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Optimum Safe Dose Estimation for Carcinogenic Agents (A Case Study Using Simulated Data)

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Abstract

In this paper we introduce one procedure to estimate safe doses, named exposed or administered dose, for carcinogenic or toxical materials. The model, relying on statistical distribution takes into account a major assumption, which is explained below.

*The probabilistic model underlying the waiting time of occurrence (such as tumor occurrence, etc.) is a renewal Weibull Process.

The literature on the topic is full of various models, using different assumptions. Most of these models consider the administered dose as effective dose, the derived model is built on this basis, and the safe doses are estimated using extrapolations near low risk doses. Under this assumption we can reach a model different from the ones used before. Our derived model will be our working model in order to estimate the administered safe dose ξ. We intend to estimate x using the final model. At the end of the study, we have estimated optimum safe dose to apply the procedure by using simulated data on computer according to the underlying model and distribution.

Keywords: *Safe Dose, Dose Response Model, Renewal Weibull Process, Tolerance.*

Özet

Bu çalışmada, kanserojen ve toksik maddeler için, maruz kalınan veya idare edilen doz olarak da adlandırılan, güvenli dozu tahmin etmek için yeni bir model tanıtıldı. Bu model, aşağıda açıklanan varsayımı temel almaktadır.

*Olasılıksal modelin temeli, meydana gelme bekleme zamanının yinelenen Weibull süreci olmasına dayanmaktadır.

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Literatürde, bu konu için farklı varsayımlar kullanılarak elde edilen çeşitli modeller bulunmaktadır. Yukarıda tanımlanan varsayım altında bulunan model literatürde daha önce tanımlanan modellerden oldukça farklıdır. Bulunan model ile maruz kalınan en güvenli doz ξ. için tahmin edici elde edilmiştir. Çalışmanın sonunda, simülasyon yolu ile elde edilen veriler modelimizde kullanlılarak optimum güvenli doz tahmin edilmiştir.

Anahtar kelimeler: *Güvenli Doz, Doz Yanıt Modeli , Yinelenen Weibull Süreci, Tolerans.*

1. Introduction

Humans' exposure to toxic substances has existed since antiquity. In recent decades humans have also been exposed to an increasing number and variety of man-made chemicals. No substance is a poison by itself, it is the dose that make a substance a poison. During last few years scientists have increasingly concerned with the problem of assessing the population's risk of being exposed to low doses of substances that may possibly be carcinogenic. This is inherently a statistical problem, although by no means exclusively so. It is also an extremely difficult problem that has exercised the minds of many biostatisticians.

In this paper we are exclusively concerned with the statistical aspects of the problem. The original version of "Delaney Clause" stipulates that if a material is found to induce cancer in man or animals after appropriate experimental testing, this material should not be used as an additive in foods. This principal is vague in the specification of the required experimental testing both with regard to the dose levels employed and the number of animals tested. The definition of safe dose being currently considered is that it should not increase the cancer incidence rate by more than (acceptable) low risk level, the increase being defined by comparison with so called spontaneous cancer "incidence rate", i.e. zero dose cancer incidence.

A substance identified as an animal carcinogen may be totally restricted for some human uses, for example as a food additive. It may still be a candidate for other human uses; however, if exposure levels associated with no or only minimally increased risk could be maintained. The establishment of human dose-response relationships required for the later situation is usually based, at least partially, on the results of animal carcinogenicity experiments. However, the dose-response relationship in animals for extremely low risks is not addressed in the standard animal carcinogenicity trial. In fact, the number of animals required to detect increased risks of the magnitude considered here precludes their direct observation. Researchers shown that often resort to assumed functional forms of the dose-response relationships in order to extrapolate the lower levels of risks, which are usually associated with extremely low doses.

A few general comments on low-dose should be kept in mind when assessing the usefulness of any of the models explained below. For example, none of the models considered here allows for a population threshold in dose below, where no increase in risk exists for any individual. Though kinetic models which allow for thresholds for individuals, can be developed the existence of thresholds for a population does not necessarily follow. Many models currently used allow for individual thresholds which here will be referred to as tolerances. Since exposure to a carcinogen even at the lowest doses may be associated with some increase in risk in the population, no absolutely safe dose is assumed to exist. Extrapolation is thus made to virtually safe doses (VSD), associated with extremely low risks, say 10^{-8} or 10^{-6}. The magnitude of this risk reflects the upper limit on the 'acceptable' increase in the number of cancer cases due to a lifetime of exposure.

