METHODS FOR LOW DOSE RISK EXTRAPOLATION BASED ON LOGISTIC DOSE RESPONSE MODEL

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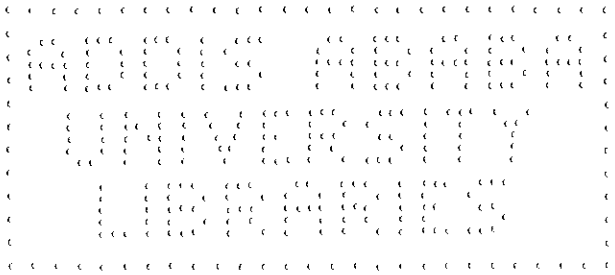
Abstract

Many methods of low dose risk assessment based on the popularly used dose response models have been suggested. The estimates of risk by the different methods were observed to differ largely. In this paper, two alternative approaches of low dose risk assessment are suggested. Both methods are based on the logistic dose response model. The underlying principle in both approaches is to make the lower tail of the logistic curve heavier. The performances of the methods are compared against standard logistic estimates and linear extrapolation estimates based on logistic model by the Monte Carlo method.

The results indicate that the performance of one of the new approaches is superior when the true dose response model is Multihit or Logistic. Linear extrapolation is the best method when the underlying model is Onehit, Multistage or Weibull. The performances of the estimators are observed to depend on the choice of number of animals per dose group and risk level to be estimated.



1. Introduction

Human populations are endangered by their exposure to a variety of naturally occurring or added substances that are found to have serious toxic effects on experimental animals and consequently are harmful to humans (Rai and Van Ryzin, 1981). Definitely many of these substances have beneficial effects as well. Hence, one should try to balance the magnitude of the risk against the benefit conferred by the substances.

Many efforts have been made to quantify the risk associated with a given exposure. (See for example: Copenhaven and Mielke, 1977; Crump, 1979; Krewski, Murdoch and Dewanji, 1986; Krewski, Murdoch and Withey, 1989; and Crump, 1996).

Among the multitude of methods that have emerged so far the oldest is the toxicological procedure which attempts to directly estimate the risk of a given dose of exposure by administering the dose directly to experimental animals. The large number of animals required to obtain any toxic response at low dose levels makes it prohibitively expensive to estimate risk directly at the expected human exposure levels. For instance, to detect one in one million level, one would need one million animals and even then there are chances that a good estimate may not be found.

Statistical methods for low dose risk estimation involve the use of a mathematical model based on a dose response data obtained from experiments on laboratory animals. A variety of mathematical models have been devised to relate exposure dose with response probability. Many authors have noted that different models may fit the experimental data set equally well but give different result when used to extrapolate risk at dose level well beyond the experimental range. Many approaches of risk estimation based on these models have been

introduced. However, no particular guideline pertaining to the selection of the appropriate model and method of risk extrapolation has received global acceptance.

In this paper alternative methods of risk extrapolation are suggested and the performance of these methods are thoroughly examined. The paper is organized into five chapters. The second chapter describes dose response modeling and discusses the problem of low dose risk extrapolation along with the contributions made by other researchers. The third chapter is concerned with the statement of the objective of the research and methods used to achieve the objectives. The results of the study are presented and discussed in chapter four. Chapter five summarizes the findings of the study.

2. Review of Literature

2.1. Introduction

Introductory description of dose response modeling and some related works on risk assessment are covered in this chapter. Literature in the area is meager. I have been greatly helped by the Medline bibliographic information database in the identification of relevant literature.

The chapter is divided into six sections including the present one. The second section defines dose response modeling and describes the commonly used dose response models with the theoretical rationales for their emergence. The third section briefly discusses the methods of incorporating spontaneous background response to the dose response model. Section four outlines risk estimation procedure covered in the literature. Section five reviews works related to the low dose extrapolation problem. The last section contains some concluding remarks.

2.2. Dose Response Models

Epidemiological and animal bioassay data constitute the two sources of data for risk estimation. Each of these sources has its limitation. Epidemiological data is superb for assessing the human risk of exposure when good data are available. However such data are usually unavailable for new substances and for existing substances it is often difficult and expensive to gather. Furthermore, even when data have been gathered, it is hard to determine retrospectively the average exposure of any individual. It is also extremely difficult to separate the effects of confounding factors, for example exposure to other substances and life style risk factor, from the effect of low dose repeated exposure to a single substance under study. Epidemiological data when available, should however be used to supplement, support

or modify the results of animal studies. (Van Ryzin,1980; Armitage,1982; Zeilinski et al., 1996).

The typical animal bioassay is carried out with groups of animals given exposure to toxic substance at fixed dose levels. At the end of the study, the number of animals showing toxic response of interest (for example: tumor, death, occurrence of disease) is recorded. The type of the data obtained from such an experiment is shown below.

Table 1: Quantal response data from animal bioassay

Dose Level	0	d_1	d_2	...	d_m
Number of animals Tested	n_0	n_1	n_2	...	n_m
Number of animals with toxic response	x_0	x_1	x_2	...	x_m

In the table dose level zero represents the control group and the other dose levels are in increasing magnitude ($d_1<d_2<...<d_m$). The animals are randomly assigned to the dose levels and all factors between animal groups are controlled with only the dose levels varying.

The translation of animal experimental data to humans poses a number of problems. First, laboratory testes are conducted at relatively high doses and it is often necessary to extrapolate from these results to lower doses that correspond to anticipated human exposure levels. Second, it is important to consider interspecies differences when extrapolating between the animal species used in laboratory studies and humans. And third, it may be necessary to extrapolate from a route of exposure chosen for experimental practicality to a different route by which humans may be exposed. Methods for dealing with the later two problems are discussed in Van Ryzin (1980) and Krewski, Murdoch and Withey (1989).

Risk estimates from animal assay data are obtained by using dose response models. A dose response model is a function given by P(d) which relates the probability that an animal under

study at dose level d will show the toxic response under consideration. In the absence of a background response and threshold dose, such a model will have P(0)=0 and P(d) > 0 for d>0 and will increase as the dose increases. A typical dose response curve is shown in the figure below.

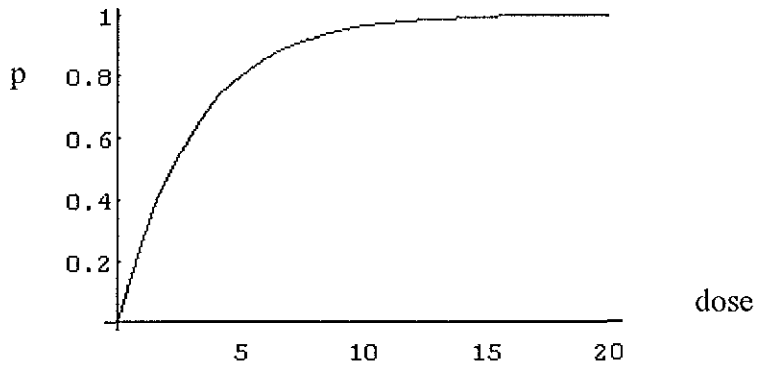


Figure 1: A typical dose response curve

From the bioassay experiment the likelihood of obtaining the data as given in the table above can be written as:

$$\prod_{i=0}^{m}\binom{n_i}{x_i}(P(d_i))^{x_i}(1-P(d_i))^{n_i-x_i}.$$

This likelihood is maximized with respect to the parameters of P(.) to get the maximum likelihood estimators of the parameters. In most cases the maximized likelihood equations cannot be solved analytically and, hence, iterative numerical methods are used.

The functional form of the dose response curve, P(d), can be chosen in two ways. These are the tolerance distribution method and the Biological method.

2.2.1. Tolerance Distribution (Mathematical) Models

The underlying principle of the tolerance distribution approach is based on the notion that an animal responds to a given dose level if that dose level exceeds its tolerance level (Collet, 1992; Krewski and Van Ryzin, 1981). If we let T to be the random variable associated with the tolerance distribution of the animal population from which the trial animals are drawn, the probability that an individual animal responds to dose d is given by:

$$P(d)=P(T<d) = \int_{-\infty}^{d} f(t)dt = F(d)$$

where f and F, respectively, are the probability density function (PDF) and cumulative distribution function (CDF) of T.

It is not in general possible to specify a given cumulative distribution that serves as a tolerance distribution of any test animal population and for any toxic substance. However, symmetric CDF's are naturally good choices. For some substances, however, the tolerances of some animals could be very high and, thus, make the assumption of symmetry implausible. In such cases taking the logarithms of the dose will bring symmetry. A general class of mathematical model is given by:

$$P(d)= F(\theta_1 + \theta_2 \log d).$$

Logistic and Normal distributions are possible choices for a tolerance distribution. Choosing logistic distribution gives rise to the Logistic model. For the Logistic model we have:

$$F(x) = [1 + e^{-x}]^{-1}$$

On the other hand choosing normal distribution yields the Probit dose response model.

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

Taking F(x) = 1-exp{-exp(x)}, which is the extreme value distribution, leads to the Weibull model.

Method of estimating the parameters of these models and the properties of the estimators are discussed in Finney (1971), Hosemer and Lemeshow (1989), Collet (1991), Aldrich and Nelson (1984), Mc Cullagh and Nelder (1989) and Cox and Snell (1992).

Copenhaven and Mielke (1977) have suggested a family of symmetric tolerance distributions. The family, which is designated as the Omega distribution, is defined by the following relations.

$$P = F(d(P))$$

$$f(d(P)) = 1 - |2P-1|^{\nu+1}$$

$$d(P) = \int_{0.5}^{P} \frac{dz}{f(d(z))}$$

for $0<P<1$ and $\nu>-1$.

The resulting model, termed as Quantit model, is given by

$$h_\nu(P_i) = \theta_0 + \theta_1 d_i; \text{ where } h_\nu(P_i) = \int_{1/2}^{P_i} (1-|2z-1|^{\nu+1})^{-1} dz$$

They indicated, in particular, this distribution reduces to a double exponential distribution when $\nu=0$, a logistic distribution when $\nu=1$ and a uniform distribution in the limiting case, $\nu \to \infty$. They also discussed a method of estimating the parameters and standard errors of the estimates.

2.2.2. Biological (Mechanistic) Models

Biological or mechanistic models are based on the notion that for each animal, a positive response is the result of the random occurrence of one or more biological events (Krewski and Van Ryzin, 1981). The Onehit, Multihit and Multistage are the popular models from this category.

The Multihit model has emerged from the hit theory suggested by Iverson and Arley and the particle theory discussed by Cornfield (Rai and Van Ryzin, 1981). The basic idea of these theories is that the biological process in question is assumed to be governed by a certain 'control center' situated in the nucleus of the cell. Excitation of this cell by being hit by the particles of the applied agent makes the cell change its behavior in a specific way that depends on the number of hits and the agent. The number of hits over a fixed time period due to dose d, denoted by X(d), can be taken as a particular realization of the general homogeneous poisson process and has the probability distribution given by:

$$P(X(d) = r) = \frac{(\theta_2 d)^r e^{-\theta_2 d}}{r!};\ r=0,1,2,\ldots.$$

If we assume that a toxic effect results from at least θ_1 hits occurring over a fixed period of time, where θ_1 is unknown positive integer, then:

$$P(X(d) \geq \theta_1) = \sum_{i=\theta_1}^{\infty} \frac{(\theta_2 d)^i e^{-\theta_2 d}}{i!} = \int_0^{\theta_2 d} \frac{t^{\theta_1 - 1} e^{-t}}{(\theta_1 - 1)!} dt = \int_0^{d} \frac{\theta_2^{\theta_1} t^{\theta_1 - 1} e^{-\theta_2 t}}{\Gamma(\theta_1)} dt \ ,\ 0<t<\infty$$

The resulting dose response model defined by:

$$P(d) = \int_0^{d} \frac{\theta_2^{\theta_1} t^{\theta_1 - 1} e^{-\theta_2 t}}{\Gamma(\theta_1)} dt$$

is known as the Multihit model.

If only one hit is required to produce a response the Multihit model reduces to $P(d)=1-e^{-\theta_2 d}$; $\theta_2>0$, known as the Onehit model. The Multihit model can also be thought as a mathematical model for the gamma tolerance distribution. The estimation procedure and properties of the multihit model are discussed in Rai and Van Ryzin (1979, 1981).

Another stochastic model is based on the assumption that the induction of irreversible self-replicating toxic effects such as carcinogenesis is the result of the occurrence of a number of different random biological events, with the age specific rate of occurrence of each event linearly related to dose. This and other assumptions lead to the Multistage model which is of the form:

$$P(d)=1-e^{-\sum_{i=1}^{J}\theta_i d^i} \quad ; \qquad \theta_i \geq 0,\ i=1,2,\ldots,J;$$

where J denotes the number of events or stages.

This model has been explored by Crump, Guess and Deal (1977), Guess and Crump (1978), Crump (1979) and Cornfield, Rai and Van Ryzin(1980). It can be easily seen that the Multistage model reduces to the Onehit model for J = 1.

Van Ryzin and Rai (1987) developed a quantal response dose response model based on the hit theory and incorporation of nonlinear kinetics governing the transformation of the administered dose to actual dose. The model is given as:

$$P(d)=1-\exp\{-[\theta_1+\theta_2(\frac{d}{1+\theta_4 d})^{\theta_3}]\}$$

This model specializes to Onehit model if $\theta_3 = 1$ and $\theta_4 = 0$, and the Weibull model if $\theta_4 = 0$. The statistical inference procedures including estimates of the parameters, their large-sample properties, goodness-of-fit test, likelihood ratio test and the resulting low dose extrapolation procedures were also given.

2.3. *Incorporation of Background*

In many experiments the response of interest can also occur spontaneously in control animals. This kind of response is known as background response and may be assumed to be independent or additive, in a stochastic manner, to the induced response.

If the spontaneous and induced responses are assumed to be independent, then the probability of observing a response of either type at dose d is given by:

$$P^*(d) = \gamma + (1-\gamma)\, P(d)$$

where $0 < \gamma < 1$ denotes the spontaneous response.

Under the additivity assumption, the background response rate may be considered as arising from an effective background dose $\delta > 0$, with

$$P^*(d) = P(d + \delta).$$

A combination of both independent and additive background may be represented by the model:

$$P^*(d) = \gamma + (1-\gamma)P(d + \delta).$$

In the presence of background response, the estimation of γ and parameters of P(.) is carried out by replacing P(d) by P*(d) in the likelihood function given in section (2.2.).

2.4. Low Dose Extrapolation

The estimate of added risk over background for a dose level d_0 that is below the smallest experimental dose is defined as:

$$\hat{\Pi}(d_0) = \hat{P}^*(d_0) - \hat{P}^*(0).$$

If there is no spontaneous background response, the estimate of the risk of dose d_0 will be $\hat{P}(d_0)$. On the other hand, the estimate of the dose that induces an added risk probability of π is d* such that $\pi = \hat{\Pi}(d^*)$. The dose d* is sometimes known as the Virtually Safe Dose (VSD) for the risk level π. Other point estimates and confidence interval estimates of VSD and risk at a small dose d_0 are found in Krewski and Van Ryzin (1981).

Several alternative methods of risk estimation have been covered in the literature. The use of 95% upper confidence bound on the true risk is advocated by many researchers (see for example Crump, 1996). Mantel et al. (1975) proposed the use of the point estimate of risk from the model in or near the experimental range followed by linear extrapolation based on other judgement. Krewski, Murdoch and Dewanji (1986) believes that the assumption of low dose linearity can be advanced by a number of arguments and suggested the use of linear extrapolation irrespective of the shape of the actual dose response. Other methods are also provided in Crump, Guess and Deal (1977), Crump (1979), Hartely and Sielken (1977), Krewski, Murdoch and Withey (1989) and Crump (1996). Some of these methods are briefly discussed in the next section.

2.5. *The Low Dose Extrapolation Problem*

Several models have come into existence for modeling the relationship between dose and response. Many researchers noted that two or more models may fit the experimental data quite well but give estimates of risk out side the experimental range that differ in many orders of magnitudes. In other words, the risk estimates highly depend on the mathematical model assumed for the underlying dose response curve.

Copenhaver and Mielke (1977) fitted Quantit, Logistic and Probit models to twenty two published data sets in order to compare the performances of the models. The values of the likelihood functions were nearly the same for the three models when $\hat{v}=1$. And also the ED50 (a dose level that effectively induces response on 50% of the subjects) estimates were found to be in close agreement for all data sets. However, pronounced difference was observed between the three method in estimating ED99 for the data sets with $\hat{v}$ close to -1 or much larger than 1. Since the omega distribution is much lighter (heavier) in the tails than the logistic distribution when v is greater (less) than 1, the logistic model will very likely over (under) estimate ED99 and its standard error. The fact that omega distribution represents a family of symmetric distributions motivates its use as presumably being capable of providing good fit for a wide variety of quantal response assay data.

For the Multistage model, Crump, Guess and Deal (1977) provided procedures for obtaining confidence intervals for risk probability and VSD based on the asymptotic properties of the maximum likelihood estimates. With the aid of a simulation study and envelope curves, they have learned the conservative nature of their confidence intervals. Using four basic data sets, it has been illustrated that the upper bounds of the asymptotic intervals vary with the choices of the number of stages. They have also noted that the upper confidence bounds of added risk

linearly decrease with dose. Thus the use of upper confidence bound on added risk tantamount to linear extrapolation.

When the degree of the polynomial of the Multistage model is to be determined by the data, Guess and Crump (1978) have observed that a dose response curve with near linearity in the low dose range fits the data better than curves that are extremely flat (Probit-like) in the low dose area. Even if the use of flat dose response curve is supported by the data, Guess and Crump advise to let Multistage infer that instead of imposing a flat dose response model. However, they admit the possibility of getting a linear extrapolation like estimates if upper 90% or 95% confidence bounds are used. The large scale (1000 animals per dose) simulation experiment they conduced has shown them the possibility of reaching at a linear model purely by chance whereas the true model is flat in the low dose area, or vice versa.

Crump (1979) reviewed briefly some methods for estimating risks of exposures for carcinogens. According to him, the Mantel and Bryan method which is based on Probit model has not been derived from a stochastic model of carcinogenesis. The other method he discussed was that suggested by Hoel et al. (1975). This method involves basing extrapolation on a linear relationship from an upper confidence bound on the response at a single experimental dose to a lower confidence bound for risk at zero dose. The method proposed by Hartley and Sielken (1977) constructs upper confidence bound on extra risk by dividing the data into smaller data groups and computing maximum likelihood estimates of the parameters in each group. Crump remarked that in order that a low dose extrapolation to have any validity, it is necessary that the dose response model relate to the actual carcinogenesis process which is not sufficiently well understood. In this connection, Crump identified some of the important areas of research which may prove helpful in understanding mode of actions of carcinogens. The areas identified include experimental design problems,

statistical procedures for use with time-to-occurrence data and mathematical models that incorporate such biological features as pharmakokinetics of carcinogens, synergistic effects, DNA repair, susceptible sub-populations and immune reactions.

Cornfield, Rai and Van Ryzin (1980) surveyed scientific basis for low dose risk assessments. They criticized a toxicological procedure which requires the postulation of a no-effect level and the use of a safety factor to extrapolate downward from the presumed no-effect level. This approach is defeated on grounds of dependence on the number of animals studied and failure to take account of the slope of the dose response curve at low doses. In addition, the assumption of existence of true no-effect (threshold) level may not be feasible for all substances. However, based on individual tolerance (threshold) levels, the problem of risk extrapolation can be approached statistically. In relation to that, they discussed the implications of the use of Onehit, Multihit and Multistage models to low dose extrapolation. Onehit model usually provides poor fit to the data set. Moreover, at low dose levels (at levels leading to less than 5% incidence rate) the one hit curve reduces to an essentially linear relationship between dose and response. This may not be acceptable for the reason that it leads to a very conservative estimate. The Multihit and Multistage model, seem to be more desirable due to their flexibility in the sense that low dose linearity results only if evidenced by the data at high doses (also Van Ryzin , 1980). The comparison of Multistage and Multihit models fitted to nine data sets revealed that with the exception of one data set, the Multistage model led to virtual safe dose (VSD) estimates lower than the Multihit model by anywhere between 2 to 50 folds. When 97.5% lower confidence limits on VSD were compared, the difference became more pronounced (20 to 1000 folds). The result for the other data set, which exhibited concavity in the experimental range, is in the reverse direction. Thus the use of Multistage in conjunction with lower confidence bound lead to prudent estimates which are

very similar to linear extrapolation. In the conclusion, Cornfield et al. advocated for some kind of compromise to be made in view of the benefit that can be conferred by the substance.

Van Ryzin (1980) reviewed methodologies of quantitative risk assessment of environmental carcinogens. Onehit, Multistage, Multihit and Weibull models were compared for low dose risk extrapolation. In the three data sets considered, the estimates of VSD had the ordering: Onehit < Multistage < Weibull < Multihit. The reason for this is that the Multistage, Multihit and Weibull models are all responding to nonlinearity in the data in the observed range and compensate for this by higher order dose terms in the Multistage model and by power of dose in Multihit and Weibull models. For two data sets in which the coefficients for the linear dose term of the Multistage model were nonzero, the estimate of Onehit and Multistage model agreed well. Van Ryzin has further noted that the VSD estimates from the Multihit and Weibull models are an order of magnitude larger at risk level 10^{-4} and two to three orders of magnitude larger at 10^{-8} level. The reason is that in the low dose range the Multihit and Weibull models do not have a linear term and behave approximately as power of dose multiplied by a constant factor. For the other data set in which the linear and quadratic term in the Multistage model vanish, the VSD estimates from Multistage, Multihit and Weibull models are from two order of magnitude larger at 10^{-4} to six orders of magnitude larger at 10^{-8} than those of Onehit model. Another method that can be used with any model is to extrapolate fully with the model to risk level 10^{-2} to 10^{-4} for instance, and then extrapolate further by a linear extrapolation. Finally, it was recommended that how conservative one wishes to be in the extrapolation should be determined by public health, biological, economic and other concerns and not by a blind choice of the Onehit (most conservative) model when it dose not fit the data.

Van Ryzin (1982) summarized the low dose behavior of the six commonly used dose response models. The summaries are given in Table 2.

Table2: Low dose behaviors of commonly used dose response models

Model	Function	Low dose behavior	
Probit	Probit(P(d))=$\theta_1+\theta_2 \log d$	$\lim_{d\to 0}\left(\frac{P(d)}{d^{\theta_2}}\right)=0$ Approaches zero faster than any power of d	
Logistic	Logit(P(d))=$\theta_1+\theta_2 \log d$	$e^{-\theta_1}d^{\theta_2}$	$\theta_2<1$ concave $\theta_2=1$ Linear $\theta_2>1$ convex
One hit	$P(d)=1-e^{-\theta_2 d}$	$\theta_2 d$	linear
Multi hit	$P(d)=\int_0^{\theta_2 d}\frac{t^{\theta_1-1}e^{-t}}{\Gamma(\theta_1)}dt$	$\frac{(\theta_2 d)^{\theta_1}}{\Gamma(\theta_1+1)}$	$\theta_1<1$ concave $\theta_1=1$ linear $\theta_1>1$ convex
Multistage	$P(d)=1-e^{-\sum_{i=1}^{\infty}\theta_i d^i}$	$\sum_{i=1}^{k}\theta_i d^i$	$\theta_1>0$ linear $\theta_1=0$ convex
Weibull	$P(d)=1-e^{-\theta_1 d^{\theta_2}}$	$\theta_1 d^{\theta_2}$	$\theta_2<1$ concave $\theta_2=1$ linear $\theta_2>1$ convex

From the low dose behaviors given in the table above, Van Ryzin gave a highly predictable ordering of risk estimates from the six models. For convex data set; Probit < Multihit ≈ Logistic ≈ Weibull < Multistage < Onehit. And for a concave data set: Probit < Onehit < Multistage < Weibull ≈ Logistic ≈ Multihit. The twenty data sets (19 convex and one concave) Krewski and Van Ryzin (1981) considered confirmed this result. Krewski and Van Ryzin also remarked that the manner in which background is incorporated will have a definite bearing on the low dose shape of the dose response curve (Rai and Van Ryzin, 1981).

