients and metabolic rates for styrene. The PBPK model used included compartments for the lung (as the site of uptake), fat (a storage depot), liver (the primary site of metabolism), richly perfused tissue (such as kidney and brain), and slowly perfused tissue (including muscle). Metabolism was saturable at inhalation exposures above 200 ppm for 6 h in mice and rats. The model was validated against other data from rats and humans, and used for dose-route, dose-level, and interspecies extrapolation.

One of the best-known examples of PBPK modeling is its application to methylene chloride (Andersen et al., 1987). With methylene chloride, all model parameters except those governing metabolism were estimated without temporal observations on tissue concentrations (Gargas et al., 1990); metabolic constants were estimated without temporal observations on tissue concentrations (Gargas et al., 1990); metabolic constants were
estimated from specialized gas-uptake studies utilizing a PBPK model for data analysis (Gargas et al., 1986).

The metabolism of methylene chloride proceeds via two pathways; oxidation by cytochrome P-450 enzyme systems, and conjugation by glutathione transferase enzymes. PBPK models for methylene chloride have focused on metabolism by these two pathways in the liver and lung, the two target sites for carcinogenicity in the mouse, and have implicated metabolites generated by the glutathione transferase pathway as being primarily responsible for tumor induction.

To date, more than 40 toxic chemicals have been subjected to PBPK modeling. Recent reviews have been provided by Andersen et al. (1993) and Krewski et al. (1993). This extensive experience with PBPK modeling has clearly established the feasibility of this methodology as a tool for tissue dosimetry.

**UNCERTAINTY, VARIABILITY AND SENSITIVITY ANALYSES**

PBPK models require information on a number of parameters (including physiological, physicochemical, and biochemical constants) in order to simulate the kinetic behaviour of a chemical and its metabolites in the body. Uncertainty in the values of these parameters results in uncertainty in model-based predictions of tissue dose. Model parameters may also vary among individuals in a particular population, resulting in variability in the tissue doses received by different individuals in that population.

Predictions of tissue dose may be more sensitive to changes in certain model parameters than others. For example, the loss of volatile chemical from within a closed chamber due to metabolism by study subjects within the chamber can be quite sensitive to the kinetic constants for metabolism.
ventilation, or even blood flow (Gargas et al., 1990). Recently, Krewski et al. (1997) examined the uncertainty and sensitivity associated with parameters in PBPK models for three volatile organic compounds. Monte Carlo simulations indicated that the rate of cardiac output and fractional blood flow to richly perfused tissues and liver were the largest contributors to uncertainty in predicted tissue doses.

Uncertainty in the values of PBPK model parameters will lead to uncertainty in the estimates of cancer risk derived from model-based predictions of tissue dose. In a pioneering paper on this subject, Portier & Kaplan (1989) used a PBPK model for methylene chloride to evaluate uncertainty in predictions of lifetime risk arising as a consequence of uncertainty in the PBPK model was used to predict the concentrations of metabolites in lung and liver tissue, and a one-stage pharmacodynamic model to predict cancer risk in relation to tissue dose. Estimates of the uncertainty in the PBPK model parameters were based on published data, when available; otherwise, coefficients of variation for uncertainty in the model parameters were assigned values of 20-200%. This analysis demonstrated that allowing for uncertainty in the model parameters led to a relatively wide range of values for the corresponding range of cancer risk estimates. Although it did not allow for correlations among the model parameters and was based on a somewhat arbitrary assignment of variability to some of them, it is instructive in demonstrating how PBPK models can be used to evaluate at least part of the uncertainty in cancer risk estimates based on joint applications of Pharmacokinetic and pharmacodynamic models. Krewski et al (1995) have addressed the question of correlation among model parameters.
Other studies of the impact of the uncertainty in the parameters of PBPK models for tetrachloroethylene (Farrar et al., 1989); benzene (Bois et al., 1991), and styrene, methylchloroform and methylene chloride (Hetrick et al., 1991) have also been conducted. This last study demonstrated that the extent of model sensitivity to parameter values may depend on the dose of the parent compound, the time at which tissue doses are predicted, and the species for which the PBPK model was developed.

It is important to recognize that, even though the uncertainty associated with cancer risk estimates for methylene chloride appeared to increase with the use of Pharmacokinetic data, such estimates may well be more accurate than those based on external measures of exposure. Consideration thus needs to be given to risk estimation methods that optimize this gain in accuracy in relation to possible increased in certainty. Statistically, it is desirable to minimize the mean squared error of estimates of risk, which takes into account both bias and precision.