Several of the more commonly used low-dose extrapolation models are present. First, Mantel and Bryan developed a model, which is constructed to use Probit in 1961. Amitage and Doll developed another model, this is called multistage model. In 1975 Hoel presented a conceptually and computationally simple extrapolation procedure, which assumes only that the dose-response relationship is convex at low-doses. In the same year Hatley and Sielken proposed a different model,' General Product Model' to extrapolate low-dose estimation. Rai and Van Ryzin(1979) have developed Gamma Multihit model based on the earlier work by Cornfield. After these models Gehring showed that the amount of vinly chloride metabolized is more linearly related to incidence than is actual exposure. He developed a pharmacokinetic model using vinly chloride, which allows for activation, detoxification and repair. Since many carcinogens require metabolic activation to achieve their active form, pharmacokinetic models may be considerable value in describing and understanding the carcinogenic process. One of the major topics concerns risk quantifications, including some measures of risk that emphasize the time of response as well as its frequency. Decision theory method was used by Sielken in 1989 for cancer risk assessment, which provides a means of evaluating sources of uncertainty.

New dose response modelling techniques which attempt to utilize more of the available scientific knowledge and expertise involve (i) representations of the exposure in terms of the dose scales based on cell turnover rates repair processes, immune system responses, and physiological and pharmacokinetic models of the absorption, delivery, metabolism, and elimination of chemicals, (ii) distributions of individual background exposure levels and individual susceptibilities to low levels of a chemical, (iii) age-

dependent changes in the number of target cells and the time- dependent effects of cell proliferation on the number of intermediate cells in a multi-stage process, and (iv) dose levels, susceptibilities, and background exposures which are not necessarily constant over time.

2. Dose Response Surface Model

Dose response models can be an important part of the quantitative cancer risk assessment supporting risk management and regulatory decision-making. For this reason, studies have been conducted since the beginning of 1950's in order to construct dose response models. Several of the most commonly used low dose extrapolation models are presented in section 2.1.

2.1 Current Low-Dose Models in Use

First, Mantel and Bryan developed a model in 1961, they assume that each animal possesses a tolerance to exposure below which it will not develop a tumor. These tolerances are assumed to be approximately log normally distributed across animals. The problem is then to determine the dose, d, which exceeds the tolerances of only a small percentage of the animals. The risk of cancer at dose d can be written as,

$$P(d) = P(0) + (1 - P(0))\, A(d) \qquad (2.1.1)$$

where, $A(d) = [P(d) - P(0)] / [1-P(0)] = \Phi(\alpha+\beta\log(d))$ and P(0) is spontaneous rate, a and b are parameters of the tolerance distribution and $\Phi(.)$ denotes the standard normal cumulative function. Based on empirical evidence, however, they suggested that setting β equal to one would lead to conservative estimates of the true optimum safe doses(OSD). This assumption of unity slope can be relaxed and the slope estimated by maximum likelihood method. The Probit (β estimated) and Mantel-Bryan ($\beta=1$) models are, however always concave at low risks while other models allow for linear or convex relationships. In relation to the other models, the Mantel-Bryan method may not be as conservative as was originally expected.

Armitage and Doll developed a multi-stage model based on the assumption that cancers originate from a single cell which has progressed through k irreversible changes which are usually referred as stages or "hits". The rate, λ_i, of the progression from stage i-1 to i, is assumed to be independent of age. The age-specific cancer incidence rate is given by,

$$I(t)= t^{k-1} (\prod_{i=1}^{k} \lambda_i) /(k-1)! \qquad (2.1.2)$$

and the probability of tumor by age T is given by

$$P(T) =1-\exp[-Q(T) (\prod_{i=1}^{k} \lambda_i) /(k-1)!] \qquad (2.1.3)$$

Where Q(T) does not depend on the λ_i's. If the rates $\lambda_i = \alpha_i+\beta_i d$ are allowed to depend on dose d in a linear fashion with $\alpha_i \geq 0$ and $\alpha_i \geq 0$ and T is taken to be the natural life expectancy of the animal, then the probability of tumor in an animal exposed to a dose of d for its entire life is

$$\begin{aligned} P(d) &= 1- \exp[-Q(T) (\prod_{i=1}^{k} \alpha_i + \beta_i d) /(k-1)!] \\ &=1-\exp(-\sum_{i=0}^{k} q_i d^i) \end{aligned} \qquad (2.1.4)$$