Using 33 one and two stage models, Portier and Hoel (1983) observed the large sample distribution of the maximum likelihood estimator of virtually safe dose (VSD). According to them, the asymptotic distribution of virtually safe dose are normal in the cases where the Multistage parameters have non zero expectations, and are skewed otherwise. With the aid of

a Monte Carlo simulation studies, they observed that the approximation given by the asymptotic theory is not good if applied to small bioassays. The simulation studies illustrated the very large estimation error that is possible when statistical routines are only used in model selection. Biological theory should also be used in model selection.

For the four parameter dose response model they developed, Van Ryzin and Rai (1987) have shown that the parameter θ_3 governs the behavior of the dose response curve in the low dose range. The curve is approximately linear if $\theta_3 = 1$, concave if $\theta_3 < 1$ and convex if $\theta_3 > 1$. The model fitted well three data sets but it yielded considerably different risk estimates than the Onehit or the Weibull models.

Krewski, Murdoch and Withey (1989) argue that in order to estimate carcinogenic risk associated with low levels of exposure, some form of reasonably robust estimation procedure that incorporates the assumption of low dose linearity is desirable. They remarked that one approach with such assumption is the model free approach proposed by Krewski, Murdoch and Dewanji (1986). According to them, this model avoids the need for the specific parametric assumption of the Multistage model but gives similar results as the Multistage model and hence the method is advantageous in cases where the Multistage model does not fit the data well.

Crump (1996) suggested that with the Multistage model lower confidence bounds on the VSD as well as upper confidence bounds on extra risk invariably vary linearly with risk or dose at low doses. Due to that the Multistage model was named as Linearized Multistage (LMS) model. The 95% upper confidence bound on extra risk at dose d is approximately given by the linear relation $\theta_1^* d$ where θ_1^* is the 95% upper confidence bound on the linear coefficient θ_1. He further discussed that whenever the true dose response is linear at low doses and the

low dose slope extends into the experimental range, risks predicted by the LMS will generally be within a factor of two of the true risk. However, if the true dose response is non-linear, then the LMS approach may overestimate the true risk by orders of magnitude. Crump believes that this problem cannot be overcome by selecting a more flexible family of models that incorporates non-linear models. Because true dose responses that are linear in the low dose range can give rise to data that appear to be non-linear, use of a more flexible model could cause the low dose risk to be underestimated by many orders of magnitude in some cases. Biologically based models will also have this limitation unless the underlying biology is sufficiently well understood that the low dose shape of the dose response curve can be predicted accurately. Thus, according to Crump it does not appear possible at present to develop a quantitative approach that would be generally applicable and that would offer significant improvements upon the crude bounding estimates of the type provided by the LMS model.

2.6. Summary

A number of models have been introduced for modeling dose responses. The properties of risk estimates from these models have also been studied. Risk extrapolation from different models may differ largely. Statistical routines alone could not help much in model selection. To that effect several approaches of extrapolation have been devised. Conservative approaches which assume low dose linearity, for instance those based on the Multistage or Onehit models, seem to have gained momentum. Many believe that low dose linearity can be supported by a number of arguments. One possible rationale accepted by advocates of low dose linearity is the assumption of additive background risk. On the other hand, many substances can have beneficial effects as well. Thus blind conservatism may result in a loss of potential benefit which may outweigh the reduction in risk. Moreover, underestimation can

also result if the true dose response is concave in the low dose area. Thus how conservative one wishes to be in extrapolation should be determined by public health, biological, economic and other social considerations.

Many researchers agree that incorporating biological information into the model helps to induce a better understanding of the problem. Among others, the effect of background dose information, kinetic transformation of administered dose to effective toxic dose, exposure time and joint effects of toxicants are cited.

3. Methodology

3.1 Objective

In the beginning of chapter two, the commonly used dose response models were introduced along with the theoretical rationales for their popularity. The problem of low dose extrapolation, which underlies the core objective of this research project, and its root causes have been discussed.

In spite of the presence of a variety of models for dose response relationships, the logistic model is widely applied for a number of reasons. The procedure for fitting logistic model is, among other things, relatively simple and available in most commercial software. Besides, the lack of definite biological theory helpful in guiding which model is appropriate in a particular situation makes it unworthy of opting for a more complex alternative to the logistic model. In addition, many authors have shown with many data sets that different models may fit the data sets equally well in the experimental range. However, these models have been noted to give quite differing answers when used to extrapolate risk outside the experimental range. A typical example taken from Van Ryzin (1980) is given below to illustrate this point. The data set is obtained from a chronic study in rats in which the response was the occurrence of liver tumor based on exposure to Dimethylnitrosamine (DMN).

Table 3: The Dimethylnitrosamine data set

Dose Level (ppm)	0	2	5	10	20	50
Number of Test animals	29	18	62	5	23	12
Number of Responses	0	0	4	2	15	10

The Onehit, Multistage, Multihit, and Weibull models fitted to this data set were also given. I fitted logistic model to the data set using SAS software. The fitted curves and their graphs are given below.

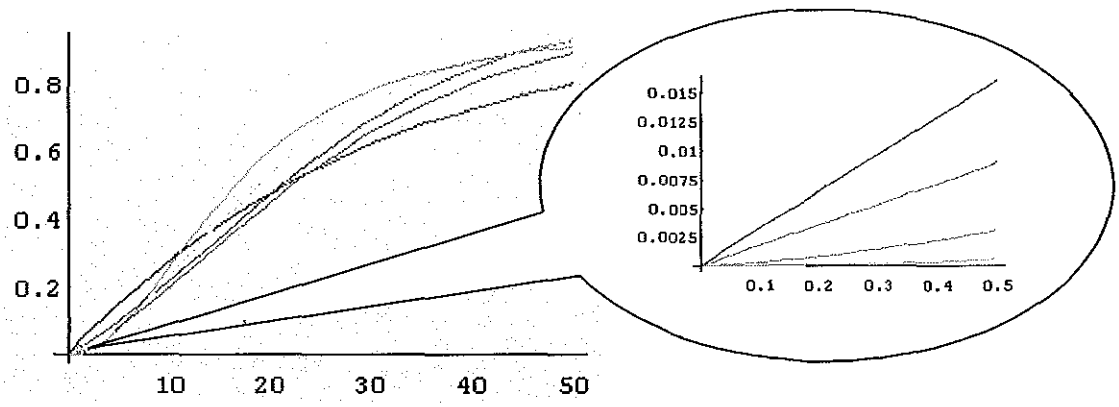


Figure 2: Graphs of the dose response models fitted to Dimethylnitrosamine data set

Table 4: Equations of the five models fitted to the Dymethylnitrosamine data set

Model	Estimated Functions	Color
Onehit	$P(d) = 1 - e^{-0.03249\,d}$	----
Multistage	$P(d) = 1 - e^{-0.01766\,d - 0.000728\,d^2}$	----
Weibull	$P(d) = 1 - e^{-0.00828\,d^{1.43}}$	----
Multihit	$P(d) = \int_0^{0.08538\,d} \frac{u^{0.91} e^{-u}}{\Gamma(1.91)} du$	
Logistic	$P(d) = [1 + e^{-(5.9205 + 2.1168 \mathrm{Log}(d))}]^{-1}$	----

For each of the models fitted, the estimate of the spontaneous response rate (γ) is zero. Low dose extrapolation of response probabilities at five dose levels are given in the table that follows.

Table 5: Low dose extrapolations from the five models given in Van Ryzin (1980)

Dose	Onehit	Multistage	Weibull	Multihit	Logistic
0.0001	3.248995E-06	1.766006E-06	1.577721E-08	1.130377E-10	9.152917E-12
0.001	3.248947E-05	1.766057E-05	4.246491E-07	9.187586E-09	1.197732E-09
0.01	3.248472E-04	1.766572E-04	1.142952E-05	7.464185E-07	1.567326E-07
0.1	3.243728E-03	1.771709E-03	3.075839E-04	6.036607E-05	2.050929E-05
1	3.196787E-02	1.821997E-02	8.245815E-03	4.666375E-03	2.676674E-03

From the table it can be seen that the risk estimates from the five models have the ordering: Logistic < Multihit < Weibull < Multistage < Onehit for all the doses considered. This ordering confirms to the ordering suggested by Krewski and Van Ryzin (1981). The discrepancy in the risk estimates increases as the dose level gets closer to zero. Near the experimental range the estimates agree reasonably well. It can also be observed that the use of logistic model leads to the most serious error if it is not the underlying model.

Albeit the arduous efforts of several prominent researches, a final solution to the problem is far from reached (Crump, 1996). The consensus advocates for the use of linear extrapolation based on a judiciously chosen model.

The principal objective in this research project is to indicate possible approaches for dealing with the problem of low dose risk assessment. The attempt will be to give insight into possible improvement that can be achieved by modifying the conventional logistic estimates. Estimators of low dose risk based on logistic regression are intuitively derived to amend the highly likely underestimation from logistic method and conservative overestimation from linear extrapolation. The performance of these estimators will be compared against the standard logistic estimate and linear extrapolation based on the logistic model. The dependence of performance of the estimators on sample size per dose group and the size of response probability to be estimated will also be explored.

3.2. Estimators Considered

Two new estimators are suggested. The motivations behind these estimators are purely intuitive. One of the estimators works by adding a point near zero dose. The other estimator is obtained by averaging logistic estimates computed by successively dropping observations

from the bottom end of the data set. The main idea of both the solutions is to make the lower tail of the logistic curve heavier.

To study the performances of the new estimators, the standard logistic estimator and linear extrapolation methods are also considered. The four estimators are described below one by one.

1. The Standard logistic Estimator

Logistic model is fitted to the experimental data set and that model is used to extrapolate response probability for doses below the smallest experimental dose. Herein after, this estimator is named as the "logistic estimator".

2. Linear Extrapolation

First the experimental data set is fitted to logistic model. Using the estimated logistic model, the response probability to the smallest experimental dose, d_1, is fitted. The estimate of the response probability for the dose d_0, which is below the smallest experimental dose, is given by:

$$\hat{P}(d_0) = \frac{\hat{P}(d_1)}{d_1} d_0$$

where $\hat{P}(.)$ is the fitted logistic equation.

3. Estimator Obtained by Adding a Point (AP)

The steps involved in this estimation procedure are:

Step 1: Logistic model is fitted using the experimental data set. Let the estimated model be:

$$\hat{P}(d) = \frac{1}{1 + e^{-(\hat{\alpha} + \hat{\beta} \log d)}}$$

Step 2: 95% Lower confidence bound, $(\log \hat{d}_L)$, of the log of dose, log d, which induces an arbitrarily chosen small risk level (say $P_o=10^{-8}$) is computed.

$$\log \hat{d}_L = \log \hat{d} - 1.96\sqrt{Var(\log \hat{d})}$$

$$\log \hat{d} = \frac{\log it(P_o) - \hat{\alpha}}{\hat{\beta}} =: g(\hat{\alpha}, \hat{\beta})$$

where $\text{logit}(P_0) = \log(\frac{P_0}{1-P_0})$

A standard result for approximating variance of the function of parameter estimates can be used to estimate $\text{Var}(\log \hat{d})$.

$$Var(\log \hat{d}) = \left(\frac{\partial g}{\partial \hat{\alpha}}\right)^2 Var(\hat{\alpha}) + \left(\frac{\partial g}{\partial \hat{\beta}}\right)^2 Var(\hat{\beta}) + 2\left(\frac{\partial g \partial g}{\partial \hat{\alpha} \partial \hat{\beta}}\right) Cov(\hat{\alpha}, \hat{\beta})$$

(see Mood, Graybill and Boes, 1974). Thus:

$$Var(\log \hat{d}) = \frac{1}{\hat{\beta}^2}\left[Var(\hat{\alpha}) + \left(\frac{\log it(P_0) - \hat{\alpha}}{\hat{\beta}}\right)^2 Var(\hat{\beta}) + 2\left(\frac{\log it(P_0) - \hat{\alpha}}{\hat{\beta}}\right) Cov(\hat{\alpha}, \hat{\beta})\right]$$

Using the corresponding estimates of $Var(\hat{\alpha})$, $Var(\hat{\beta})$ and $\text{Cov}(\hat{\alpha}, \hat{\beta})$, the estimate $\widehat{\text{Var}}(\log \hat{d})$ of $\text{Var}(\log \hat{d})$ can be obtained.

Step 3: Using $(\hat{d}_L, P_o)$ as an additional observation in the experimental data set, logistic model is fitted and is used to obtain risk estimates in low dose area.

4. Estimator Obtained by Dropping Points Successively (DPS)

Let $\hat{P}_j(d)$ be the logistic model fitted by dropping the last j observations. The estimates from $\hat{P}_j(d)$'s are combined using simple arithmetic mean.

$$\text{Mean} = \frac{\sum_{j=0}^{m-3} \hat{P}_j(d)}{m-2}$$

3.3. Methods and Materials

It is very difficult to study the performances of the estimators analytically, and hence, the Monte Carlo approach will be extensively used. Five different underlying models will be studied. In each case, we assume the true model is completely known and we try to study how reasonably well are the estimations close to the true value. The five models to be considered are the, Onehit, Multistage, Weibull, Multihit and Logistic. To take realistic values for the parameters, the estimates of each of these models when fitted to the dimethylnitrosamine data set given in section (3.1.) will be used as true models.

According to the results of Krewski and Van Ryzin (1981), except Onehit and Multistage, which have a linear shape in the low dose area, the other three models have low dose convexity. Because estimates of the spontaneous response rate is zero, taking those models estimated in section (3.1.) as true models has the implication of assuming the absence of background response. Consequently, the application of the findings of this research will be valid only when these assumptions are met. However, these assumptions are likely to be satisfied in many quantal response bioassay data sets. For instance, Van Ryzin (1982) has noticed that only one of the 20 data sets Krewski and Van Ryzin (1981) examined did have concavity in the experimental range.

3.4. The Monte Carlo Simulation Experiment

Realizations of random processes are the raw materials of classical statistical inference. An important way in which observations on random process may be used is in the development of statistical theory. An instance of this use may be in studying the performance of competing estimators. More recently such sampling experiment using computer generated samples,

known as Monte Carlo method, has become a common place in situations where the mathematics become intractable (Kennedy and Gentle, 1980).

Taking the number of animals per dose group to be the same three sizes per dose group (n_i=30, 50 and 100) are considered. A total of fifteen Monte Carlo simulation experiments one for each combination of a true model and sample size per dose group are conducted. In each case, the probabilities of response, $P(d_i)$, at each experimental dose are computed using the assumed true model. These simulation probabilities are tabulated in Appendix I.

Although conducting large number of simulation runs helps ensure the reliability of the results, a trial of 1000 simulation runs for n=30 case has proved no difference to that of 100 simulation runs. Hence, in each simulation experiment, hundred data sets were generated. Each data set is composed of simulated random samples from binomial distributions with parameters n and $P(d_i)$, i=1,2,...,5.

To compare the performances of the estimators, estimation of the response probabilities 10^{-6} and 10^{-4} are considered.

3.5. Evaluation of Estimators

The most commonly used measure of performance (closeness) of an estimator is the average squared error, or the mean squared error (MSE). An estimator with smaller MSE is better that one with larger MSE. The MSE of an estimator can be decomposed as the sum of the variance and the square of the bias. For MSE to be small both the variance and the bias should be small (Lindgren, 1976).

In a simulation study, empirical MSE, Variance and Mean can be computed as an approximation to the corresponding true values. The empirical values are computed as:

$$\text{MSE} = \frac{\sum_{i=1}^{N}(\hat{P}_i - P)^2}{N}$$

$$\text{Variance} = \frac{\sum_{i=1}^{N}(\hat{P}_i - Mean)^2}{N} \text{ and}$$

$$\text{Mean} = \frac{\sum_{i=1}^{N}\hat{P}_i}{N}$$

where $\hat{P}_i$ - is the estimate from the i^{th} simulation

N - is the total number of simulations and

P – is the true value to be estimated.

The MSE has a potential drawback of being very sensitive to extreme values. The minimum and maximum of the estimated values can be examined to see how likely MSE has been influenced by extreme values.

The empirical risks of the estimators, when used as a basis for making decision, can also be considered as a means of assessing the performance of the estimators. Since the objective of risk assessment is the protection of public health, decision based on an underestimate value leads to risking human lives, which is quite undesirable. To that effect, the use of $[\ln(\frac{\hat{P}}{P})]^2$ as a loss function is believed reasonable because as a result more weights are assigned to underestimation errors. More over, this measure is less sensitive to extreme errors.

The empirical risk is given by:

$$\text{Risk} = \frac{\sum_{i=1}^{N}\left(\ln(\frac{\hat{P}_i}{P})\right)^2}{N}$$

where $\hat{P}_i$, P and N are as defined above.

To take advantage of their visual impressions and easiness for comparison, the graphs of $\frac{\hat{P}_i}{P}$ will be plotted against the simulation trials. The frequency distributions of $\frac{\hat{P}_i}{P}$ will also be analyzed.

3.6. The Computer Programs

In the Monte Carlo study, there are two major tasks involved. These are generation of the data sets and computation of the estimates. The two tasks are coded as self-contained separate programs. In the programs double precision arithmetic is used. The validity of the programs were ensured by parallel runs with SAS and S-Plus packages and manual checks.

3.6.1. The Simulation Program

The program that generates the simulated data sets requires the following data inputs.

a. The number of animals (subjects) at each dose level

b. The probabilities of response at each dose level

c. The number of simulations to carry out

The first two inputs have to be supplied as binary files of integers and real, respectively. The third input needs to be entered through the keyboard. The program gives the simulated data sets as a binary file of array of integers. For generating the hundred data sets, it has been noticed that a maximum of five seconds are taken by the NEC 550D laptop computer. This model of computer is equipped with 8 MB of RAM and a Cyrix 586 processor running at 100 MHz.

3.6.2. The Estimation Programs

The programs, which do the estimations, take the inputs:

(a) The dose levels experimented

(b) The number of animals per dose group

(c) The simulated data sets

(d) The doses for which risk estimates are desired

The first input is a file of real numbers. The description of the next two are the same as those in section (3.6.1). The last one is keyboard input. The outputs of the programs go to files of array of real numbers. On the NEC 550D laptop computer, the program has been observed to take a maximum of ten seconds.

3.7. Algorithms

3.7.1. Sampling from the Binomial Distribution

Several alternative methods are available for obtaining a random sample from the Binomial distribution (Fishmann, 1979). The Bernoulli method, which is the simplest, is employed in this study. In the Bernoulli method a pseudo-random number U is generated from a uniform distribution defined over the interval (0,1). A variable X which takes the value 1 if $0 < U < p$ or 0 otherwise can be regarded as a random sample from a Bernoulli distribution with parameter p. The property that a binomial distribution with parameter n and p is the sum of n independent Bernoulli variables, each with parameter p, can be used to get a sample from Binomial distribution (Cooke, Craven and Clarke, 1990).

The uniform random sequence generator used is the one devised by Wichmann and Hill (1987). Wichmann and Hill first constructed three multiplicative congruential random sequence generators for a 16-bit machine and combined them to generate a single but better random sequence. The three multiplicative congruential generators are:

$$X_{i+1} = (171*(X_i \bmod 177) - 2*(X_i \operatorname{div} 177)$$

$$Y_{i+1} = (172*(Y_i \bmod 176) - 35*(Y_i \operatorname{div} 176)$$

$$Z_{i+1} = (170*(Z_i \bmod 178) - 63*(Z_i \operatorname{div} 178)$$

The lengths of the sequences X, Y and Z are 30269, 30307 and 30323, respectively. Dividing each element of the sequences by the respective length of the sequences changes the sequences into sequences of random numbers from uniform distributions defined over (0,1). The three sequences of uniform random numbers are combined into a single sequence by

adding the corresponding elements of each sequence and taking the fractional part of the sums. Wichmann and Hill asserted that the generator has passed all the tests it was subject to with flying colors.

The PASCAL version of this algorithm supplied by the authors is directly incorporated in the program that generates the experimental data sets.

3.7.2. Estimation of Logistic Model

The iterative Weighted Least Square algorithm given in Collet (1991) is used to fit logistic regression. According to the algorithm, the estimates of logistic parameters in the $(r+1)^{th}$ iteration is:

$$\hat{\beta}^{r+1} = (X'W_rX)^{-1}X'W_rZ_r$$

where $\hat{\beta}^r$ - is the vector $\begin{pmatrix}\hat{\alpha}_r \\ \hat{\beta}_r\end{pmatrix}$ of logistic parameter estimates

X - is an m x 2 matrix with a vector of 1's in the first column and a vector of the logarithm of experimental doses in the second column.

W_r - is an m x m diagonal matrix of iterative weights with the i^{th} diagonal element $w_i = n_i\hat{P}_i(1-\hat{P}_i)$ and $\hat{P}_i = \dfrac{1}{1+e^{-(\hat{\alpha}_r+\hat{\beta}_r \log d)}}$.

Z_r - is a vector with the i^{th} element $z_i = \hat{\eta}_i + \dfrac{\left(y_i - n_i\hat{P}_i\right)}{n_i\hat{P}_i(1-\hat{P}_i)}$ and

$\hat{\eta}_r = \alpha_r + \beta_r \log d_i$, and y_i is the number of animals responded in the i^{th} dose group.

The iteration stops when the difference between successive deviances does not exceed a pre-specified small number, say ε. An ε value of 10^{-9} is chosen in this study. For this value of ε, it has been observed that convergence occurs with a maximum of 7 iterations.

4. Results and Discussion

4.1. Introduction

As stated in the previous chapter, the results of the simulation study are described using empirical measures of closeness, frequency distributions and graphical means. The chapter is organized in three sections including this one. The second section outlines the results of the study. And the last section is devoted to discussion of the results

4.2. Results

The results for different underling models are put in separate sections. For each assumed true model, a consistent ordering is adopted in the presentation of the results. Table of measures of closeness along with the behavior of these measures as sample size per dose group (n) and the response probability to be estimated changes are pointed out. Next, few paragraphs and a table depicting the frequency distribution of the estimators follow. The scatter plots and features on the plots to which attention should be drawn are described in the end.

To facilitate ease of comprehension, estimation errors are sometimes explained in terms of orders of magnitudes. For example, if the true response probability is 10^{-6} and the estimator estimates it as 2.3×10^{-9}, we say the estimated value is less than the true value by three orders of magnitude. Similarly, if the true response probability is 10^{-6} and the estimated value is 6×10^{-4} ($600X10^{-6}$) we say the estimated value exceeds the true value by two orders of magnitude. If the true risk is one in one million and the estimated value is between 0.1 and 10, exclusive, in one million, we say the estimate and the true value agree in terms of order of magnitude. In short, this approach amounts to expressing the ratio of the estimated value to the true value in scientific notation and comparing the powers.

The classes of the frequency distributions are made logarithmically spaced. The classes used are $\leq 10^{-2}$, 10^{-2}-10^{-1}, 10^{-1}-10^{1}, 10^{1}-10^{2},$\geq 10^{2}$ and are labeled as –2,-1,0,1 and 2, respectively.

In the scatter plots, the horizontal axis contains the simulation trials and the vertical axis contains the estimated response probability divided by the true response probability. The vertical axis is scaled logarithmically to be able to display as wide range of errors as possible. This has also the effect of giving larger weights to underestimation errors. To simplify the comparison of the estimators, the scatter diagrams of the four estimators are plotted on the same X-Y axis using colors and legends to identify the estimators.