The coefficients q_i ar.e typically estimated by maximum likelihood subject to the constraint $q_i \geq 0$. Implicit in this model is the treatment of a spontaneous tumor rate with Abbott's formula

$$A(d) = 1- \exp(-\sum_{i=1}^{k} q_i d^i) \qquad (2.1.5)$$

For extremely low values of d,

$$\log(A(d)) \sim \log(q_\lambda) + \lambda \log(d) \qquad (2.1.6)$$

where λ denotes the lowest power of dose with non zero coefficients.

The theoretical foundation of the multistage model has also been utilized to establish useful epidemiologic research and analysis strategies.

Supporting evidence indicates that the multi-stage model may be reasonable extrapolation model. The multistage model has been generalized to incorporate time to tumor data (Hartley and Sielken, 1977).They use 'product form' for the hazard rate F specifying that F factorizes into a function of x(dose) and a function of t(time), i.e.

$$F(t,x;\alpha,\beta)=g(x; \alpha)h(t; \beta) \qquad (2.1.7)$$

This extension leads to alternative methods of measuring the increased risk of cancer associated with exposure to a given dose.

In 1975 Hoel presented a conceptually and computationally simple extrapolation procedure, which assumes only that the dose-response relationship is convex at low doses. Consider an experiment conducted at a single dose, d^*, with the observed proportion of animals with tumor denoted by $\hat{p}(d^*)$. If a convex dose response relationship holds for $0< d < d^*$ and $P(0) = 0$, then the straight line through the origin

$$P(d)=d[\hat{p}(d^*)/d^*] \tag{2.1.8}$$

provides an upper bound for the true dose-response relationship at the low doses. Conservative estimates for the optimum safe dose(OSD) can be obtained from this straight line. Linearity at low doses is also consistent with the multistage model. In fact the OSD's from linear extrapolation and multistage model are usually quite similar.

In 1979 Rai and Van Ryzin developed another model (Gamma Multihit) based on earlier work by Cornfield which is also based on "hits" but assumes that the number of hits follows a Poisson distribution with parameter qd. The probability that a cell has experienced k or more hits by time t is

$$P(d)=\sum_{i=k}^{\infty}\frac{(\theta d)^i e^{-\theta d}}{i!}=\int_0^d\left[\theta^k t^{k-1}\exp(-\theta t)/\Gamma(k)\right]dt \tag{2.1.9}$$

Where $\theta>0$, $k>0$ and $G(k)$ is the complete gamma function. Rai and Van Ryzin propose that a spontaneous tumor rate incorporated in the model using Abbott's formula with

$$A(d)=\int_0^d\left[\theta^k t^{k-1}\exp(-\theta t)/\Gamma(k)\right]dt \tag{2.1.10}$$

The estimates for k and θ are obtained by maximum likelihood and extrapolation is performed, as before, from the upper confidence limit for θ.

3. The General Weibull Model For Carcinogenic Hazard Rate

In animal experiment studies the suspected carcinogen agent is applied to (n) animals exposed to certain levels of doses from the suspected substance. It is assumed that each experimental animal is exposed to a dose and will be sacrificed at the end of the experiment duration at time t, also we assume that the data consist of time to tumor observed from the exposed animals due to the effect of the carcinogenic agent.

In order to specify the strategy of our approach on the type of the data that our model is addressed with we have to outline the type of protocols that administers the experiment.

Protocol-1: This protocol includes direct observation or estimation of time to tumor in animals exposed to carcinogen substance, includes also estimated time to tumor at necropsy for animals dying before sacrifice.

Protocol-2: The time to tumor is unknown until the end of the experiment (until t) in animals exposed to carcinogen substances. The tumor is observed after the animals are sacrificed and necropsy is done.

Protocol-3: At the end of the experiment, animals with necropsy are observed to have no tumor.

According to the above protocols the number of animals (n) in the experiment has been divided in to three categories as follows.

k_1 : The number of animals subject to protocol-1.

k_2 : The number of animals subject to protocol-2.

k_3 : The number of animals subject to protocol-3.

The distribution model for the likelihood function of the data under consideration will be generated as the product of the likelihood in each category, knowing that the observed tumor times in category 1 comprise order statistics for independent observed time $t_1 < t_2 < \ldots < t_{k1}$ and the rest of the categories will deal with time duration of incidences up to the end of the experiment.

We assume that incidence rate of tumor occurrences $\lambda(t)$ depend on time t and can be expressed as

$$\lambda(t)= \left(\frac{t}{\theta}\right)^{\beta d} \qquad (3.1)$$

This assumption will lead us to Non Homogeneous Poisson Process (NHPP), (Bain, L. J. and Engeldard, M., 1991) with incidence rate

$$v(t)=\frac{\beta d}{\theta}\left(\frac{t}{\theta}\right)^{\beta d-1} \qquad (3.1)$$

It is well known from literature (e.g. see, Bain, L.J. and Engeldard, M., 1991) that the waiting time for the first occurrence in NHPP is distributed as Weibull distribution, with parameters θ and β.

$$f(t)= \frac{\beta d}{\theta}\left(\frac{t}{\theta}\right)^{\beta d-1} e^{-\left(\frac{t}{\theta}\right)^{\beta d}} \qquad 0<t<\infty,\ \theta>0,\ \beta>0,\ d>0 \tag{3.3}$$

where θ , β are scale and shape parameters respectively.

As most of the animal experiments reveal the structure of the conditions under which they have to be performed, the independency of the units is crucial for most of the cases. We can postulate that the k_1 animals in the first category comprise k_1 order statistics of a Weibull process and the sample likelihood will consist from the likelihood on category 1 given in equation (3.6). Since we consider the observations in this category as a truncated Weibull process.(see, Bain, L.J. and Engeldard, M., 1991)

$$g_\tau(t)=\frac{\beta d}{\tau}\left(\frac{t}{\tau}\right)^{\beta d-1} \qquad 0<t<\tau \tag{3.4}$$

with observed times $0 < t_1 < t_2 <\ldots< tk_1<\tau$ and since the number of animals with positive tumors N is NHP random variable with mean $\left(\frac{t}{\theta}\right)^{\beta d}$ then the conditional joint probability density function(p.d.f.) for $0<t_1< t_2<\ldots< tk_1< \tau$ given $N(\tau)=k_1$ is

$$g_\tau(t_1,t_2,t_3,\ldots, t_{k_1} \mid k_1)= k_1!\left(\frac{\beta d}{\tau}\right)^{k_1}\prod_{i=1}^{k_1}\left(\frac{t_i}{\tau}\right)^{\beta d-1} \tag{3.5}$$

and hence the joint p.d.f. for $t_1, t_2,\ldots,$,k_1 will be

$$g_\tau(t_1,t_2,t_3,\ldots,k_1) = g_\tau(t_1,t_2,t_3,\ldots,t_{k1} \mid k_1)P(N(\tau)=k_1)=$$

$$k_1!\left(\frac{\beta d}{\tau}\right)^{k_1}\prod_{i=1}^{k_1}\left(\frac{t_i}{\tau}\right)^{\beta d-1} \frac{e^{-\left(\frac{\tau}{\theta}\right)^{\beta d}}\left(\frac{\tau}{\theta}\right)^{\beta d k_1}}{k_1!}$$

$$g_\tau(t_1,t_2,t_3,\ldots, t_{k_1},k_1)=\left(\frac{\beta d}{\theta}\right)^{k_1}\prod_{i=1}^{k_1}\left(\frac{t_i}{\theta}\right)^{\beta d-1} e^{-\left(\frac{\tau}{\theta}\right)^{\beta d}} \quad 0<t_1<t_2<\ldots< t_{k_1} <\tau \tag{3.6}$$

and for the second category we are having k_2 independent animals with positive necropsy at time τ, with cumulative distribution function (c.d.f) is ,

$$P(\tau)=(1-e^{-\left(\frac{\tau}{\theta}\right)^{\beta d}})^{k_2} \tag{3.7}$$

Finally the likelihood in the third category of k_3 independent animals with negative necropsy at time τ is,