4.2.1. Onehit Model

It can be seen from the table below that for both 10^{-4} and 10^{-6} response probabilities, linear extrapolation has the smallest MSE for all sample sizes. The largest MSE is attained by DPS for all sample sizes. As sample size per dose group increases the MSE of all estimators are observed to decrease. The MSE of AP and DPS decrease at a faster rate. Linear extrapolation was the most stable (minimum variance) for all sample sizes. DPS has the largest variance for all sample sizes. The variances of all the estimators decrease as sample size per dose group increases. However, the variances of Logistic, AP and DPS decrease at a faster rate than that of linear extrapolation.

Table 6: Empirical measures of closeness for Onehit model

n=30			Logistic	AP	DPS	Linear
	10^{-6}	MSE	4.188E-12	2.506E-09	1.378E-05	1.878E-13
		Variance	3.922E-12	2.344E-09	1.332E-05	1.259E-13
		Mean	4.837E-07	1.373E-05	6.819E-04	7.514E-07
		Minimum	0.000E+00	3.857E-10	9.267E-11	1.898E-07
		Maximum	1.836E-05	4.409E-04	2.785E-02	1.819E-06
		Risk	4.991E+00	1.351E+00	3.870E+00	7.420E-02
	10^{-4}	MSE	1.170E-08	5.944E-07	2.932E-05	1.878E-09
		Variance	8.013E-09	5.182E-07	2.778E-05	1.260E-09
		Mean	3.927E-05	3.760E-04	1.340E-03	7.514E-05
		Minimum	1.715E-08	7.396E-07	2.044E-07	1.898E-05
		Maximum	6.701E-04	5.207E-03	3.517E-02	1.819E-04
		Risk	2.096E+00	5.613E-01	1.517E+00	7.419E-02
n=50	10^{-6}	MSE	1.356E-12	1.570E-10	1.231E-07	1.080E-13
		Variance	7.300E-13	1.516E-10	1.166E-07	6.168E-14
		Mean	2.087E-07	3.334E-06	8.150E-05	7.849E-07
		Minimum	5.000E-11	2.668E-09	6.042E-11	1.813E-07
		Maximum	8.087E-06	1.161E-04	2.637E-03	1.380E-06
		Risk	3.333E+00	7.663E-01	2.685E+00	4.238E-02
	10^{-4}	MSE	7.681E-09	7.508E-08	2.035E-06	1.080E-09
		Variance	2.214E-09	7.067E-08	1.888E-06	6.169E-10
		Mean	2.606E-05	1.664E-04	4.824E-04	7.849E-05
		Minimum	1.454E-07	2.061E-06	1.521E-07	1.813E-05
		Maximum	3.911E-04	2.192E-03	7.760E-03	1.380E-04
		Risk	1.298E+00	3.108E-01	1.049E+00	4.237E-02
n=100	10^{-6}	MSE	8.826E-13	1.074E-12	1.685E-10	1.016E-13
		Variance	2.151E-14	7.773E-13	1.619E-10	3.684E-14
		Mean	7.203E-08	4.553E-07	3.563E-06	7.455E-07
		Minimum	5.100E-10	4.297E-09	1.227E-09	3.652E-07
		Maximum	1.113E-06	6.665E-06	1.051E-04	1.252E-06
		Risk	3.169E+00	1.069E+00	1.333E+00	3.291E-02
	10^{-4}	MSE	7.362E-09	5.665E-09	5.110E-08	1.016E-09
		Variance	3.574E-10	3.618E-09	5.097E-08	3.684E-10
		Mean	1.630E-05	5.476E-05	1.116E-04	7.455E-05
		Minimum	8.456E-07	3.379E-06	1.429E-06	3.652E-05
		Maximum	1.211E-04	3.852E-04	1.730E-03	1.252E-04
		Risk	1.221E+00	3.972E-01	5.409E-01	3.290E-02

Except AP and DPS for n=30 and n=50 and only DPS for n=100, all estimators lead to downward bias. The means of all estimators but linear extrapolation decreased as n increased. For all sample sizes and response probabilities DPS estimates covered wide range of values. The empirical risks of the estimators (for the loss function $[\ln(\frac{\hat{P}_i}{P})]^2$) indicate that linear

extrapolation leads to the smallest risk for all sample sizes. It is also noted that AP and DPS have smaller risks than the logistic for all sample sizes. Except AP, the risks of all the other estimators decrease as n increases. AP attains its smallest risk for n=50. In comparing the empirical measures of closeness between 10^{-6} and 10^{-4} response probability estimations, we observe that MSE's for estimating response probability 10^{-6} are smaller than MSE's for estimating response probability 10^{-4}. The same pattern is also observed for the variances. On the contrary, all estimators result in smaller risk when estimating response probability 10^{-4} than 10^{-6}.

A look at the frequency distribution (Table 7) reveals that linear extrapolation leads to estimates very close to the true value for both 10^{-6} and 10^{-4} response probabilities and for all sample sizes. All the estimators perform better (give less number of errors with extreme orders) in estimating 10^{-4} response probability than 10^{-6} response probability. It can also be observed that for the response probability 10^{-6}, 71% of logistic, 20% of AP, 20% of DPS and 0% of linear extrapolation; 49 % of logistic, 19 of AP, 36% of DPS and 0% of linear extrapolation; and 84% of logistic, 34% of AP, 37% of DPS and 0% of Linear extrapolation are observed to be smaller than the true value by not less than one order of magnitude for n=30, 50 and 100, respectively.

Table 7: Frequency distribution for the estimators for Onehit model

		N=30				n=50				n=100			
		Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear
10^{-6}	<=-2	45	4	1	0	29	4	17	0	27	6	7	0
	-1	26	16	19	0	40	15	19	0	57	28	30	0
	0	28	61	36	100	31	75	45	100	16	66	57	100
	1	1	16	13	0	0	5	11	0	0	0	5	0
	>=2	0	3	11	0	0	1	8	0	0	0	1	0
10^{-4}	<=-2	16	1	8	0	5	0	4	0	3	0	0	0
	-1	35	8	22	0	36	5	19	0	49	10	16	0
	0	49	80	55	100	59	93	66	100	48	90	82	100
	1	0	11	12	0	0	2	11	0	0	0	2	0
	>=2	0	0	3	0	0	0	0	0	0	0	0	0

For the case of 10^{-4} response probability, 51% of logistic, 9% of AP, 30% of DPS and 0% Linear extrapolation are smaller than the true value by one or more orders of magnitudes for n=30. The corresponding percentages for the cases of n=50 and n=100 are 41%, 5%, 23% and 0%; and 52 %, 10%, 16% and 0%, respectively.

The plots (Figures 3-8) on the other hand reveal that for 10^{-6} response probability, logistic leads to the largest underestimation for all sample sizes. The performance of AP for n=50 is desirable. Although linear extrapolation yields small error, it leads to underestimation in most of the cases. In the case of 10^{-4} response probability as well, linear extrapolation leads to many small errors of underestimation. For n=30 and n=50, the behavior of AP is likeable.

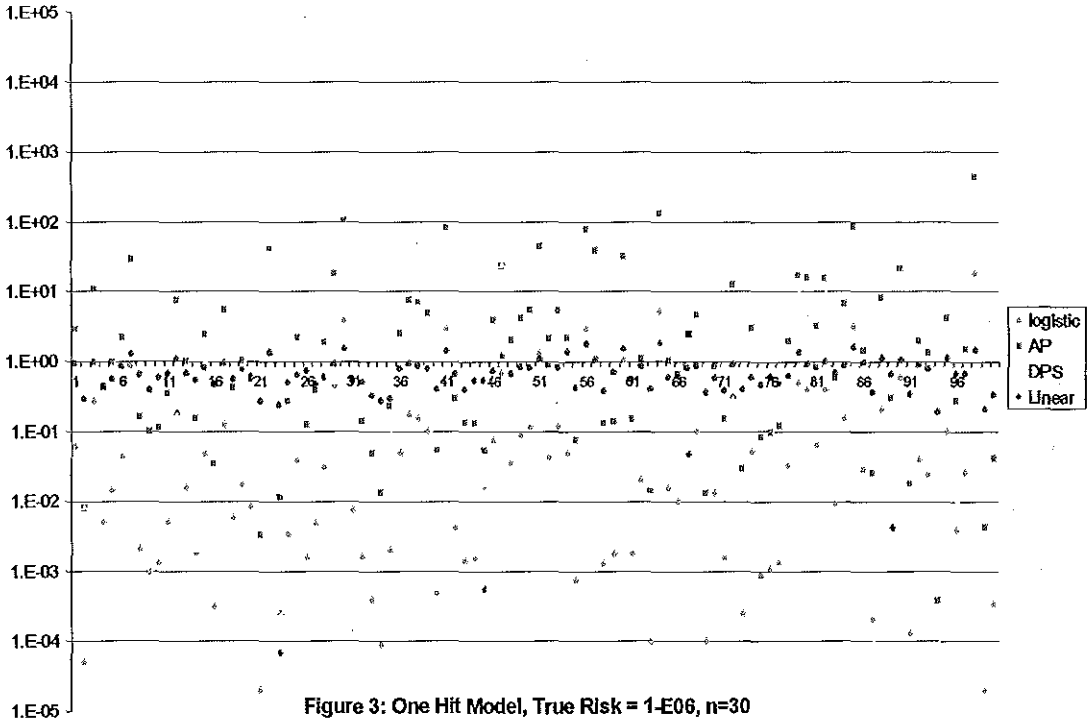


Figure 3: One Hit Model, True Risk = 1-E06, n=30

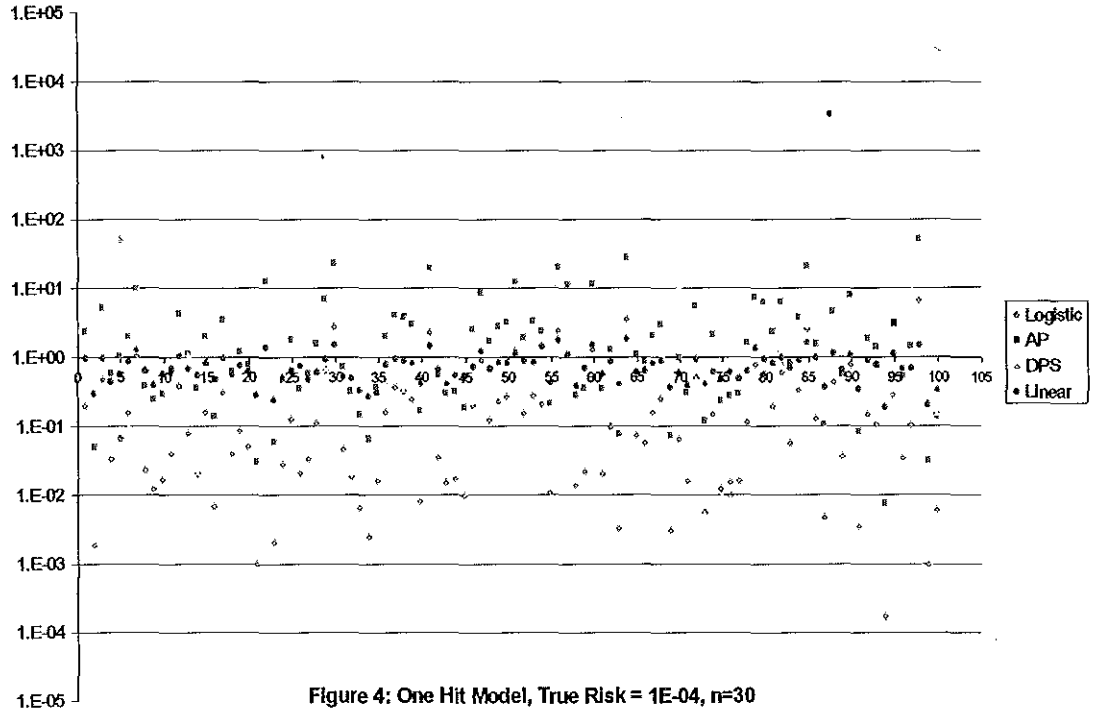


Figure 4: One Hit Model, True Risk = 1E-04, n=30

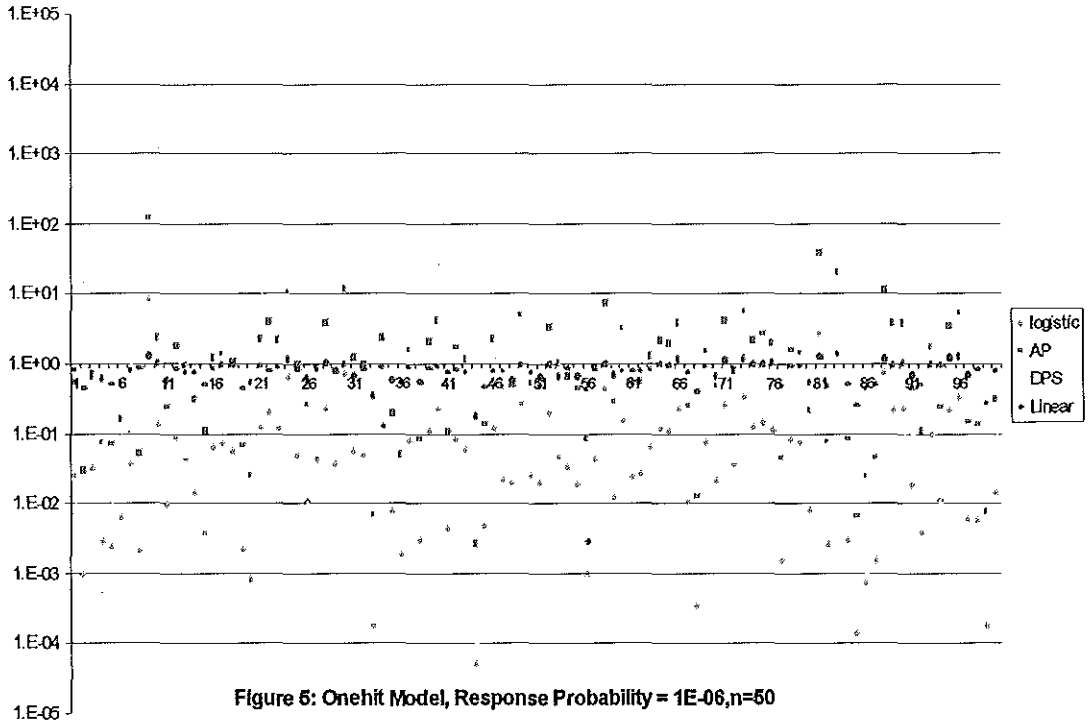


Figure 5: Onehit Model, Response Probability = 1E-06,n=50

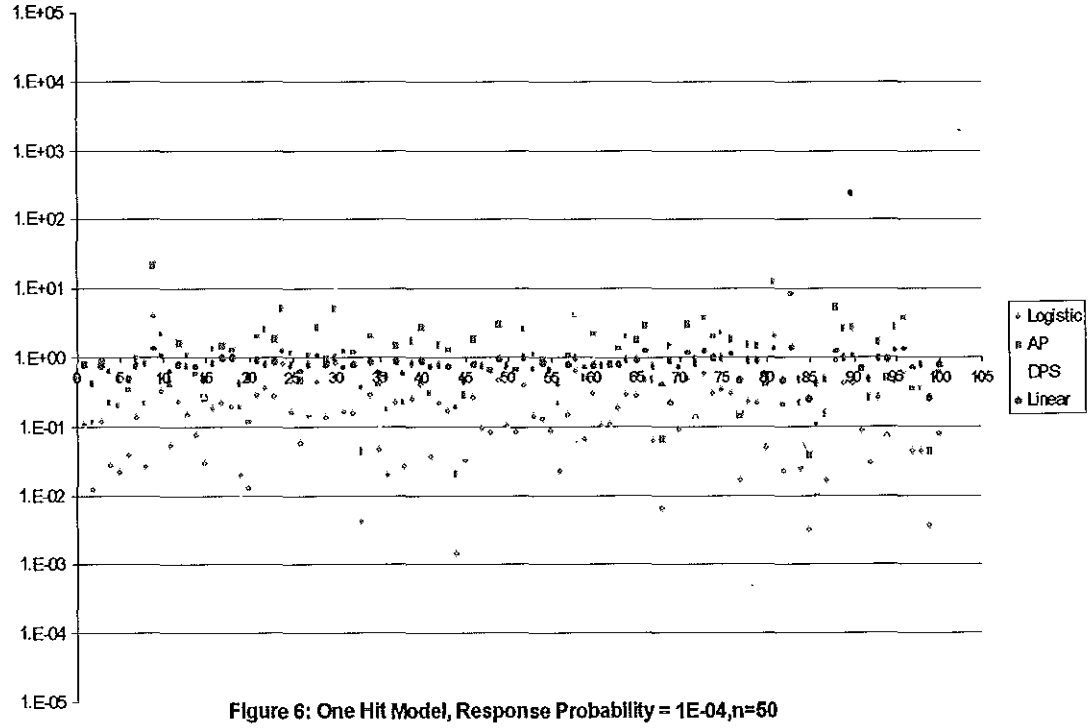


Figure 6: One Hit Model, Response Probability = 1E-04,n=50

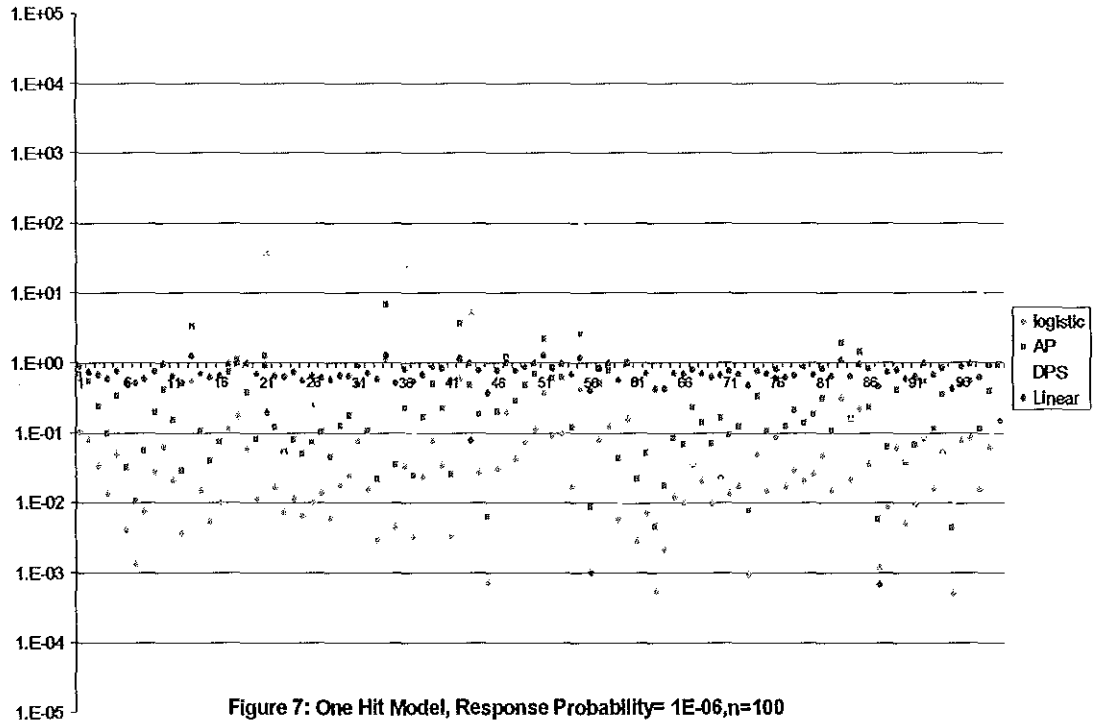


Figure 7: One Hit Model, Response Probability= 1E-06,n=100

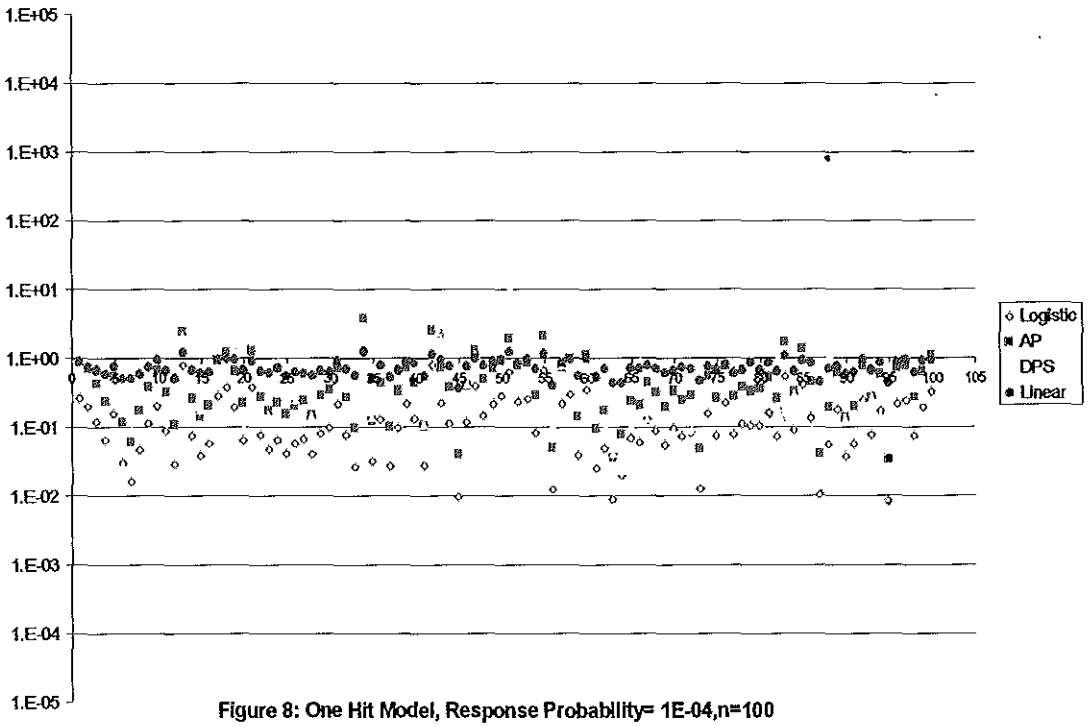


Figure 8: One Hit Model, Response Probability= 1E-04,n=100

4.2.2. Multistage Model

For both 10^{-4} and 10^{-6} response probabilities, linear extrapolation has the smallest MSE for all sample sizes. For 10^{-6} response probability, the largest MSE is observed for DPS for all sample sizes. When estimating response probability 10^{-4}, however, the largest MSE is taken by logistic for n=100 and DPS for n=30 and n=50. For both 10^{-4} and 10^{-6} response probabilities, the MSE for DPS decreases with increasing sample size and that of Logistic and AP remain nearly the same as sample size change. Logistic estimates were the most stable (minimum variance) for all the sample sizes studied. DPS takes the largest variance for all sample sizes. The variances of all the estimators decrease with increasing sample size. But the variances of Logistic, AP and DPS are observed to decrease at a faster rate. The MSE and variances of DPS differ from that of the others by a very large amount. When estimating 10^{-6} response probability, a very large downward bias is observed for logistic estimation for all sample sizes. In the case of both 10^{-4} and 10^{-6} response probabilities, except DPS which gives an upward bias for n=30 and n=50, downward bias are obtained for all estimators and sample sizes. The means of all the estimators decrease as n increases. Linear extrapolation leads to the smallest risk for all sample sizes. The largest risks are taken by logistic estimation for all sample sizes. For 10^{-6} response probability, the risks of DPS and Linear extrapolation decrease as sample size increases. However for the case of 10^{-4} response probability, except for AP, the risks of the estimators decrease with increasing sample size.