$$Q(\tau)=e^{-\left(\frac{\tau}{\theta}\right)^{\beta d k_3}} \tag{3.8}$$

Therefore the likelihood function for the entire data will be given as

$$L=\underbrace{\left(\frac{\beta d}{\theta}\right)^{k_1}\prod_{i=1}^{k_1}\left(\frac{t_i}{\theta}\right)^{\beta d-1}e^{-\left(\frac{\tau}{\theta}\right)^{\beta d}}}_{\text{Protocol- 1}}\ \underbrace{(1-e^{-\left(\frac{\tau}{\theta}\right)^{\beta d}})^{k_2}}_{\text{Protocol - 2}}\ \underbrace{e^{-\left(\frac{\tau}{\theta}\right)^{\beta d k_3}}}_{\text{Protocol - 3}},0<t_1<t_2<\ldots<t_{k_1}<\tau \tag{3.9}$$

4. Safe Dose Equation

Since the incidence rate for NHPP is

$$v(t)=\frac{\beta d}{\theta}\left(\frac{t}{\theta}\right)^{\beta d-1} \tag{4.1}$$

and this function is the same as the hazard rate for Weibull process, this will lead us to assume the following relationship of the dose levels applied to the animals with the rate of occurrence of tumors in animals following NHPP $\lambda(t)=\left(\frac{t}{\theta}\right)^{\beta d}$.

The safe dose level ξ (if exist) specifies an agreeable change in the cancer rate over the spontaneous cancer rate (such as $\pi=10^{-8}$) and can be deduced from the following equation

$$\pi=P(t,\xi;\theta,\beta)-P(t,0;\theta,\beta) \tag{4.2}$$

The above equation can be written as

$$Tol(\tau)=\frac{Q(t,\xi;\theta,\beta)}{Q(t,0;\theta,\beta)}=1-\frac{\pi}{Q(t,0;\theta,\beta)} \tag{4.3}$$

where $P(t,\xi;\theta,\beta)$ is c.d.f. of random variable t and $Q=1- P(t,\xi;\theta,\beta)$ so that the "tolerance" $Tol(\tau)$ is defined as a permissible percentage reduction in the spontaneous tumor free proportion. $Tol(\tau)$ will be a quantity slightly smaller than 1 and we shall specify $Tol(\tau)$ rather than p.

The cumulative distribution function for the time to tumor t in a population of animals exposed to dose d with parameters θ, β is

$$P(t,\xi;\theta,\beta)= 1- e^{-\left(\frac{t}{\theta}\right)^{\beta\xi}} \tag{4.4}$$

From equation (4.3) $Q(t,0; \theta,\beta)$ equals 1 and the tolerance we will have

$$Tol(\tau)= e^{-\left(\frac{t}{\theta}\right)^{\beta\xi}} \tag{4.5}$$

Therefore

$$LogTol(\tau)= -\left(\frac{t}{\theta}\right)^{\beta\xi} \tag{4.6}$$

Solving for x we will have

$$\xi = \frac{1}{\beta}\frac{\log\left(\log\left(\frac{1}{Tol(\tau\ )}\right)\right)}{\log\left(\frac{t}{\theta}\right)} \tag{4.7}$$

Clerarly, if in equation (4.7) the true θ, β were replaced by their maximum likelihood estimatoins (MLE) $\hat{\theta},\hat{\beta}$ and the unique root ξ of (4.7) computed, this would represent the MLE of the optimum safe dose ξ.

$$\hat{\xi} = \frac{1}{\hat{\beta}}\frac{\log\left(\log\left(\frac{1}{Tol(\tau)}\right)\right)}{\log\left(\frac{t}{\hat{\theta}}\right)} \tag{4.8}$$

5. Optimum Safe Dose Estimation

In order to have an estimation, $\hat{\xi}$ for the optimum safe dose, we will use the MLE procedure to estimate the model parameters. To obtain the collected data from clinical trials is very difficult to use this procedure. In some clinical trials, we can not observe time to tumor data correctly. Because of this we could not apply real data. In this study, instead of real data we use simulated data to estimate the model parameters.

Several parameters of the simulation study were held constant for the experiment. The duration time for the experiment, τ, was taken as τ=104 weeks (104 weeks (two years) is the most popular duration time in bioassay experiments. The value of Tol(τ), the permissible percentage reduction in the spontaneous tumor free rate, was chosen as 0.99999. The time to tumor, t, were generated for different dose levels from truncated two parameters Weibull distribution using the small macro in statistical software package MINITAB.