Table 8: Empirical measures of closeness for Multistage model

n=30			Logistic	AP	DPS	Linear
	10^{-6}	MSE	9.969E-13	1.114E-12	2.867E-04	3.519E-13
		Variance	1.819E-16	3.458E-13	2.825E-04	9.667E-14
		Mean	2.448E-09	1.243E-07	2.032E-03	4.956E-07
		Minimum	0.000E+00	3.620E-13	0.000E+00	4.099E-08
		Maximum	1.039E-07	4.662E-06	1.677E-01	1.661E-06
		Risk	1.526E+01	7.408E+00	8.242E+00	2.628E-01
	10^{-4}	MSE	9.751E-09	8.884E-09	1.032E-04	3.521E-09
		Variance	2.174E-11	2.596E-09	1.004E-04	9.667E-10
		Mean	1.462E-06	2.080E-05	1.778E-03	4.956E-05
		Minimum	6.000E-11	1.135E-08	2.507E-11	4.099E-06
		Maximum	3.294E-05	3.580E-04	9.726E-02	1.661E-04
		Risk	8.940E+00	2.519E+00	3.839E+00	2.628E-01
n=50	10^{-6}	MSE	1.000E-12	9.726E-13	4.093E-07	3.201E-13
		Variance	2.555E-18	1.336E-15	4.009E-07	5.976E-14
		Mean	5.829E-10	1.528E-08	9.256E-05	4.906E-07
		Minimum	0.000E+00	2.793E-12	5.480E-13	9.689E-08
		Maximum	1.207E-08	2.642E-07	6.290E-03	1.117E-06
		Risk	1.582E+01	8.879E+00	5.033E+00	1.947E-01
	10^{-4}	MSE	9.850E-09	8.732E-09	2.106E-06	3.203E-09
		Variance	2.147E-12	1.144E-10	2.028E-06	5.976E-10
		Mean	8.615E-07	7.266E-06	3.793E-04	4.906E-05
		Minimum	1.640E-09	4.321E-08	1.540E-08	9.689E-06
		Maximum	8.996E-06	6.307E-05	1.297E-02	1.117E-04
		Risk	7.722E+00	3.020E+00	1.915E+00	1.948E-01
n=100	10^{-6}	MSE	1.001E-12	9.985E-13	4.488E-12	3.236E-13
		Variance	2.036E-19	1.093E-17	4.412E-12	2.777E-14
		Mean	1.886E-10	1.530E-09	7.245E-07	4.569E-07
		Minimum	0.000E+00	2.192E-12	4.188E-11	1.697E-07
		Maximum	3.120E-09	2.222E-08	1.464E-05	9.586E-07
		Risk	1.708E+01	1.295E+01	4.310E+00	1.657E-01
	10^{-4}	MSE	9.927E-09	9.666E-09	7.841E-09	3.238E-09
		Variance	4.223E-13	5.306E-12	3.908E-09	2.777E-10
		Mean	4.652E-07	1.811E-06	3.738E-05	4.569E-05
		Minimum	6.190E-09	3.839E-08	1.707E-07	1.697E-05
		Maximum	3.930E-06	1.357E-05	3.345E-04	9.586E-05
		Risk	7.579E+00	4.476E+00	1.680E+00	1.658E-01

For all sample sizes the MSE and variances are larger when estimating 10^{-4} response probability than 10^{-6} response probability. However the risks are smaller when estimating risk probability of 10^{-4} than 10^{-6} except for the case of linear extrapolation.

From Table 9, it can be discerned that in estimating response probability of 10^{-6}, 99% of logistic, 84% of AP, 45% of DPS and 4% of linear extrapolation lead to risk estimates which

are smaller than the true value by at least one order of magnitude. For n=50, 100% of logistic, 96% of AP, 51% of DPS and 1% of linear extrapolation estimations produce estimates lower than the true value by one or more orders of magnitudes. For the case of n=100, 100% of logistic, 100% of AP and 65% of DPS have estimates smaller than the true value by not less that one orders of magnitudes. Larger overestimation are observed in 21%, 16% and 1% of DPS estimations for n=30, 50 and 100, respectively.

Table 9: Frequency distribution for the estimators for Multistage model

		n=30				n=50				n=100			
		Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear
10^{-6}	<=-2	98	56	35	0	99	73	34	0	100	97	33	0
	-1	1	28	23	4	1	23	23	1	0	3	32	0
	0	1	16	21	96	0	4	27	99	0	0	34	100
	1	0	0	10	0	0	0	8	0	0	0	1	0
	>=2	0	0	11	0	0	0	8	0	0	0	0	0
10^{-4}	<=-2	74	18	20	0	79	24	12	0	89	49	14	0
	-1	24	44	26	4	21	56	29	1	11	49	37	0
	0	2	38	40	96	0	20	50	99	0	2	49	100
	1	0	0	10	0	0	0	8	0	0	0	0	0
	>=2	0	0	4	0	0	0	1	0	0	0	0	0

When response probability to be estimated is 10^{-4}, 98%, 62%, 46% and 4% of Logistic, AP, DPS and Linear extrapolation, respectively, have estimates smaller than the true value by at least one order of magnitude. These percentages for n=50 and n=100 are 100%, 80%, 41% and 1%; and 100%, 98%, 51% and 0%, respectively.

In the plots (Figures 9-14) it is observable that in the estimation of response probability 10^{-6}, except for very few cases of n=30, logistic, AP and linear extrapolations lead to underestimation for almost all the simulations and all sample sizes studied. The underestimation from logistic is seen to be very enormous. The large variability of DPS estimates is clearly observable. DPS estimations, with quite a number of overestimation cases, cannot be taken as favorable due to their excessive difference in magnitude from the true value, in particular for n=30 and n=50. Logistic estimation has resulted in estimates which are smaller than the true value by many orders of magnitudes in 28%, 22% and 25% of the

estimates for n=30, 50 and 100, respectively. Also 2% of DPS for n=30 are very small. These values are not included in the plots because their inclusion would otherwise suppress the impression of the other values.

For the case of 10^{-4} response probability, linear extrapolation, AP and Logistic give underestimation for all sample sizes except for the few cases of n=30.

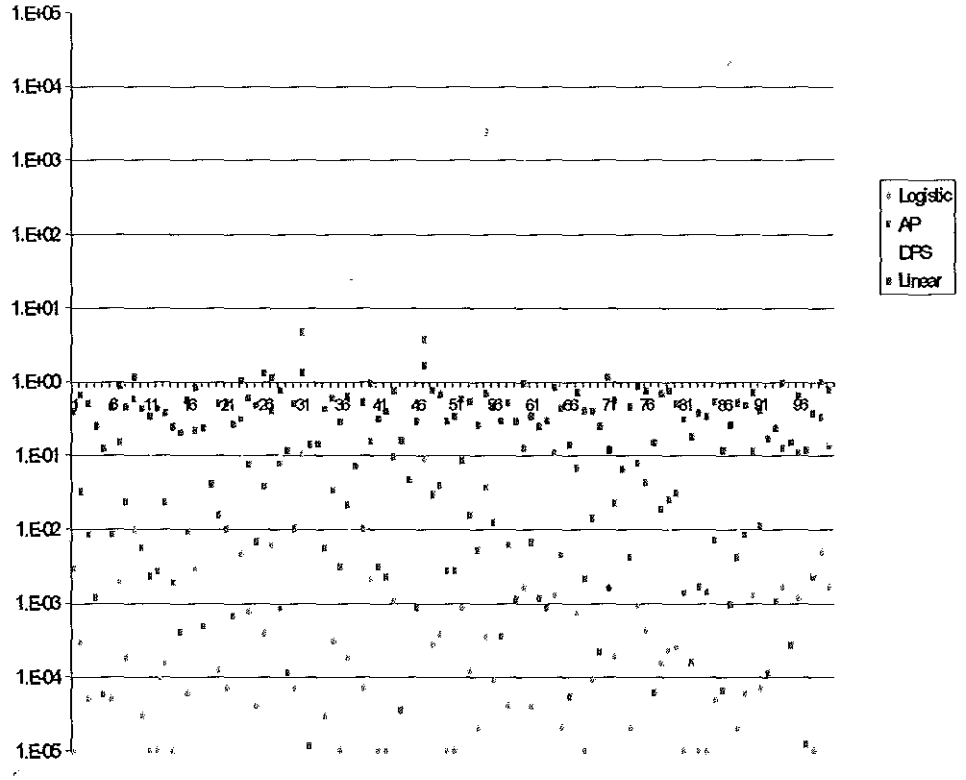


Figure 9: MultiStage Model, Response Probability = 1E-06, n=30

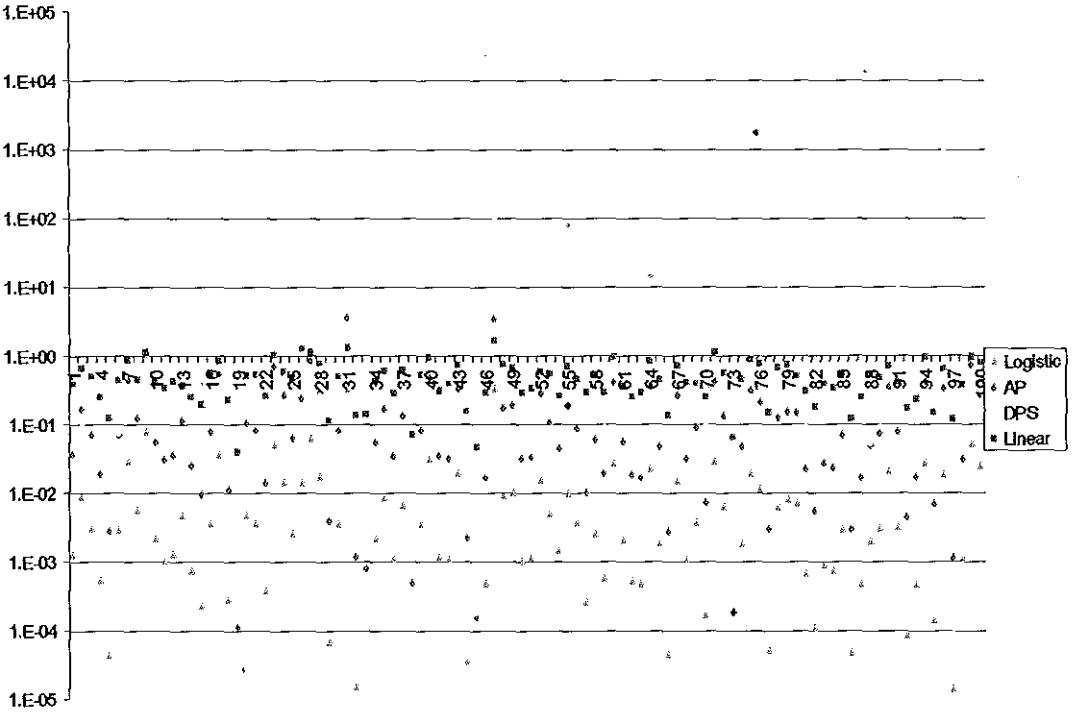


Figure 10: Multistage Model, Response Probability = 1E-04, n=30

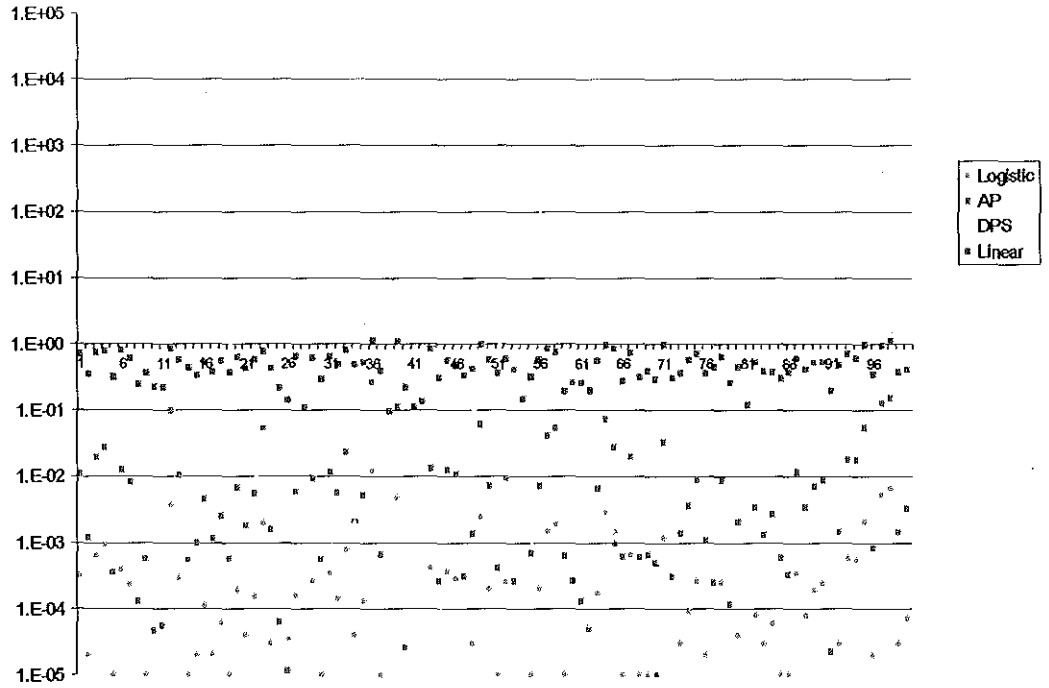


Figure 11: Multi Stage Model, Response Probability = 1E-06,n=50

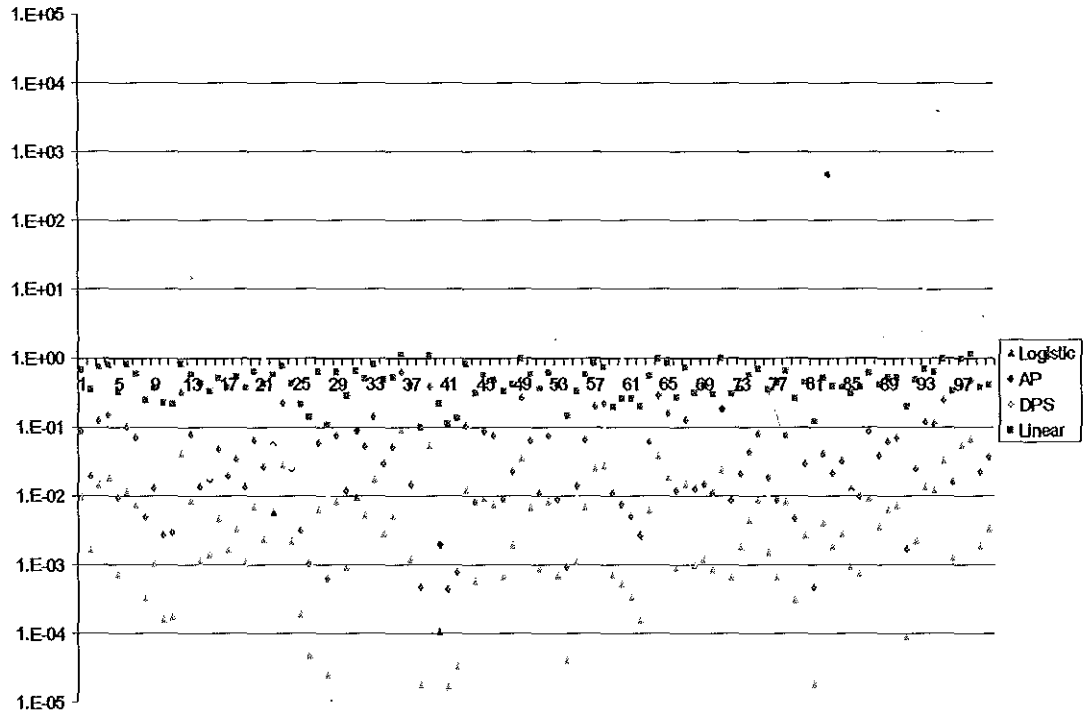


Figure 12: Multi Stage Model, Response Probability = 1E-04, n=50

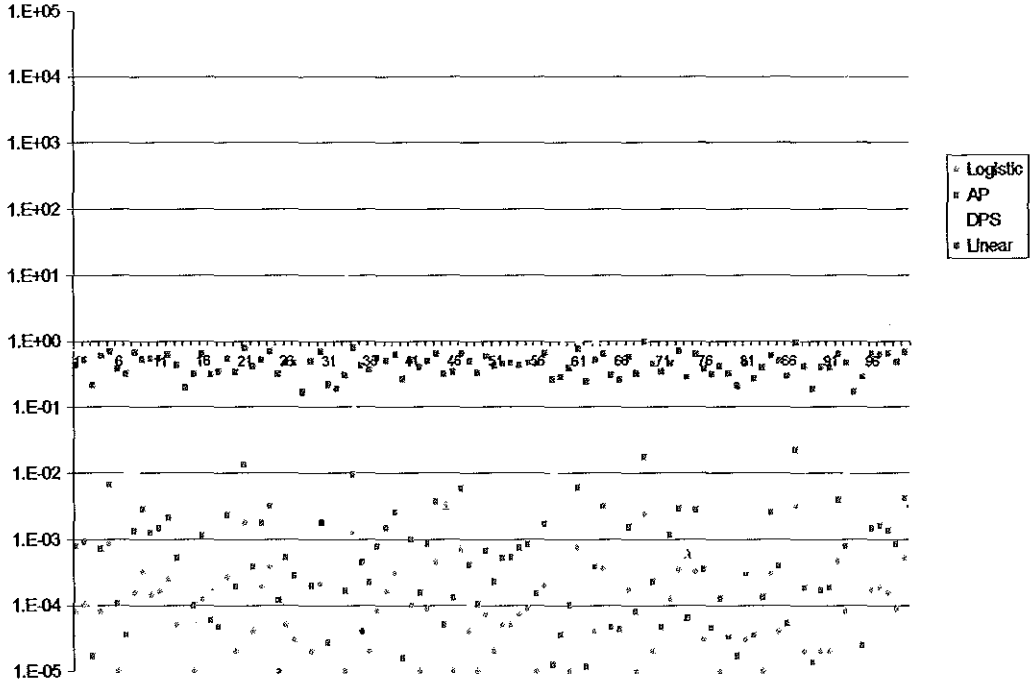


Figure13: Multi Stage Model, Response Probability = 1E-06,n=100

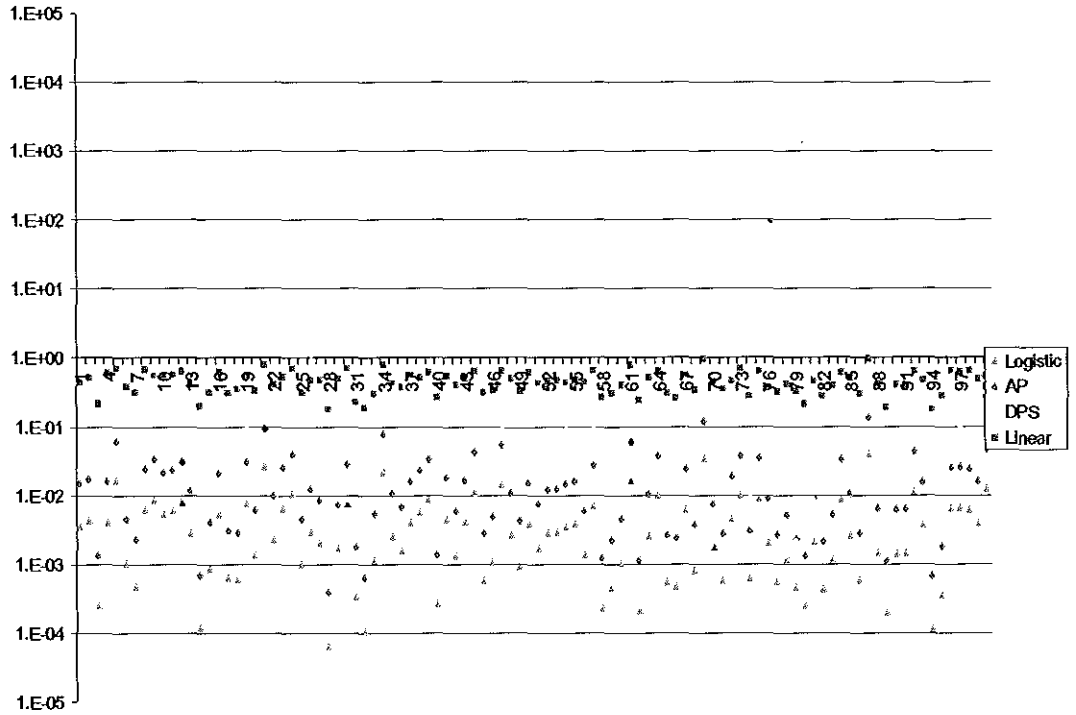


Figure 14: Multi Stage Model, Response Probability = 1E-04, n=100

4.2.3. Weibull Model

In estimating both 10^{-4} and 10^{-6} risk probabilities, logistic gives the smallest MSE for n=30 and n=50. For n=100, AP results in the smallest MSE. But for n=100, the MSE of AP and logistic are close to each other. For n=30 and n=50, DPS takes the largest MSE whereas linear extrapolation assumes the largest MSE for n=100. For Logistic estimation, the smallest MSE is obtained for n=50. For 10^{-6} response probability, the MSE's of AP and DPS decrease with increasing sample size. For 10^{-4} response probability, on the other hand, the MSE's of Logistic, DPS and Linear extrapolation decrease as n increases. For both 10^{-4} and 10^{-6} levels, Logistic estimates have the smallest variability for all the three sample sizes. The largest variances are assumed by DPS for all sample sizes. For all the estimators the variances decrease with increasing sample size with that of Logistic, AP and DPS at a faster rate. For n=30 and n=50 all estimators except logistic have upward bias. The bias from linear extrapolation and DPS appear to be larger. Only DPS and linear extrapolation have upward bias for n=100. Other than that of linear extrapolation, the means of the remaining estimators decrease as sample size increases. Linear extrapolation has the smallest risk for n=30 and n=100. When n=50, AP takes the smallest risk for 10^{-6} response probability and linear extrapolation takes the smallest for 10^{-4} response probability. Logistic yields the largest risk for all sample sizes. The risks of logistic and DPS estimations decrease with increasing sample size.

Table 11: Empirical measures of closeness for Weibull model

n=30			Logistic	AP	DPS	Linear
	10^{-6}	MSE	1.246E-12	1.750E-10	1.562E-07	1.754E-10
		Variance	6.027E-13	1.647E-10	1.487E-07	6.536E-11
		Mean	1.983E-07	4.208E-06	8.787E-05	1.149E-05
		Minimum	1.000E-11	2.079E-09	7.326E-12	1.117E-06
		Maximum	6.615E-06	1.030E-04	3.368E-03	4.453E-05
		Risk	6.109E+00	1.199E+00	3.308E+00	1.007E+00
	10^{-4}	MSE	8.608E-09	1.207E-07	2.324E-06	7.620E-08
		Variance	2.813E-09	1.116E-07	2.155E-06	4.098E-08
		Mean	2.388E-05	1.954E-04	5.111E-04	2.877E-04
		Minimum	4.459E-08	1.903E-06	4.650E-08	2.796E-05
		Maximum	4.072E-04	2.372E-03	1.125E-02	1.115E-03
		Risk	2.433E+00	4.897E-01	1.335E+00	2.335E-01
n=50	10^{-6}	MSE	8.491E-13	6.771E-12	3.575E-09	1.814E-10
		Variance	6.595E-14	6.664E-12	3.369E-09	4.630E-11
		Mean	1.151E-07	1.326E-06	1.535E-05	1.262E-05
		Minimum	5.000E-11	2.447E-09	2.295E-10	2.526E-06
		Maximum	1.723E-06	1.650E-05	5.374E-04	3.236E-05
		Risk	4.196E+00	9.880E-01	1.929E+00	1.135E+00
	10^{-4}	MSE	7.202E-09	1.821E-08	2.103E-07	7.573E-08
		Variance	9.216E-10	1.816E-08	1.926E-07	2.903E-08
		Mean	2.075E-05	1.071E-04	2.331E-04	3.161E-04
		Minimum	1.896E-07	2.358E-06	4.157E-07	6.325E-05
		Maximum	1.690E-04	7.245E-04	2.754E-03	8.101E-04
		Risk	1.602E+00	3.717E-01	7.502E-01	2.487E-01
n=100	10^{-6}	MSE	9.253E-13	7.948E-13	3.714E-11	1.171E-10
		Variance	9.066E-15	1.704E-13	3.469E-11	1.960E-11
		Mean	4.282E-08	2.098E-07	2.564E-06	1.087E-05
		Minimum	4.300E-10	3.550E-09	7.057E-10	3.373E-06
		Maximum	7.029E-07	2.999E-06	3.674E-05	2.661E-05
		Risk	3.941E+00	1.576E+00	1.453E+00	1.034E+00
	10^{-4}	MSE	7.982E-09	5.717E-09	1.815E-08	4.197E-08
		Variance	2.108E-10	1.411E-09	1.815E-08	1.229E-08
		Mean	1.185E-05	3.438E-05	1.011E-04	2.723E-04
		Minimum	7.296E-07	2.974E-06	9.609E-07	8.447E-05
		Maximum	9.489E-05	2.421E-04	8.040E-04	6.662E-04
		Risk	1.512E+00	5.789E-01	5.898E-01	1.908E-01

The MSE's and variances of all the estimators increase when response probability to be estimated increases from 10^{-6} to 10^{-4}. However, the risk measures are larger when estimating 10^{-6} response probability than 10^{-4} response probability.

From the frequency table below, it can be computed that when estimating response probability 10^{-6}, 77% of logistic, 26% of AP and 34% of DPS estimates are smaller than the

true value at least by one order of magnitude. For n=50, 76% of logistic, 31% of AP and 30% of DPS are smaller than the true value by one or more orders of magnitude. For n=30 and n=50, no linear extrapolation estimate is found to be less that the true value by one or more orders of magnitudes. In the case of n=100, 92%, 56%, 32% and 50% of logistic, AP, DPS and Linear extrapolation, respectively, happen to be less than the true value with at least one order of magnitude.

Table 12: Frequency distribution for the estimators for Weibull model

		n=30				n=50				n=100			
		Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear
10^{-6}	<=-2	54	8	17	0	38	6	11	0	37	6	9	0
	-1	23	18	17	0	38	25	19	0	55	50	23	50
	0	23	64	43	51	24	67	50	44	8	44	61	50
	1	0	9	14	49	0	2	17	56	0	0	7	0
	>=2	0	1	9	0	0	0	3	0	0	0	0	0
10^{-4}	<=-2	21	0	8	0	8	0	2	0	3	0	1	0
	-1	40	14	17	0	49	8	19	0	60	23	18	100
	0	39	83	64	99	43	92	74	100	37	77	81	0
	1	0	3	10	1	0	0	5	0	0	0	0	0
	>=2	0	0	1	0	0	0	0	0	0	0	0	0

For 10^{-4} response probability estimation, 61% of logistic, 14% of AP and 25% of DPS are observed to be less than the true value by at least one order of magnitude for n=30. The proportion of estimates lower than the true value with at least one order of magnitude are 57%, 8%, 21% and 0% in logistic, AP, DPS and Linear extrapolation, respectively. These proportions for n=100 are 63%, 23%, 19% and 0%, respectively.

From the plots (Figure 15-20) it can be observed that in the case of 10^{-6} risk estimation, linear extrapolation results in overestimation of order one for almost all simulations and all sample size cases. Except in few cases of n=30, logistic results in underestimation in almost all cases and for all sample sizes.

When estimating 10^{-4} response probability, linear extrapolation has the most desirable feature for all sample sizes. Most of logistic estimations are below the true value for all sample sizes.

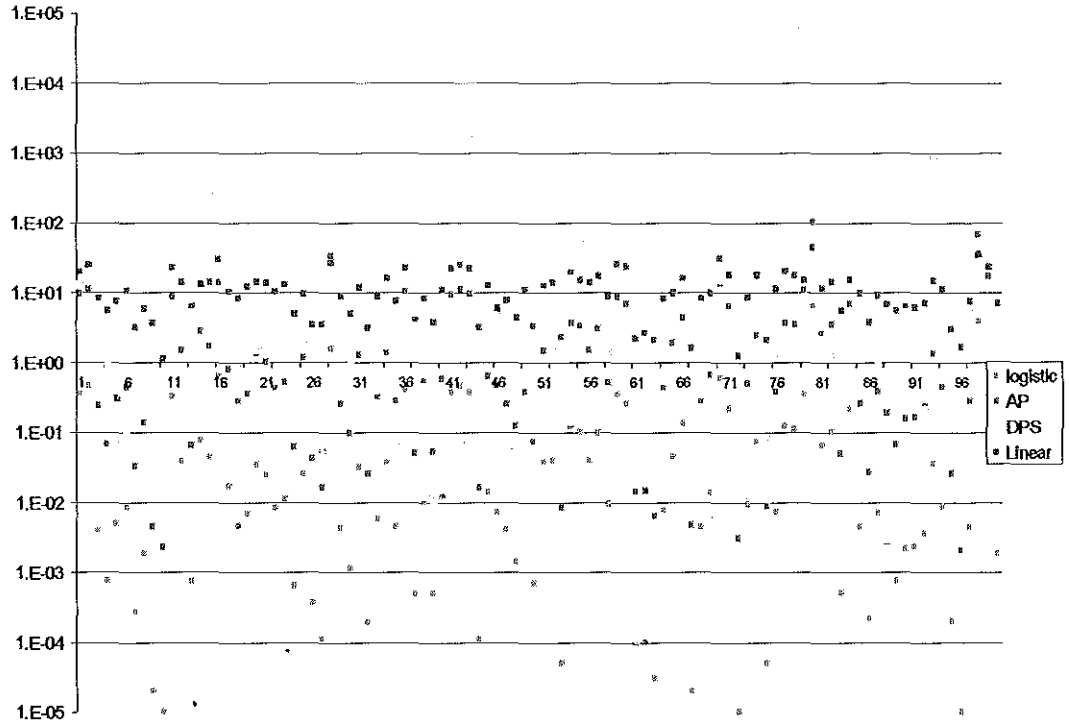


Figure 15: Weibull Model , Response Probability= 1E-06,n=30

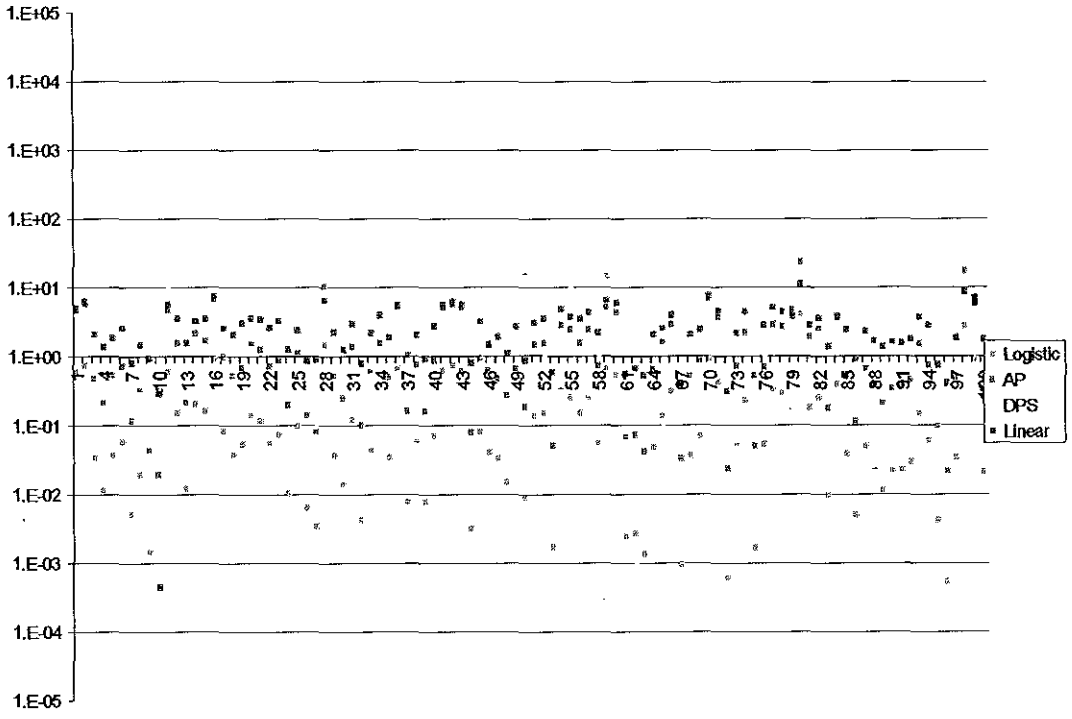


Figure 16: Weibull Model, Response Probability = 1E-04,n=30

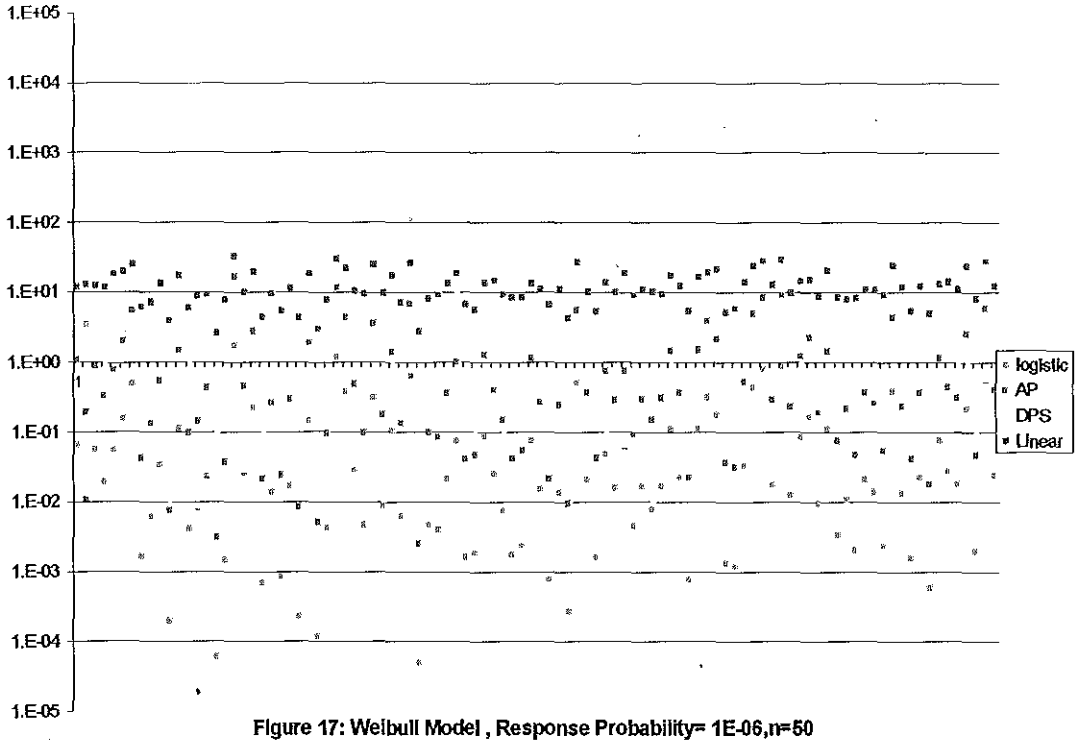


Figure 17: Weibull Model , Response Probability= 1E-06,n=50

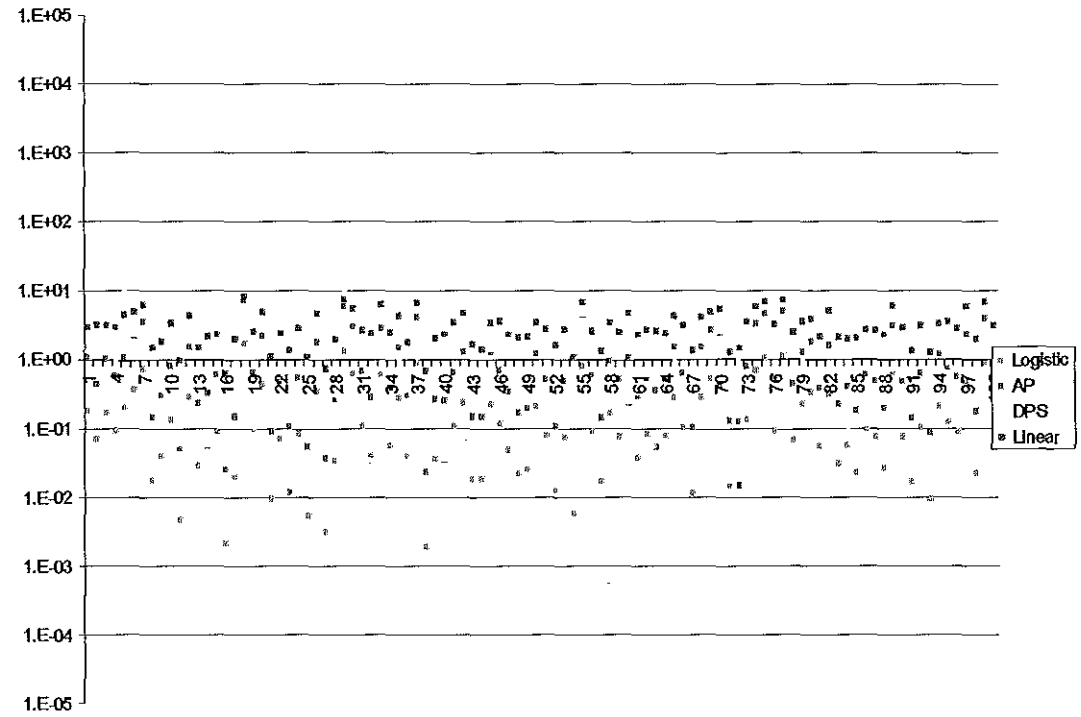


Figure 18: Weibull Model, Response Probability = 1E-04,n=50

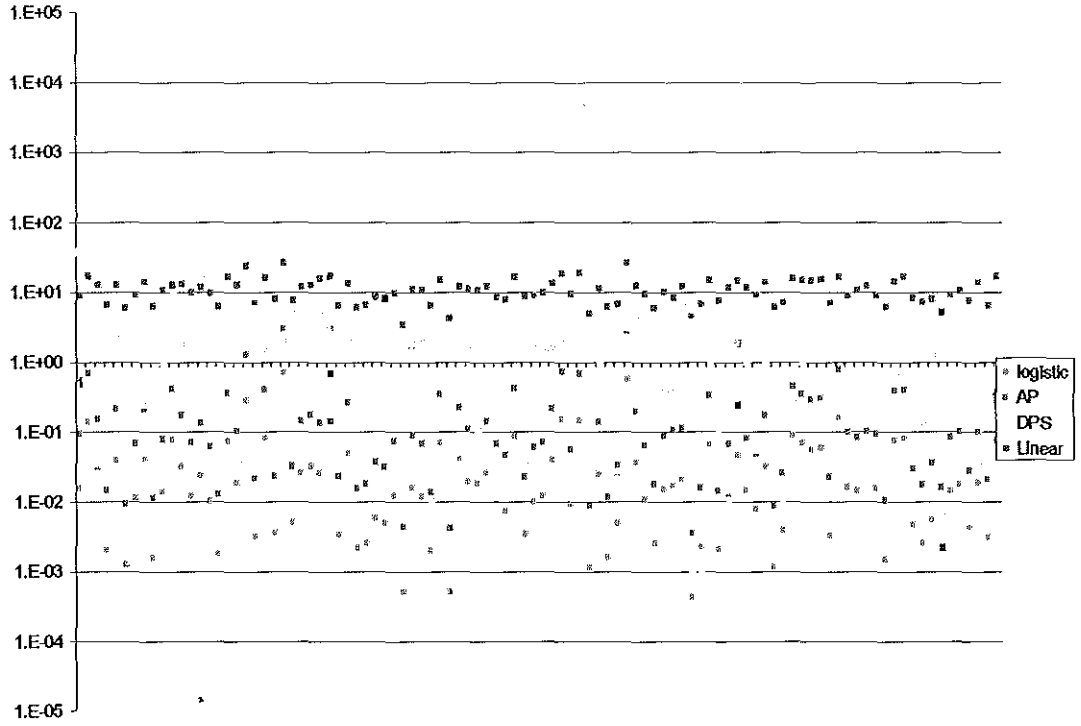


Figure 119: Weibull Model , Response Probability = 1E-06,n=100

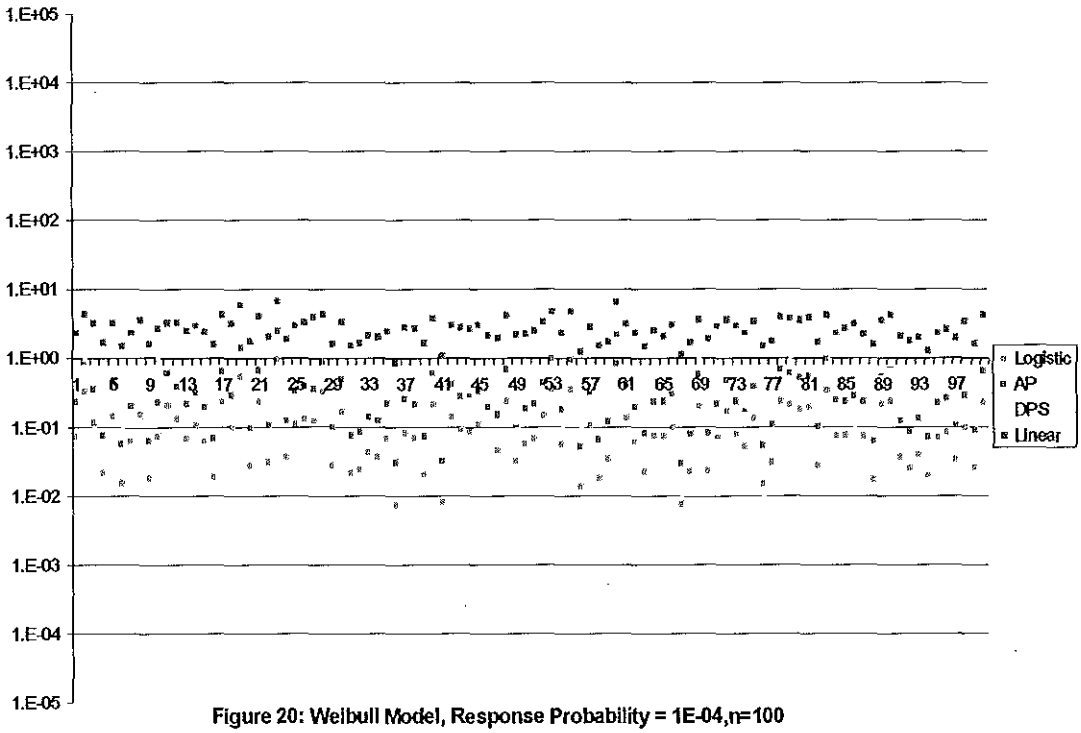


Figure 20: Weibull Model, Response Probability = 1E-04,n=100

4.2.4. Multihit Model

In estimating both 10^{-4} and 10^{-6} response probabilities, logistic estimator assumes the smallest MSE for all sample sizes. The largest MSE is taken by DPS for n=30 and n=50 and by linear extrapolation for n=100. The MSE for AP and linear extrapolation decreases as sample size increases with that of AP at a faster rate. The increase in MSE of DPS as n change from 30 to 50 is very large. Logistic estimation has the smallest variance for all sample sizes. The largest variance is taken by DPS for all sample sizes. For 10^{-6} response probability, except for DPS the variances of the other estimators decrease with increasing sample size. For 10^{-4} response probability, however, the variances of AP and linear extrapolation decrease as sample size increases. The means of the estimators reveal that except for logistic estimation, upward bias is observed for all other estimators for all sample sizes. In the case of 10^{-6} response probability, large upward biases are observed in DPS and linear extrapolation estimations. For n=30 and n=100, linear extrapolation results in the largest upward bias. For n=50, the largest upward bias is obtained from DPS. For 10^{-4} response probability and for all sample sizes studied, only logistic estimation gave downward bias. For both 10^{-4} and 10^{-6} response probabilities and for all sample sizes, the estimator with the smallest risk is AP. For 10^{-6} response probability, the next smallest risk is taken by DPS for all sample sizes. For the cases of 10^{-4} response probability, however, the second smallest risk is taken by DPS for n=50 and n=100 and it is by linear extrapolation for n=30. Except for linear extrapolation, which has an increasing risk as n increases, the risks of the other estimators decrease with increasing sample size.

Table 13: Empirical measures of closeness for Multihit model

n=30			Logistic	AP	DPS	Linear
	10^{-6}	MSE	2.772E-12	5.191E-10	6.044E-08	5.822E-09
		Variance	2.694E-12	4.068E-10	5.813E-08	1.872E-09
		Mean	7.208E-07	1.160E-05	4.904E-05	6.385E-05
		Minimum	1.000E-11	2.862E-09	1.013E-09	3.286E-06
		Maximum	1.072E-05	1.233E-04	2.238E-03	2.279E-04
		Risk	2.263E+00	9.670E-01	1.851E+00	2.983E+00
	10^{-4}	MSE	9.132E-09	2.939E-07	6.599E-07	6.115E-07
		Variance	7.347E-09	2.067E-07	5.789E-07	2.342E-07
		Mean	5.775E-05	3.953E-04	3.846E-04	7.143E-04
		Minimum	3.591E-08	1.980E-06	6.700E-07	3.676E-05
		Maximum	5.127E-04	2.549E-03	5.685E-03	2.549E-03
		Risk	1.046E+00	4.229E-01	7.234E-01	6.671E-01
n=50	10^{-6}	MSE	3.132E-12	1.641E-10	1.529E-06	5.820E-09
		Variance	3.090E-12	1.367E-10	1.500E-06	1.739E-09
		Mean	7.939E-07	6.236E-06	1.730E-04	6.488E-05
		Minimum	4.000E-11	2.582E-09	6.541E-10	4.177E-06
		Maximum	1.087E-05	6.752E-05	1.164E-02	2.438E-04
		Risk	1.674E+00	6.631E-01	1.645E+00	3.057E+00
	10^{-4}	MSE	9.665E-09	1.227E-07	4.098E-06	6.092E-07
		Variance	8.111E-09	9.905E-08	3.920E-06	2.176E-07
		Mean	6.059E-05	2.538E-04	5.218E-04	7.258E-04
		Minimum	9.888E-08	1.672E-06	6.180E-07	4.673E-05
		Maximum	5.337E-04	1.766E-03	1.643E-02	2.727E-03
		Risk	7.760E-01	2.930E-01	6.519E-01	6.812E-01
n=100	10^{-6}	MSE	7.085E-13	4.469E-12	1.315E-09	4.723E-09
		Variance	3.555E-13	4.158E-12	1.209E-09	6.428E-10
		Mean	4.059E-07	1.558E-06	1.128E-05	6.488E-05
		Minimum	3.730E-09	2.570E-08	8.066E-09	1.889E-05
		Maximum	3.997E-06	1.332E-05	2.603E-04	1.437E-04
		Risk	9.078E-01	2.989E-01	8.257E-01	3.191E+00
	10^{-4}	MSE	4.662E-09	8.715E-09	1.114E-07	4.720E-07
		Variance	1.681E-09	8.526E-09	9.825E-08	8.044E-08
		Mean	4.540E-05	1.137E-04	2.146E-04	7.257E-04
		Minimum	2.290E-06	8.298E-06	3.617E-06	2.113E-04
		Maximum	2.430E-04	5.399E-04	2.061E-03	1.607E-03
		Risk	4.187E-01	1.356E-01	2.925E-01	7.141E-01

From the above table it can also be noted that the MSE and variances of the estimators are larger when estimating 10^{-4} response probability than 10^{-6} response probability. The risk measures, however, are smaller when the response probability to be estimated is 10^{-4} than when it is 10^{-6}.