Using the simulated time to tumor data from the experiment we find an MLE estimate from the likelihood function generating category 1.i.e.

$$L_1=\left(\frac{\beta d}{\theta}\right)^{k_1}\prod_{i=1}^{k_1}\left(\frac{t_i}{\theta}\right)^{\beta d-1} e^{-\left(\frac{\tau}{\theta}\right)^{\beta d}} \quad 0<t_1<t_2<t_3<\ldots<t_{k_1}<\tau \tag{5.1}$$

The estimates of θ,β turns out to be

$$\hat{\theta}=\frac{\tau}{k_1^{1/\hat{\beta}d}},\ \hat{\beta}=\frac{k_1 d}{\sum_{i=1}^{k_1}(\ln\frac{\tau}{t_i})} \tag{5.2}$$

Using the simulated data we obtained the optimum safe dose estimations which are shown in Table 5.1.

Table 5.1 MLE of Safe Dose Estimation for Different Dose Levels

Dose Level	$\hat{\beta}$	$\hat{\theta}$	Mean ξ
d_1=6.1	10.749	96.677	4.602
d_2=12.1	10.895	100.291	1.932
d_3=18.1	10.888	101.504	0.826

In this study time to tumor distribution was the Weibull distribution $P(t,d;\theta,\beta)=1-\exp(-(t/\theta)^{\beta d})$. When we use this, we can calculate probability of time to tumor for given dose levels and mean of safe dose estimation. Calculated values are given in Table 5.2.

Table 5.2 Probability of Time to Tumor for Different Dose Levels

Dose Level	$\hat{\beta}$	$\hat{\theta}$	Mean ξ	$P(\tau,d_x;\theta,\beta)$	$P(\tau,\xi;\theta,\beta)$
d_1=6.1	10.749	96.677	4.602	0.999999	0.993993
d_2=12.1	10.895	100.291	1.932	0.999999	0.883252
d_3=18.1	10.888	101.504	0.826	0.999999	0.711855

According to the results of the simulation Table 5.1 presents, the MLE of each parameters and Table 5.2 presents, probability of time to tumor for given doses and mean of the estimated safe doses. By examination of these values specifically $P(\tau,\xi;\theta,\beta)$ and comparison with $P(\tau,d_x;\theta,\beta)$, we see that very reasonable safe dose estimates are obtained. Because $P(\tau,\xi;\theta,\beta)$ is less than $P(\tau,d_x;\theta,\beta)$.

6. Conclusion

The aim of this study is to introduce a procedure to estimate safe doses, named exposed or administered dose, for carcinogenic or toxical materials. The model, relying on statistical distribution, takes into account a major assumption, which is explained below.

- The probabilistic model underlying the waiting time of occurrence (such as tumor occurrence, etc.) is a renewal Weibull Process.

By taking this assumption into account we can reach a model, which has not been used before. Our model is different, because we use the Weibull process and order statistics to construct this model. For this reason, it can be stated that this study may bring some new perspectives in the field of carcinogenic and toxical materials.

Our derived model is our working model in order to estimate the optimum safe dose ξ. Finally, we apply the procedure by using simulated data on computer according to the underlying model and distribution. Then we obtain reasonable estimation of optimum safe dose.

For instance, as shown in Table 5.2 when test animals are exposed to a dose of 12.1 it is calculated that probability of time to tumor is 0.99999. As a result of simulation study, estimated safe dose (ξ=1.932) given to the test animals decreases the mentioned probability to 0.8832. This denotes that estimated dose decreases the probability of time to tumor.

This model equation may play a considerable role in determining the safe dose especially in food and drug sectors, which use carcinogenic substances as additives.

7. Further Research

Dose response models can be an important part of the quantitative cancer risk assessments supporting management and regulatory decision making. Current dose response models have limited biological rationale and tend to greatly over-simplify the carcinogenic process. While complete understanding of carcinogenic mechanisms and all encompassing models are still beyond our grasp, new approaches to dose response modeling can provide opportunities for these models to incorporate more scientific information. A new family of dose response models called the Individualized Response Models is introduced and shown to provide such opportunities. The models allow for the use of more biologically relevant dose scales such as those provided by physiologically based pharmacokinetic models of the absorption, delivery, metabolism, and elimination of a chemical as well as research on cell turnover rates, repair mechanisms, and immune system responses even if these phenomena are age-dependent.