A look at the frequency table (Table 14) reveals that for the response probability 10^{-6}, 48% of logistic, 4% of AP, 21% of DPS and 0% of linear extrapolation; 43 % of logistic, 45 of AP, 16% of DPS and 0% of linear extrapolation; and 32% of logistic, 7% of AP, 7% of DPS and 0% of Linear extrapolation are observed to be smaller than the true vale by not less than one order of magnitude for n=30, 50 and 100, respectively.

Table 14: Frequency distribution for the estimators for Multihit model

		n=30				n=50				n=100			
		Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear
10^{-6}	<=-2	17	1	6	0	12	1	7	0	2	0	2	0
	-1	31	3	15	0	31	3	9	0	30	7	5	0
	0	50	61	46	4	56	78	64	1	68	91	76	0
	1	2	33	28	77	1	18	14	80	0	2	14	92
	>=2	0	2	5	19	0	0	6	19	0	0	3	8
10^{-4}	<=-2	5	0	4	0	2	0	3	0	0	0	0	0
	-1	30	3	8	0	26	2	7	0	13	1	4	0
	0	65	90	81	73	72	94	82	74	87	99	92	84
	1	0	7	7	27	0	4	6	26	0	0	4	16
	>=2	0	0	0	0	0	0	2	0	0	0	0	0

For the case of 10^{-4} response probability, 53% of logistic, 3% of AP and 12% of DPS and 0% linear extrapolation are smaller than the true value with one or more orders of magnitude for n=30. The corresponding percentages for the cases of n=50 and n=100 are 28%, 2%, 1% and 0%; 13%, 1%, 4% and 0%, respectively.

The plots (Figures 21-26) of the estimators for 10^{-6} response probability show that large overestimation follows from linear extrapolation. In almost all the simulations and all sample sizes the linear extrapolation estimations exceed the true value with at least one order of magnitude. Except in few cases of n=30, logistic estimations fall below the true value for all sample sizes. For n=30, AP and DPS seem to have larger overestimation errors. The overestimation appears to improve for increasing sample size. AP has very desirable feature for the sample sizes n=50 and n=100. Except for the large variability, the features exhibited by DPS are to some extent favorable.

When interest lies in estimating response probability 10^{-4}, the underestimation resulting from logistic estimation is clearly observable. Though not very large, linear extrapolation leads to overestimation for all sample sizes. AP and DPS behave quite desirably for n=50 and n=100.

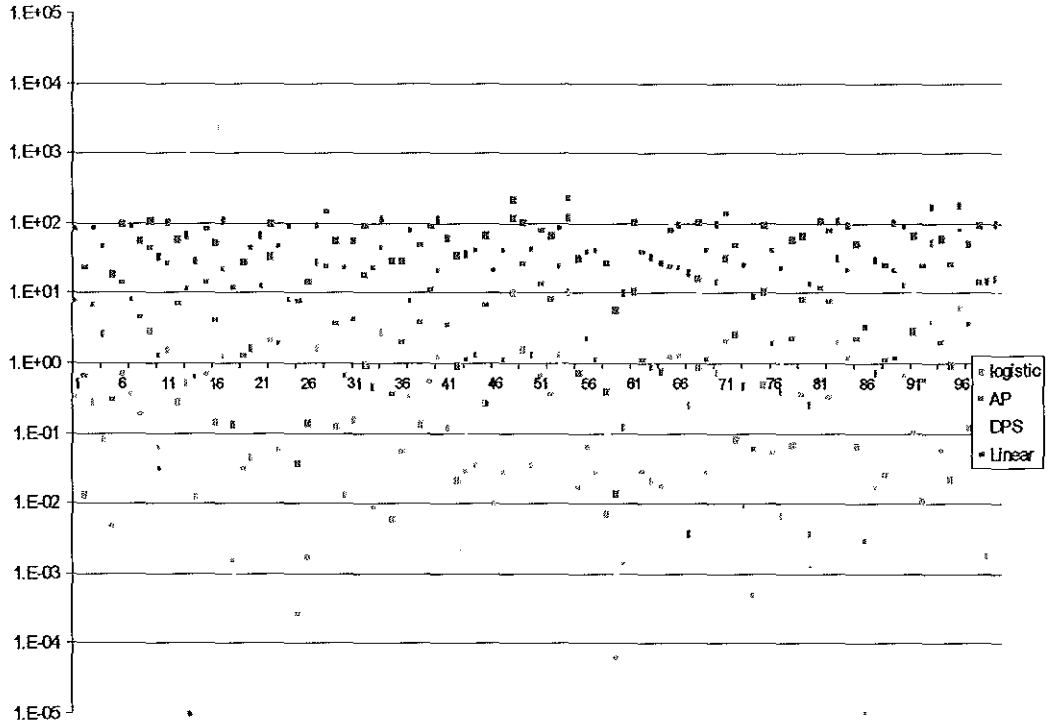


Figure 21: Multihit Model, Response Probability = 1E-06,n=30

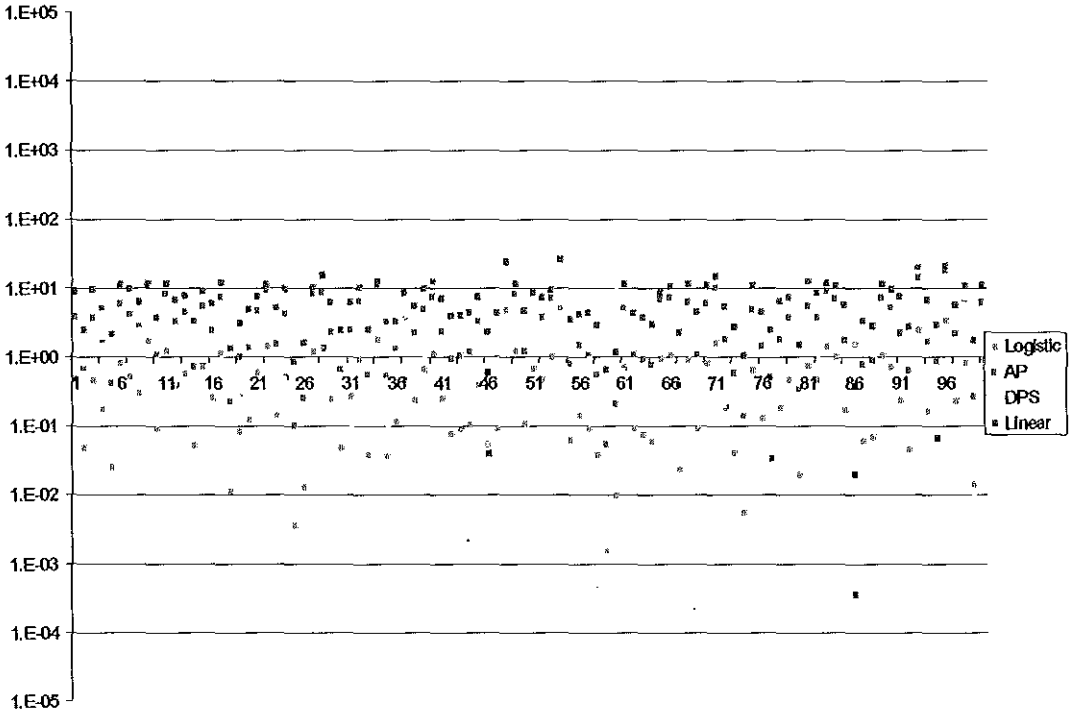


Figure 22: Multihit Model, Response Probability = 1E-04,n=30

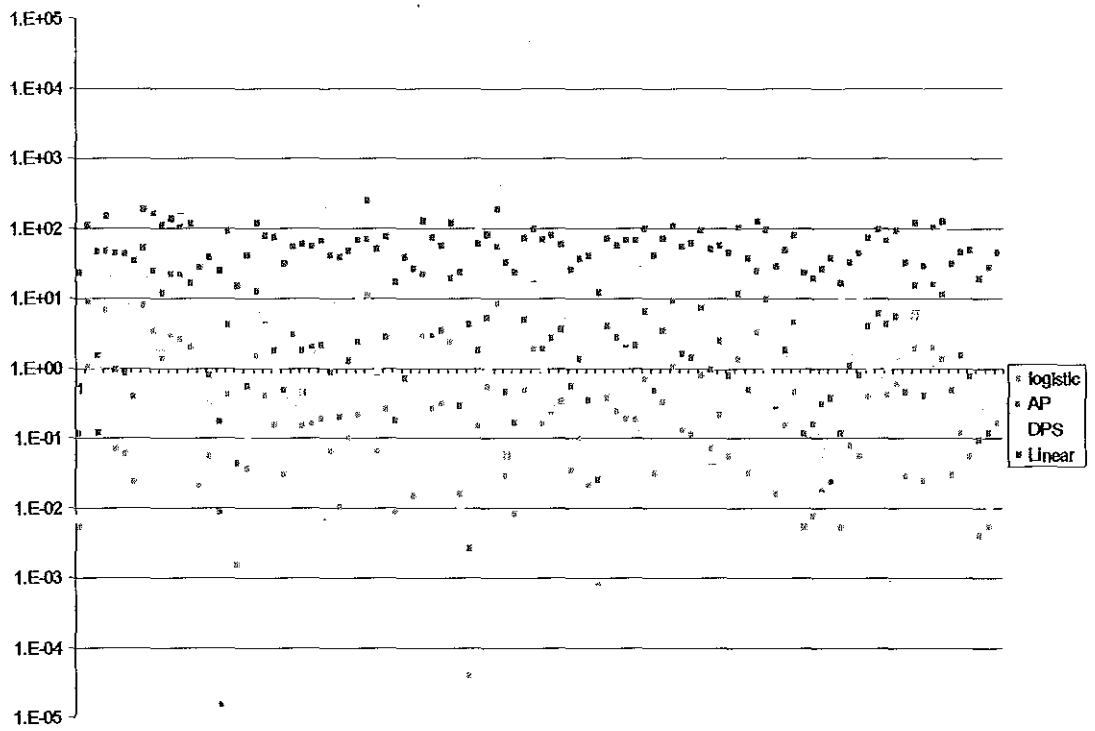


Figure 23: Multihit Model, Response Probability = 1E-06,n=50

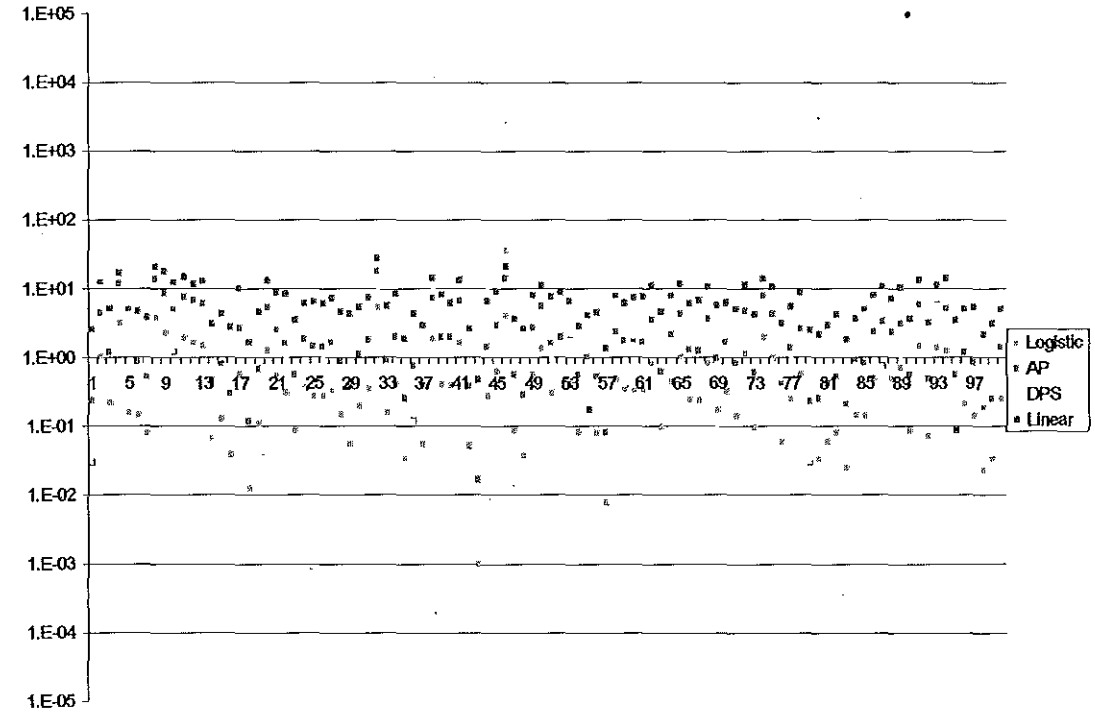


Figure 24: Multihit Model, Response Probability = 1E-04,n=50

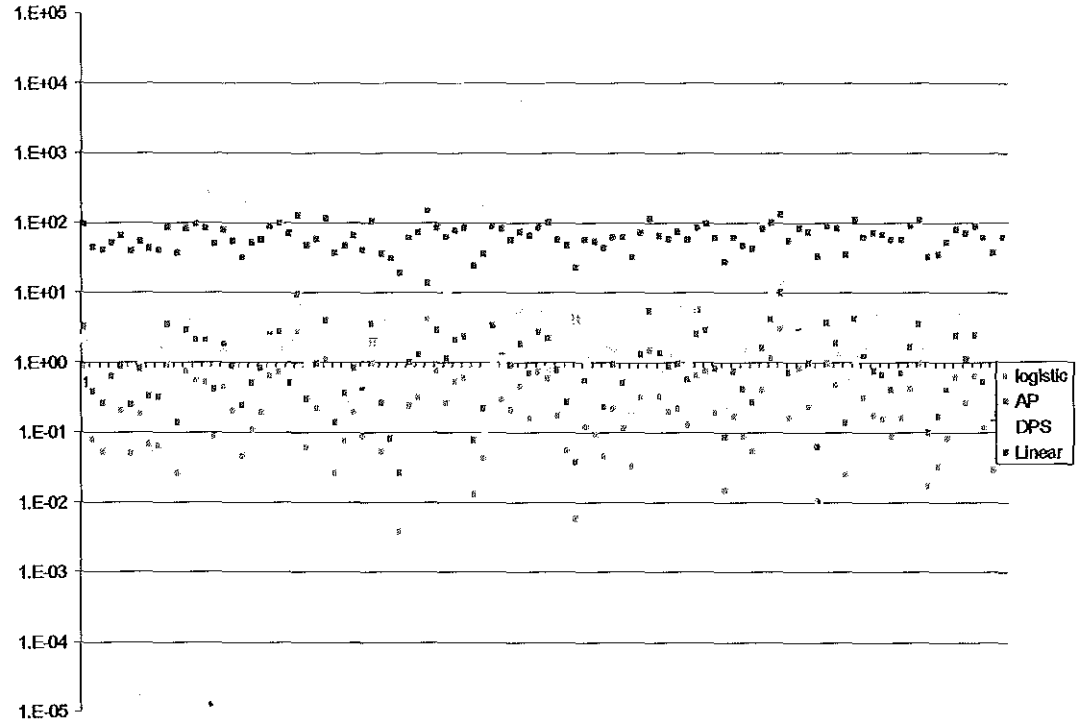


Figure 25: Multi Hit Model, Response Probability = 1E-06,n=100

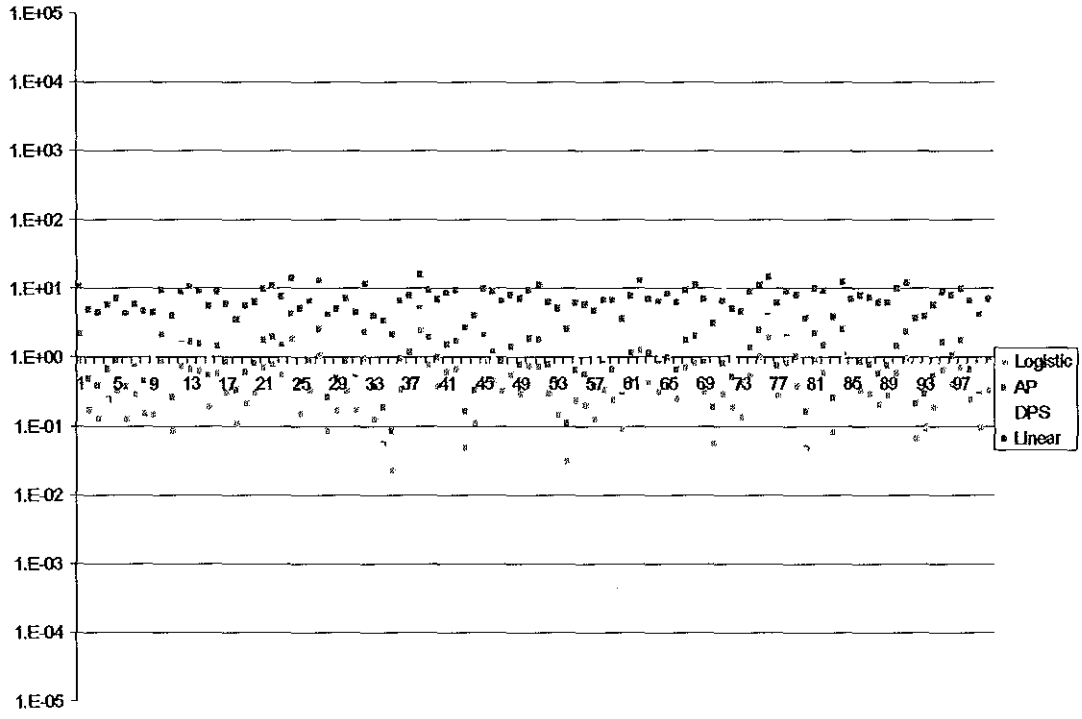


Figure 26: Multihit Model, Response Probability = 1E-04,n=100

4.3.5. Logistic Model

For both 10^{-4} and 10^{-6} response probabilities, logistic assumes the smallest MSE for all sample sizes. The largest MSE is taken by linear extrapolation for all sample sizes. The MSE's for logistic, AP and DPS decrease with increasing sample size with that of AP and DPS at a faster rate. For n=50 and n=100 the MSE for linear extrapolation largely differs from the MSE of AP and DPS. AP and DPS have nearly equal MSE for n=100. The variance of logistic is the smallest for all sample sizes. The variance of linear extrapolation is the largest for all the sample sizes studied. The variances for all the estimators decrease with increasing sample size with the variance of logistic, AP and DPS at a faster rate. Linear extrapolation takes the largest variance for all sample sizes. All estimators lead to upward bias for all sample sizes. Except for linear extrapolation, the means of the other estimators decrease with increasing sample size. Linear extrapolation takes its smallest mean for n=50. The risk from logistic is the smallest for all sample sizes. The next smallest risk is taken by DPS for n=30 and n=100. For n=50, AP has the second smallest risk. Linear extrapolation takes the largest risk for all sample sizes. For all the estimators, the risks decrease as n increases.

Table 15: Empirical measures of closeness for Logistic model

n=30			Logistic	AP	DPS	Linear
	10^{-6}	MSE	1.100E-10	9.893E-09	1.131E-08	3.378E-08
		Variance	9.846E-11	7.618E-09	1.044E-08	1.077E-08
		Mean	4.398E-06	4.870E-05	3.061E-05	1.527E-04
		Minimum	1.700E-10	3.332E-08	1.370E-10	6.227E-06
		Maximum	7.617E-05	6.280E-04	8.168E-04	5.450E-04
		Risk	1.293E+00	1.957E+00	1.602E+00	4.388E+00
	10^{-4}	MSE	8.221E-08	2.190E-06	6.018E-07	2.385E-06
		Variance	7.356E-08	1.326E-06	5.145E-07	8.358E-07
		Mean	1.930E-04	1.030E-03	3.954E-04	1.345E-03
		Minimum	2.645E-07	9.101E-06	1.979E-07	5.484E-05
		Maximum	1.596E-03	6.455E-03	4.492E-03	4.800E-03
		Risk	5.777E-01	8.572E-01	6.507E-01	1.149E+00
n=50	10^{-6}	MSE	1.862E-11	6.880E-10	6.774E-10	2.253E-08
		Variance	1.777E-11	5.359E-10	5.905E-10	5.368E-09
		Mean	1.921E-06	1.334E-05	1.032E-05	1.320E-04
		Minimum	1.200E-09	4.080E-08	8.080E-10	1.312E-05
		Maximum	3.634E-05	1.885E-04	1.441E-04	4.469E-04
		Risk	7.611E-01	9.556E-01	1.173E+00	4.261E+00
	10^{-4}	MSE	2.284E-08	3.503E-07	1.382E-07	1.545E-06
		Variance	2.240E-08	2.184E-07	1.188E-07	4.164E-07
		Mean	1.209E-04	4.632E-04	2.393E-04	1.163E-03
		Minimum	1.024E-06	1.087E-05	6.884E-07	1.156E-04
		Maximum	1.119E-03	3.301E-03	1.714E-03	3.936E-03
		Risk	3.408E-01	4.228E-01	4.956E-01	1.056E+00
n=100	10^{-6}	MSE	4.462E-12	5.851E-11	6.429E-11	2.303E-08
		Variance	4.014E-12	3.713E-11	5.465E-11	2.956E-09
		Mean	1.670E-06	5.625E-06	4.104E-06	1.427E-04
		Minimum	1.206E-08	7.562E-08	1.756E-08	3.250E-05
		Maximum	9.735E-06	2.930E-05	5.099E-05	2.806E-04
		Risk	2.849E-01	5.000E-01	4.663E-01	4.530E+00
	10^{-4}	MSE	9.890E-09	7.291E-08	3.246E-08	1.567E-06
		Variance	9.313E-09	3.946E-08	2.663E-08	2.293E-07
		Mean	1.240E-04	2.829E-04	1.764E-04	1.257E-03
		Minimum	5.180E-06	1.758E-05	5.531E-06	2.863E-04
		Maximum	4.530E-04	9.389E-04	8.720E-04	2.472E-03
		Risk	1.275E-01	2.208E-01	1.840E-01	1.167E+00

For all sample sizes the MSE and variances are larger when estimating 10^{-4} response probability than 10^{-6} response probability. However the risks are smaller when estimating risk probability of 10^{-4} than 10^{-6} except for the case of linear extrapolation.

The frequency table (Table 16) shows that when estimating response probability 10^{-6}, 20% of logistic, 3% of AP and 13% of DPS estimates are smaller than the true value at least with an

order of magnitude. For n=50, 19% of logistic, 1% of AP and 19% of DPS are smaller than the true value by one or more orders of magnitude. In the case of n=100, 4%, 1% and 6% logistic, AP and DPS, respectively, happen to be less than the true value with at least one order of magnitude. As n increases, increasingly large number of estimates from linear extrapolation exceed the true value by more that two orders of magnitudes.

For 10^{-4} response probability estimation, 12% of logistic, 1% of AP and 11% of DPS are observed to be less than the true value by at least one order of magnitude for n=30. The proportion of estimates lower than the true value with at least one order of magnitude are 9% and 11% in logistic and AP, respectively. These proportions for n=100, are 1% and 1%, respectively. For n=50 and n=100 very large number of logistic, AP and DPS estimates are in agreement with the true value in terms of orders of magnitudes.

Table 16: Frequency distribution for the estimators for Logistic model

		n=30				n=50				n=100			
		Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear	Logistic	AP	DPS	Linear
10^{-6}	<=-2	9	0	5	0	5	0	3	0	0	0	0	0
	-1	11	3	9	0	14	1	16	0	4	1	6	0
	0	66	38	60	1	78	61	60	0	96	85	83	0
	1	14	45	19	34	3	37	18	38	0	14	11	20
	>=2	0	14	7	65	0	1	3	62	0	0	0	80
10^{-4}	<=-2	3	0	2	0	0	0	1	0	0	0	0	0
	-1	9	1	9	0	9	0	9	0	1	0	1	0
	0	85	63	76	42	90	91	83	46	99	100	99	33
	1	3	36	13	58	1	9	7	54	0	0	0	67
	>=2	0	0	0	0	0	0	0	0	0	0	0	0

The plots (Figures 27-32) reveal that for 10^{-6} response probability linear extrapolation seems to give the largest estimate for all sample sizes. The huge overestimation for this estimator is obviously featured for n=100. AP performs favorably well n=100. For 10^{-4} response probability, AP shows desirable behavior for all sample sizes. In particular for n=50 and n=100 its behavior is quite superb. For both 10^{-4} and 10^{-6} cases, the number of underestimation cases decrease as n increases and the estimates from AP and DPS become

more concentrated around with little upward bias. Linear extrapolation is unaffected by the change in n.

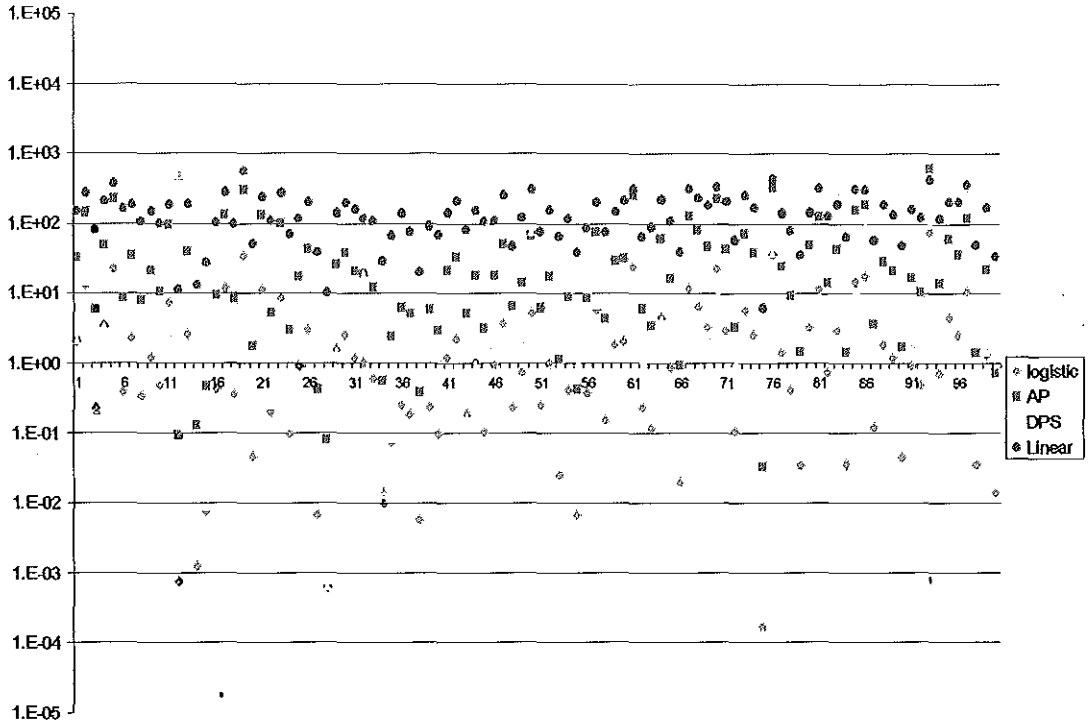


Figure 27: Logistic Model, Response Probability = 1E-06,n=30

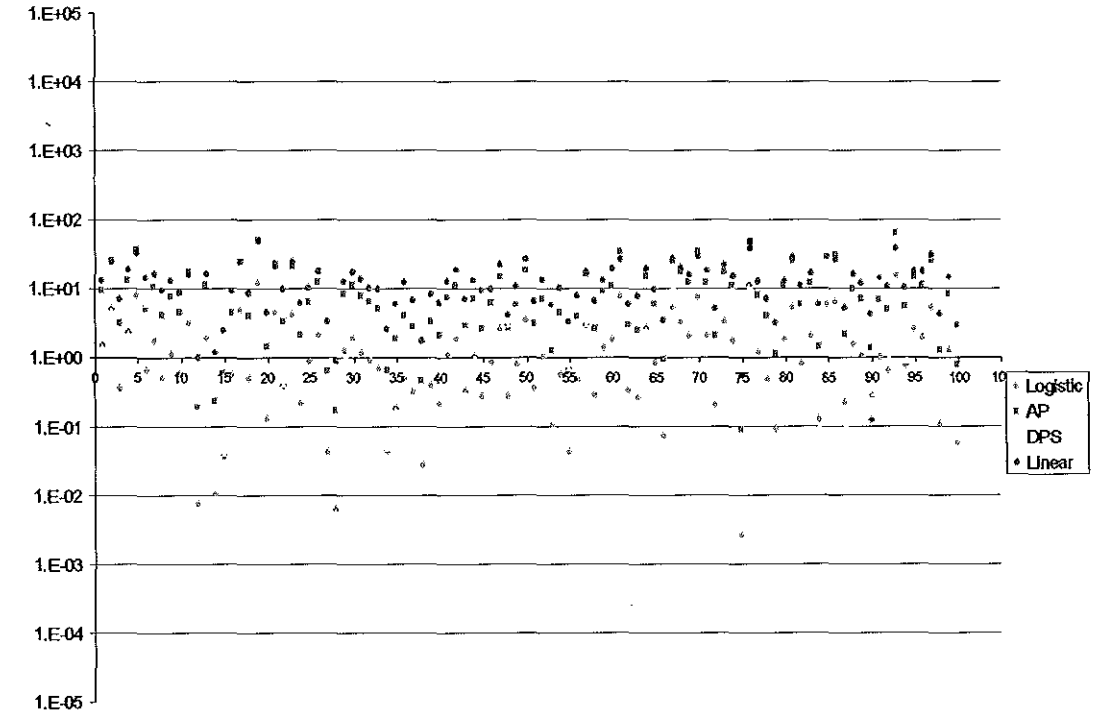


Figure 28: Logistic Model, Response Pronbability = 1E-04,n=30

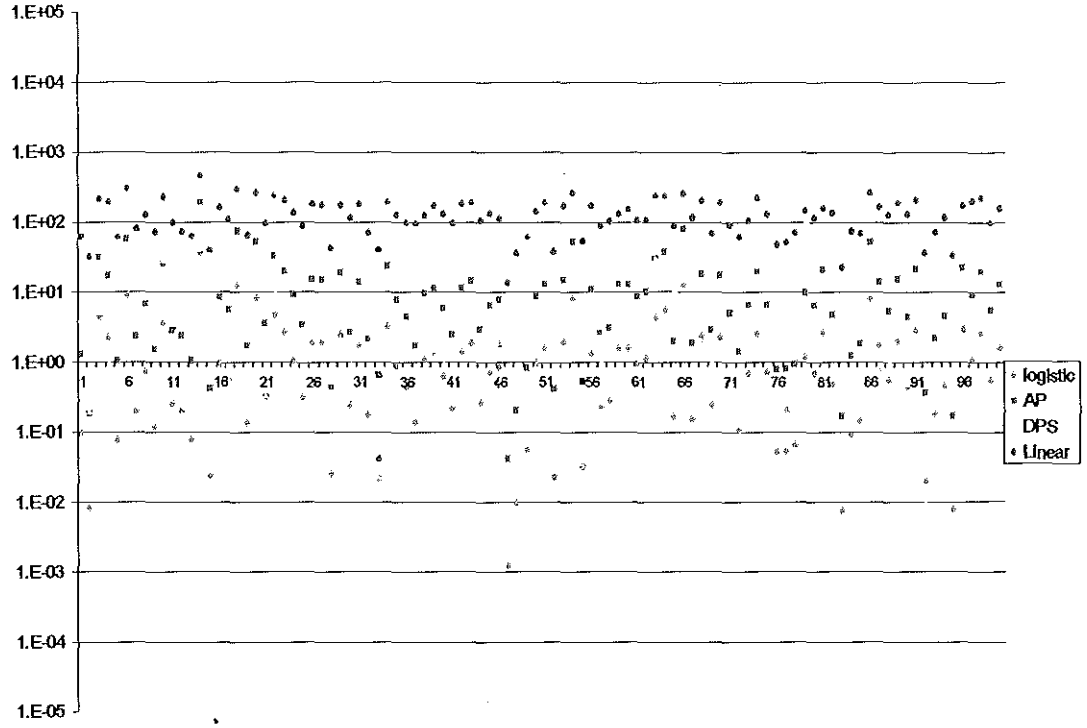


Figure 29: Logistic Model, Response Probability = 1E-06,n=50

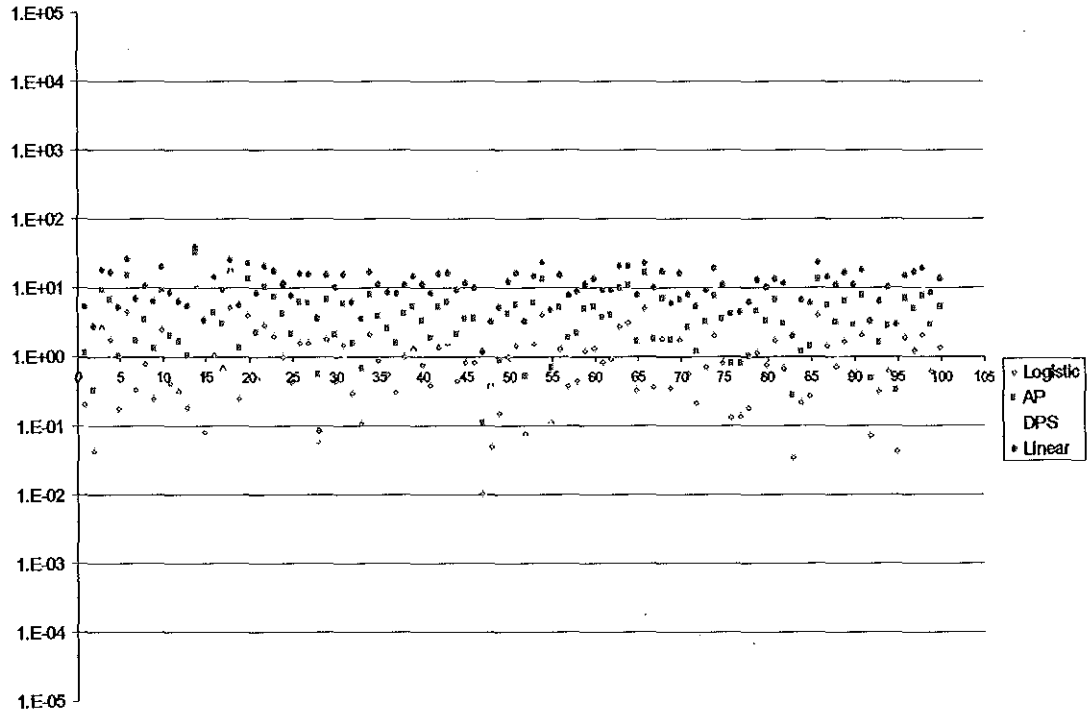


Figure 30: Logistic Model, Response Probability = 1E-04,n=50

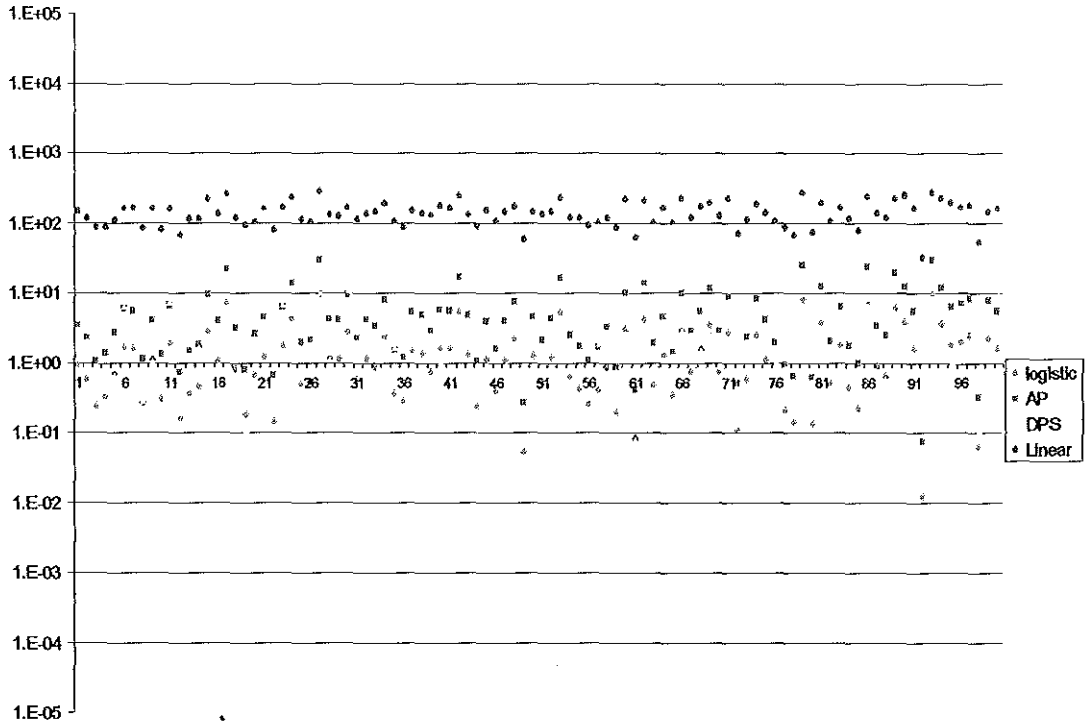


Figure 31: Logistic Model, Response Probability = 1E-06,n=100

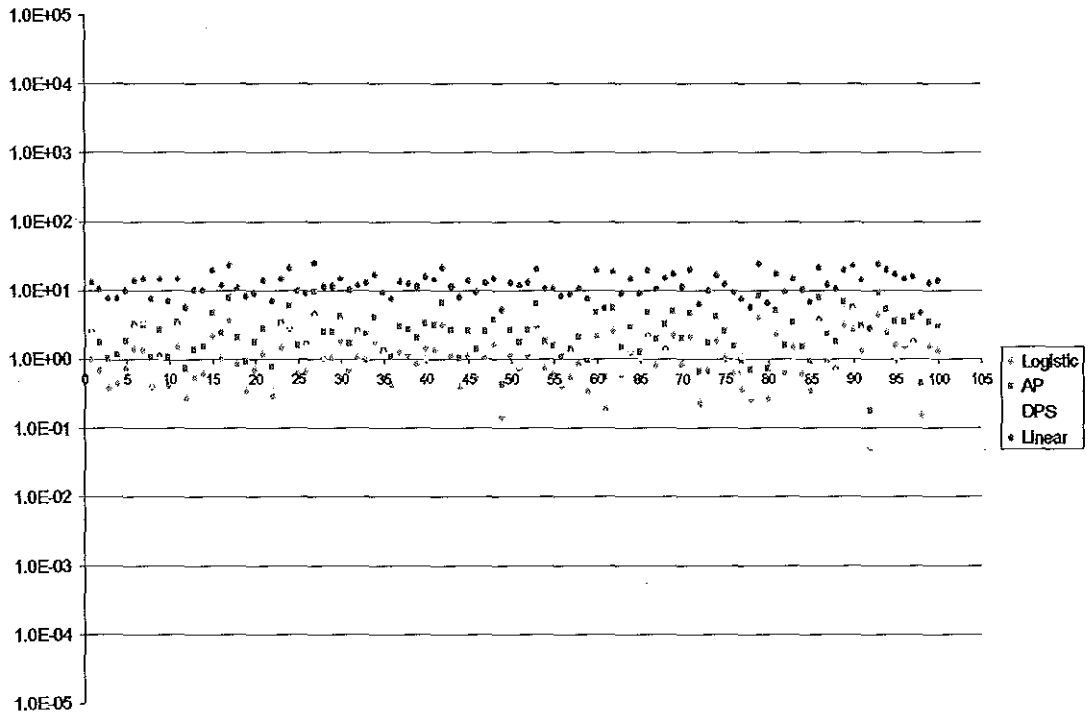


Figure 32: Logistic Model, Response Probability = 1E-04,n=100

4.3. Discussion

The Onehit curve has always low dose linearity. This could be a possible reason for the strong support linear extrapolation received from the empirical measures of closeness. The approximation of this model by the logistic is likely to result in underestimation unless the fitted logistic model has low dose concavity. It has to be noted that low dose concavity is unlikely to be supported by data generated from one hit model in particular when the number of animals per dose group is small. This is evidenced by the extreme underestimation values from logistic when n=30. Justifiably enough, linear extrapolation based on logistic model, which is flatter than the Onehit model, may also lead to underestimation. With the objective of protecting human health, however, underestimation errors are more serious than overestimation error. In this regard, AP estimation which has superior performance than logistic and DPS in terms of the measure of risk can be considered. In other words, MSE seems to fail here as a good criterion for assessing the performance of the estimators if underestimation should be avoided for the reason mentioned above. In particular, when the sample size is 50, AP has desirable features (see Figures 3-6 and Table 7). In addition, the fact that the MSE and variance of AP show a fast decreasing trend as sample size per dose group increases is an attractive feature. This endows it a wider opportunity to be considered as an immediate alternative to linear extrapolation especially when sample size per dose group is larger.

The Multistage model considered in this study has low dose linearity because the coefficient of the linear dose term is greater than zero. For the same reason given to the Onehit case, underestimation is likely to occur from logistic estimation. Again for the multistage case linear extrapolation is superior in terms of the MSE and risk criteria. AP, which essentially is a logistic type, was also observed to lead to many underestimation errors. The very large

variability of DPS coupled with its tendency to give large overestimation limits its use as a favorable estimator. Among the five models considered the estimations from logistic and AP tend to be the most stable when the true model is Multistage.

The Weibull model considered as the true model has low dose convexity. Thus, we expect overestimation from linear extrapolation and underestimation from logistic estimation. The results are in concordance with our expectation. Even if MSE favors logistic, from the point of view of reducing risk to human health the choice of linear extrapolation, which has the smallest risk, is the best. On the other hand, AP was observed to have the second smallest risk for all sample sizes. Furthermore, the MSE and risk of AP were observed to decrease as n increases.

For the Multihit model logistic performs superior to the other estimators in terms of MSE. But if the risk measure is considered, AP is found to be the best. Here also MSE seems to fail us as a good criterion since it favored the logistic which is dominated by underestimation. Moreover, AP also assumed the second smallest MSE on top of its superiority with regard to the risk measure. Furthermore, the fact that the MSE of AP decreases at a faster rate as n increases is another desirable property (see Figures 33 and 34 below).

When the underlying model is logistic, the large overestimation from linear extrapolation is apparent. From this it can also be learned that linear extrapolation leads to very large overestimation if based on a model steeper than logistic in the low dose area regardless of the form of the true dose response curve. In the case of an underlying logistic model no error of model selection is committed and, hence, the only error comes as a result of binomial sampling variability. For this reason we cannot expect logistic to perform inferior to the other estimators. Nevertheless, on the account of reduced risk to human health, the behavior of AP is quite favorable when estimating 10^{-6} response probability and when sample size per dose

group is 100. In the same lines the patterns exhibited by AP when estimating 10^{-4} response probability is very attractive.