This model may be improved by using the pharmacokinetic model. In our models x represents the effective safe dose. If we assume that the real effect of the exposed dose or administered dose D_A, is a pharmacokinetic model transform for D_A, we can use a pharmacokinetic model given in (Anderson, M.W., etal 1989) which is in the form,

$$\xi = \frac{\phi_1 \xi_A}{\phi_2 + \xi_A} \tag{7.1}$$

Where ξ_A is the administered safe dose and are parameters. Equation (4.8) becomes

$$\xi = \frac{\phi_1 \xi_A}{\phi_2 + \xi_A} = \frac{1}{\hat{\beta}} \frac{\log\left(\log\left(\frac{1}{\mathrm{Tol}(\tau)}\right)\right)}{\log\left(\frac{t}{\hat{\theta}}\right)} \tag{7.2}$$

Solving Equation (7.2) for ξ_A,

$$\hat{\xi}_A = \frac{\hat{\phi}_2 \log\left[\log\left(\frac{1}{\mathrm{Tol}(\tau)}\right)\right]}{\hat{\phi}_1 \hat{\beta} \log\left(\frac{t}{\theta}\right) - \log\left[\log\left(\frac{1}{\mathrm{Tol}(\tau)}\right)\right]} \tag{7.3}$$

The estimation of the pharmacokinetic model parameters f_1, f_2 must be obtained from a study on the pharmacokinetic phenomena of the substance under consideration by a specialist in this field.

Clearly, if in equation (7.3) the true θ, β, ϕ_1, ϕ_2 were replaced by their estimators and the unique root ξ of (7.3) computed, this would represent the MLE of the optimum safe dose ξ which is based on pharmacokinetic models.

REFERENCES

C.Lu Frank, Jr.R.L.Sielken, ´Assessment of safety/risk of chemicals: inception and evolution of the ADI and dose response modeling procedures', *Toxicology Letters*, 59(1991), pp.5-40.

D.D.Boss, C.Brownie, ´Mixture Models for Continuous Data in Dose-Response Studies When Some Animals are Unaffected by Treatment', *Biometrics*, 47(1991), pp.1489-1504.

H.O.Hartley, Jr.R.L.Sielken, ´Estimation of "Safe Doses" in Carcinogenic Experiments', *Biometrics*, 33(1977), pp.1-30.

Jr.R.L.Sielken, ´Useful Tools for Evaluating and Presenting More Science in Quantitative Cancer Risk Assessments', *Toxic Substances Journal*, 9(1989), pp.353-404.

Jr.R.L.Sielken, ´Incorporating More Science into Cancer Dose-Response Extrapolations, *Toxic Substances Journal*, 11(1990), pp.87-94.

J.Van Ryzin, K. Rai, *The Use of Quantal Response Data to Make Predictions, in The Scientific Basis of Toxicity Assessment* (New York: Elsevier North-Holland, 1979).

L.J.Bain, M. Engelhardt, *Statistical Analysis of Reliability and Life Testing Models Theory and Methods* (New York: Marcel Dekker, inc, 1991).

M.W. Anderson, D.G. Hoel, N.L.Kaplan, ´A General Scheme for the Incorporation of Pharmacokinetics in Low-Dose Risk Estimation for Chemical Carcinogenesis: Example-Vinly Chloride', *Toxicology and Applied Pharmacology*, 55(1980), pp.154-161.

M.D.Finkelstein, A.D.Schoenfeld, ´Analysis of Multiple Tumor Data from a Rodent Carcinogenicity Experiment', *Biometrics*, 45(1989), pp.219-230.

N.E. Day, ´The Armitage-Doll Multistage Model of Carcinogenesis', *Statistics of Medicine*, 9(1990), pp.677-679.

P.Armitage, ´The Assessment of Low-Dose Carcinogenicity', *Biometrics*, supplement (1982), pp.19-129.

P.Armitage, R.Doll, ´A Two-Stage Theory of Carcinogenesis in relation to the age Distribution of Human Cancer', *British Journal of Cancer,* 8(1957) pp.1-12.