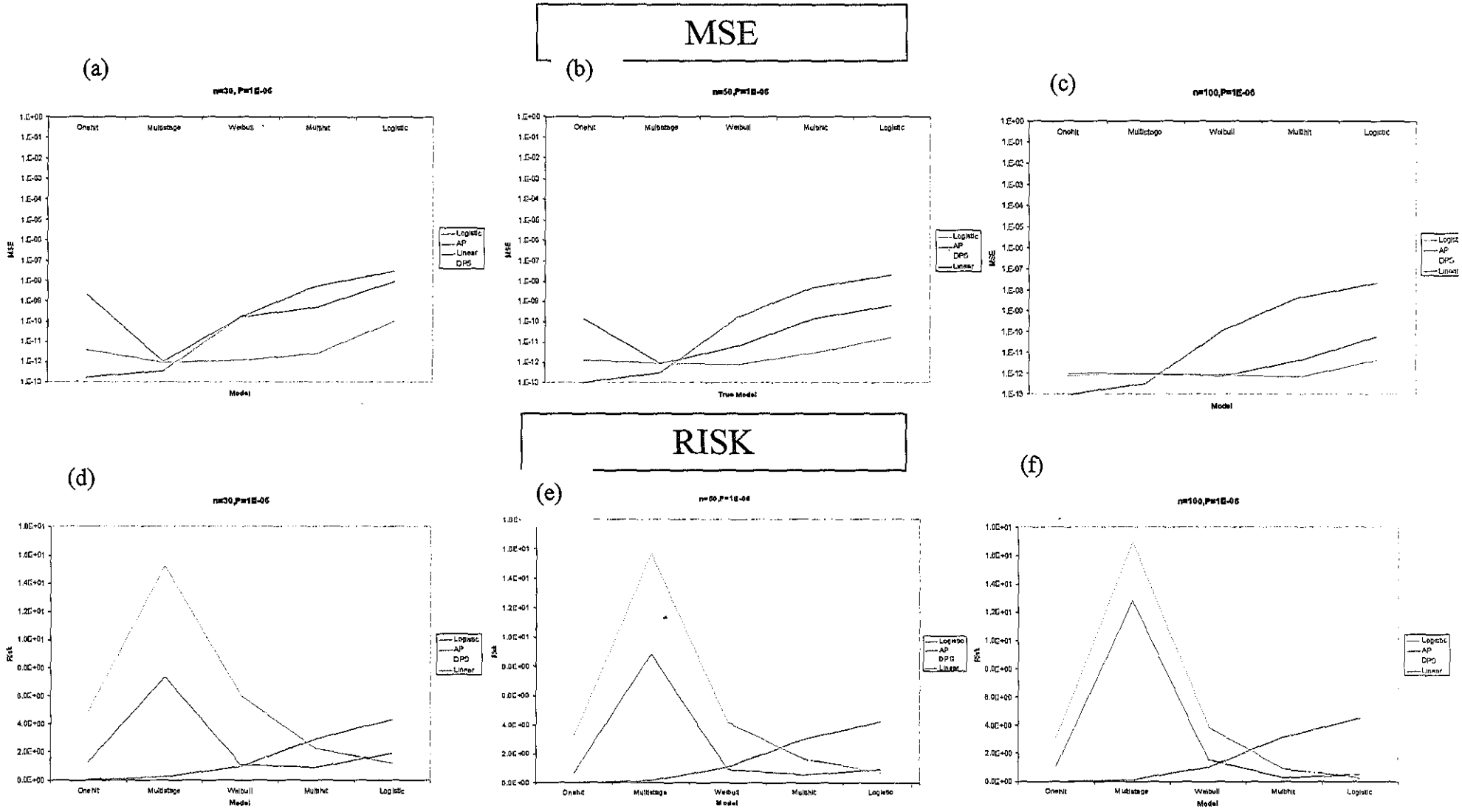


Figure 33: Line graph of MSE and Risk for Response Probability = 10^{-6}

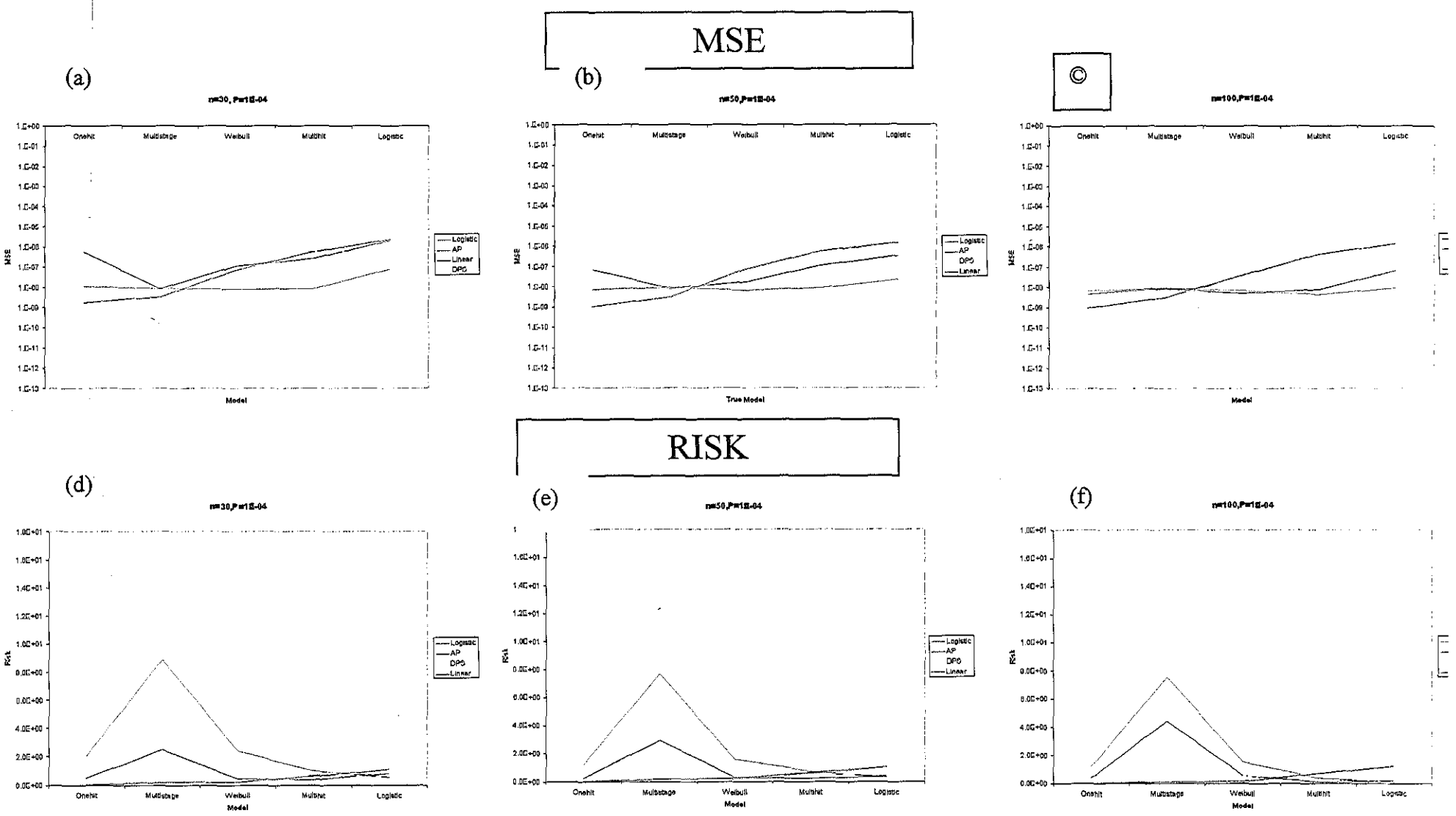


Figure 34: Plot of MSE and Risk for response probability = 10^{-4}

In general which criteria (MSE and Risk) is better in comparing the estimators seeks further investigation. In our case, however, the two criteria do not lead to the same conclusion. A good case in point is when the true model is Multistage. In cases where the two criteria select different estimators as best the scatter plots can be looked at to select the best one.

Both the risk measure and MSE suggest linear extrapolation as best when the true model is Onehit or multistage which have low dose linearity. For the other models, MSE identified logistic as superior except for n=100 of Weibull model in which case AP is the best. According to the risk measure, linear extrapolation is the best for n=30 and n=100 and AP is the best for n=50 of Weibull model. AP is the best for all sample sizes in Multihit model. In the case of logistic model, the risk measure indicates the performances of Logistic, AP and DPS are nearly the same.

Even if DPS has not been found to be best for any model, the line graphs of MSE and Risk (Figures 33 and 34) show that its performance improves increasingly as n increases. Similarly, AP and Logistic also reveal an improving trend as n changes. On the other hand, Linear extrapolation seems to be unaffected by the change in n.

Furthermore, all estimators were seen to be more stable when sample size per dose group increases. Extrapolating response probability closer to the experimental range is better than those values far away. However, the empirical MSE's and variances of the estimators are smaller when estimating 10^{-6} response probability than 10^{-4} response probability. The scatter plots and the risk measures, on the other hand, imply that the estimators perform better when the response probability to be estimated is 10^{-6} than when is 10^{-4}. This could be one possible indication of the failure of MSE as a good criterion for the estimation problem considered in this project.

5. Summary

The performances of two intuitively appealing new approaches for low dose risk extrapolation were studied under five different models and three sample sizes per dose group. One of the approaches, labeled as AP, works by adding a point near zero dose. The other approach, shorthanded as DPS, averages logistic estimates computed by successively dropping observations from the bottom end of the data set. The performances of these estimators were compared with each other and the standard estimate from logistic model and linear extrapolation based on logistic model. The models considered were Onehit, Multistage, Weibull, Multihit and Logistic. For each combination of sample size and true model, a total of fifteen Monte Carlo experiments were conducted. To work with realistic values of the parameters of the models, these models as fitted to the Dimethylnitrosamine data set were used. Empirical MSE and a risk measure for a judiciously chosen loss function were used as a criteria for assessing the performances of the estimators.

The results indicate that the performance of AP is superior when the true model is Multihit or Logistic. When the underlying model is Onehit, Multistage or Weibull, linear extrapolation is best. The Logistic estimator was observed to be dominated by underestimation errors unless the true model itself is logistic. However, from the point of view of reduction of risk to public health, underestimation is undesirable. DPS estimations were observed to be highly unstable. However, the performance of DPS has been noticed to increasingly improve as sample size per dose group increases. In some cases, its performance was noted to exceed that of logistic. The overestimation from linear extrapolation is enormous when the true model is Multihit or logistic. All estimators, except linear extrapolation, have shown dependence on sample size per dose group. The study is inconclusive as to the suitable choice of sample size per dose

group for each estimator. Estimations of risk probabilities close to the experimental range are done better than those far away.

The findings described in the previous paragraph are valid only if the underlying dose response model have low dose convexity in the cases of Weibull, Multihit and Logistic and low dose linearity in the cases of Onehit and Multistage. When the Multistage model has low dose convexity the performances of the estimators may differ from what is found in this study. The absence of background is also another assumption imposed on the models. Hence verification of this assumption is also necessary before taking the findings of the study for granted for a given application.

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Appendix I : The Simulation Probabilities

Toxin	Dose	One hit	Multistage	Weibull	Multihit	Logistic
Liver Tumor	2	0.0629138	0.0375104	0.0220632	0.0165915	0.0115068
Dimethylnitrosamine	5	0.1499414	0.1010250	0.0793818	0.0810760	0.0749074
Rats	10	0.2774004	0.2207318	0.1997724	0.2340379	0.2599193
ppm	20	0.4778498	0.4750226	0.4514553	0.5372512	0.6036905
Van Ryzin (1980)	50	0.8029898	0.9329958	0.8920585	0.9343009	0.9137629

Appendix II: The Computer Programs

```
Program Estimate(Input,Output,DataFile,SimFile,OutFile);
{This program computes logistic and Linear extrapolation estimates}.
Type ExpReal = Array[0..20] of Real;
     ExpInt = Array[0..20] of Integer;
     Beta = Array[0..1] of Real;
     OutRec = Record
            Log_Est: Array[1..5] of Real;
            New_Est: Array[1..5] of Real;
            End;
Var SimFile: File of ExpInt;
    OutFile,Coeffile: Text;
    DoseFile:File of Real;
    NumbFile:File of Integer;
    OutData:Outrec;
    SimData:ExpInt;
    DoseName,NumbName,CoefName,SimName,OutName: String[13];
    D0: Array[1..5] of Real;
    q,m,i,j,l:Integer;
    D:ExpReal;
    N:ExpInt;
    B1:Beta;
    Dose,Deviance,Slope:Real;
    Numb:Integer;
    st1:string[12];


Procedure Read_Data;
Var i:Integer;
Begin
     m := 0;
     WHile NOT EOF(DoseFile) Do
         Begin
              Read(DoseFile,Dose);
                D[m]:=Dose;
              Read(NumbFile,Numb);
                N[m]:= Numb;
                M:=M+1;
         End;
       m := m-1;
End;

Function Prob(B:Beta;Dose:Real):Real;
Begin
  Prob:= 1/(1+Exp(-(B[0] + B[1]*Dose)));
End;

Procedure Logistic(Top:Integer;Var  Y:ExpInt; Var B:Beta;Var
Deviance:Real);
Const Epsilon = 0.000001;

Var Z,P,W:ExpReal;
    J,I:Integer;
    Prev_Dev:Real;

Procedure Initialize;
Var i:Integer;
Begin
For i:= Top to m Do
    Begin
```

```
          P[i] := (Y[i]+0.5)/(N[i]+1);
          Z[i] := ln(P[i]/(1-P[i]));
          W[i] := N[i]*P[i]*(1-P[i]);
     End;
End;

Procedure WLS;
Var i:Integer;
     E,SW, WD,WD2,WZ,WZD,Det,t:Real;
Begin
      E:=0;SW:=0;WD:=0;WD2:=0;WZ:=0; WZD:=0;Det:=0;
      Deviance := 0;
      For i:= top to m Do
          Begin
               WD := WD+W[i]*D[i];
               SW := SW+W[i];
               WD2 := WD2 + W[i]*D[i]*D[i];
               WZ := WZ + W[i]*Z[i];
               WZD := WZD + W[i]*Z[i]*D[i];
           End;
       Det := SW*WD2 - WD*WD;
       B[0] := ((WD2*WZ) - (WD*WZD))/Det;
       B[1] := ((SW*WZD) - (WZ*WD))/Det;
       For i:= top to m Do
           Begin
                E:=B[0]+B[1]*D[i];
                P[i]:=Exp(E)/(1+Exp(E));
                W[i]:= N[i]*P[i]*(1-P[i]);
                Z[i]:= E + (Y[i]-N[i]*P[i])/(N[i]*P[i]*(1-P[i]));
                If (Y[i] <> 0) and (Y[i] <> N[i]) then
                Deviance := Deviance + 2*(Y[i]*(ln(Y[i])-Ln(N[i]*P[i]))+
                          (N[i]-Y[i])*(Ln(N[i]-Y[i])-Ln(N[i]*(1-P[i]))));
           End;
End;
Begin
      Initialize;
      Deviance:=0;
      Prev_Dev:=0;
      Repeat
            Prev_Dev := Deviance;
            WLS;
      Until Abs(Deviance - Prev_Dev) <= Epsilon ;
End;
Begin
      Write('Dose file: ');
      Readln(DoseName);
      Write('Number of animals file: ');
      Readln(NumbName);
      Write('Simulation data file: ');
      Readln(SimName);
      Write('OutPut file : ');
      Readln(OutName);
      Write('Coefficient file : ');
      Readln(CoefName);
      Assign(DoseFile,DoseName);
      Assign(NumbFile,NumbName);
      Assign(SimFile,SimName);
      Assign(OutFile,OutName);
      Assign(Coeffile,CoefName);
      Reset(DoseFile);
      Reset(NumbFile);
      Reset(SimFile);
      Rewrite(OutFile);
```

```
      Rewrite(Coeffile);
      Write('Number of Low doses to estimate risk at : ');
      Readln(l);
      Write('Enter the ',l,' doses separated by comma:  ');
      For i:= 1 to l do
          begin
           Read(D0[i]);
           D0[i] :=ln(D0[i]);
          End;
      Writeln;
      Read_Data;
      while not EOF(SimFile) do
            Begin
                 Read(SimFile,SimData);
                 For i := 1 to l do
                     Begin
                         Outdata.Log_Est[i]:=0;
                         OutData.New_Est[i]:=0;
                      End;
                 Logistic(0,SimData,B1,Deviance);
                 For i := 0 to m do Write(Coeffile,SimData[i],' ');
                 Writeln(coeffile,B1[0]:12:8,' ',B1[1]:12:8,'',Deviance:13:7);
                 For i:= 1 to l do OutData.Log_Est[i] := Prob(B1,D0[i]);
                 {For j:=0 to m-2 do
                   Begin
                     Logistic(j,SimData,B1,Deviance);
                     For i:= 1 to l do
                         OutData.New_Est[i] := OutData.New_Est[i] +
                                               Prob(B1,ln(D0[i]));
                   End;}
                 Slope :=  Prob(B1,D[0])/Exp(D[0]) ;
                 For i := 1 to l do
                          OutData.New_Est[i] := Slope * Exp(D0[i]);
                 For i := 1 to l do
                          Write(OutFile,OutData.Log_Est[i]:14:12,' ');
                 For i:= 1 to l do
                          Write(OutFile,OutData.New_Est[i]:14:12,' ');
                 Writeln(OutFile);
            End;
Close(DoseFile);
Close(NumbFile);
Close(SimFile);
Close(OutFile);
Close(coeffile);
End.

{$N+}
Program Estimate(Input,Output,DataFile,SimFile,OutFile);
{This program produces AP estimates}
Type ExpReal = Array[0..20] of Double;
     ExpInt = Array[0..20] of Integer;
     ExpInt1 = Array[0..20] of Double;
     Beta = Array[0..1] of Double;
     OutRec = Record
              New_Est: Array[1..5] of Double;
              End;
Const P0 = 0.00000001;
Var SimFile: File of ExpInt;
    OutFile: Text;
    DoseFile:File of Real;
    NumbFile:File of Integer;
    OutData:Outrec;
    SimData:ExpInt;
```

```
    DoseName,NumbName,SimName,OutName: String[13];
    D0: Array[1..5] of double;
    U,q,m,i,j,l:Integer;
    D:ExpReal;
    N:ExpInt1;
    B1, B11:Beta;
    Dose: Real;
    Logit_p0:Double;
    Numb:Integer;
    st1:string[12];
    VarD,VarB0,VarB1,Cov,VarB01,VarB11,Cov1,P:Double;

Procedure Read_Data;
Var i:Integer;
Begin
     m := 0;
     WHile NOT EOF(DoseFile) Do
         Begin
              Read(DoseFile,Dose);
                D[m]:=Dose;
              Read(NumbFile,Numb);
                N[m]:= Numb;
                M := M+1;
         End;
       m := m-1;
End;

Function Prob(B:Beta;Dose:Double):Double;
Begin
  Prob:= Exp(B[0] + B[1]*Dose)/(1+Exp(B[0] + B[1]*Dose));
End;

Procedure Logistic(Top:Integer;Var Y:ExpInt;Var B:Beta;Var
VarB0,VarB1,Cov:Double);
Const Epsilon = 0.000000001;

Var Z,P,W:ExpReal;
    J,I:Integer;
    Deviance,Prev_Dev:Double;
    SW, WD,WD2,WZ,WZD,Det: Double;

Procedure Initialize;
Var i:Integer;
Begin
For i:= top to m Do
    Begin
         P[i] := (Y[i]+0.5)/(N[i]+1);
         Z[i] := ln(P[i]/(1-P[i]));
         W[i] := N[i]*P[i]*(1-P[i]);
    End;
End;

Procedure WLS;
Var i:Integer;
    E:Double;
Begin
     E:=0;SW:=0;WD:=0;WD2:=0;WZ:=0; WZD:=0;Det:=0;
     Deviance := 0;
     For i:= top to m Do
         Begin
              WD := WD+W[i]*D[i];
              SW := SW+W[i];
              WD2 := WD2 + W[i]*D[i]*D[i];
```

```
            WZ := WZ + W[i]*Z[i];
            WZD := WZD + W[i]*Z[i]*D[i];
        End;
     Det := SW*WD2 - WD*WD;
     B[0] := ((WD2*WZ) - (WD*WZD))/Det;
     B[1] := ((SW*WZD) - (WZ*WD))/Det;
     For i:= top to m Do
         Begin
              E:=B[0]+B[1]*D[i];
              P[i]:= Exp(E)/(1+Exp(E));
              W[i]:= N[i]*P[i]*(1-P[i]);
              Z[i]:= E + (Y[i]-N[i]*P[i])/(N[i]*P[i]*(1-P[i]));
              If (Y[i] <> 0) and (Y[i] <> N[i]) then
              Deviance := Deviance + 2*(Y[i]*(ln(Y[i])-Ln(N[i]*P[i]))+
                       (N[i]-Y[i])*(Ln(N[i]-Y[i])-Ln(N[i]*(1-P[i]))));
         End;
End;
Begin
     Initialize;
     Deviance:=0;
     Prev_Dev:=0;
     q := 0;
     Repeat
          q := q + 1;
          Writeln('Iteration ..',q);
          Prev_Dev := Deviance;
          WLS;
     Until Abs(Deviance - Prev_Dev) <= Epsilon ;
     VarB0 := WD2/Det;
     VarB1 := SW/Det;
     Cov   :=-Wd/Det;
End;
Begin
     Write('Dose file: ');
     Readln(DoseName);
     Write('Number of animals file: ');
     Readln(NumbName);
     Write('Simulation data file: ');
     Readln(SimName);
     Write('OutPut file : ');
     Readln(OutName);
     Assign(DoseFile,DoseName);
     Assign(NumbFile,NumbName);
     Assign(SimFile,SimName);
     Assign(OutFile,OutName);
     Reset(DoseFile);
     Reset(NumbFile);
     Reset(SimFile);
     Rewrite(OutFile);
     Write('Number of Low doses to estimate risk at : ');
     Readln(l);
     Write('Enter the ',l,' doses separated by comma:  ');
     For i:= 1 to l do
         Begin
              Read(D0[i]);
              D0[i] := Ln(D0[i]);
         End;
     Writeln;
     Read_Data;
     While not EOF(SimFile) do
          Begin
               Read(SimFile,SimData);
               For i := 1 to l do OutData.New_Est[i] := 0;
```

```
    Dose:Real;
    Numb:Integer;
    st1:string[12];

Procedure Read_Data;
Var i:Integer;
Begin
     m := 0;
     WHile NOT EOF(DoseFile) Do
         Begin
              Read(DoseFile,Dose);
                D[m]:=Dose;
              Read(NumbFile,Numb);
                N[m]:= Numb;
                M:=M+1;
         End;
       m := m-1;
End;

Function Prob(B:Beta;Dose:Real):Double;
Begin
  Prob:= 1/(1+Exp(-(B[0] + B[1]*Dose)));
End;

Procedure Logistic(Bottom:Integer;Var Y:ExpInt; Var B:Beta);
Const Epsilon = 0.000000001;

Var Z,P,W:ExpReal;
    t,J,I:Integer;
    Deviance,Prev_Dev:Real;

Procedure Initialize;
Var i:Integer;
Begin
For i:= 0 to Bottom Do
    Begin
         P[i] := (Y[i]+0.5)/(N[i]+1);
         Z[i] := ln(P[i]/(1-P[i]));
         W[i] := N[i]*P[i]*(1-P[i]);
    End;
End;

Procedure WLS;
Var i:Integer;
    E,SW, WD,WD2,WZ,WZD,Det:Real;
Begin
     E:=0;SW:=0;WD:=0;WD2:=0;WZ:=0; WZD:=0;Det:=0;
     Deviance := 0;
     For i:= 0 to Bottom Do
         Begin
              WD := WD+W[i]*D[i];
              SW := SW+W[i];
              WD2 := WD2 + W[i]*D[i]*D[i];
              WZ := WZ + W[i]*Z[i];
              WZD := WZD + W[i]*Z[i]*D[i];
          End;
      Det := SW*WD2 - WD*WD;
      B[0] := ((WD2*WZ) - (WD*WZD))/Det;
      B[1] := ((SW*WZD) - (WZ*WD))/Det;
      For i:= 0 to Bottom Do
          Begin
               E:=B[0]+B[1]*D[i];
               P[i]:=Exp(E)/(1+Exp(E));
```

```
                W[i]:= N[i]*P[i]*(1-P[i]);
                Z[i]:= E + (Y[i]-N[i]*P[i])/(N[i]*P[i]*(1-P[i]));
                If (Y[i] <> 0) and (Y[i] <> N[i]) then
                Deviance := Deviance + 2*(Y[i]*(ln(Y[i])-Ln(N[i]*P[i]))+
                        (N[i]-Y[i])*(Ln(N[i]-Y[i])-Ln(N[i]*(1-P[i]))));
          End;
End;
Begin
     Initialize;
     Deviance:=0;
     Prev_Dev:=0;
     t:=0;
     Repeat
          t := t + 1;
          writeln('iteration... ', t);
          Prev_Dev := Deviance;
          WLS;
     Until Abs(Deviance - Prev_Dev) <= Epsilon ;
End;
Begin
     Write('Dose file: ');
     Readln(DoseName);
     Write('Number of animals file: ');
     Readln(NumbName);
     Write('Simulation data file: ');
     Readln(SimName);
     Write('OutPut file : ');
     Readln(OutName);
     Assign(DoseFile,DoseName);
     Assign(NumbFile,NumbName);
     Assign(SimFile,SimName);
     Assign(OutFile,OutName);
     Reset(DoseFile);
     Reset(NumbFile);
     Reset(SimFile);
     Rewrite(OutFile);
     Write('Number of Low doses to estimate risk at : ');
     Readln(l);
     Write('Enter the ',l,' doses separated by comma:  ');
     For i:= 1 to l do Read(D0[i]);
     Writeln;
     Read_Data;
     While not EOF(SimFile) do
          Begin
               Read(SimFile,SimData);
               For i := 1 to l do
                   Begin
                       OutData.New_Est[i]:=0;
                   End;
               For j:=  m downto 2 do
                 Begin
                   Logistic(j,SimData,B1);
                   For i:= 1 to l do
                       OutData.New_Est[i] := OutData.New_Est[i] +
                                             Prob(B1,ln(D0[i]));
                 End;
               For i := 1 to l do
                        OutData.New_Est[i] := OutData.New_Est[i]/(m-1);
               For i:= 1 to l do
                        Write(OutFile,OutData.New_Est[i]:18:15,' ');
               Writeln(OutFile);
          End;
 Close(DoseFile);
```

```
    Assign(NumbFile,NumbName);
    Assign(ProbFile,ProbName);
    Assign(OutFile,Filename);
    Reset(NumbFile);
    Reset(ProbFile);
    Rewrite(OutFile);
    Write('Enter Number of Simulations: ');
    Readln(k);
    Read_Data;
     For l := 1 to k do
       Begin
         For J := 0 to m do OutData.B[j] := 0;
         For J := 0 to m do
              For I := 1 to N[j] do
                  Begin
                        If Uni_Rand - P[j] <= 0
                           Then OutData.B[j] := OutData.B[j] + 1;
                  End;
         Write(Outfile,OutData);
       End;
     Close(NumbFile);
     Close(ProbFile);
     Close(OutFile);
End.
```