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Nonparametric Procedure for Identifying the Minimum Effective Dose with Ordinal Response Data

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ABSTRACT

The primary interest of drug development studies is identifying the lowest dose level producing a desirable effect over that of the zero-dose control, which is referred as the minimum effective dose (MED). In this paper, we suggest a nonparametric procedure for identifying the MED with binary or ordered categorical response data. Proposed test and Williams' test are compared by Monte Carlo simulation study and discussed.

keywords : Binary response; Minimum effective dose (MED); Nonparametric test; Monte Carlo study; Ordinal response

1. Introduction

In exploration of dose-response relationships, focus of toxicological and drug development studies is different. While the main interest of toxicological studies is the safety of the toxin under consideration, the primary concern of drug development studies is identifying the lowest dose level producing a desirable effect over that of the zero-dose control, which is commonly referred as the minimum effective dose (MED : Ruberg, 1989). Test procedures for identifying the MED have been proposed by several authors for continuous response variables. For instance, Williams (1971, 1972) designed a test procedure for comparing dose treatments with a zero-dose control concerning a normally distributed response. The test procedure uses a statistic based on isotonic regression estimates of the sample means for a monotonic dose-response relationship. Shirley (1977) suggested a nonparametric version of Williams' test. Moreover, Williams (1986) proposed a more powerful test by reranking the observations at

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each stage of Shirley's test procedure.

However, it is observed frequently response variables are measured with a set of binary or ordered categories, that is, ordinal responses. When responses are binary, Williams (1988) considered the elementary statistical problem of testing for differences between a set of probabilities. For $i = 0, 1, \cdots, k$, let Y_i be independently distributed random variables, each with a binomial distribution $B(n_i, \theta_i)$, where θ_i is the probability of success in the ith treatment. Williams (1988) compared $k+1$ dose groups by testing $H_0 : \theta_0 = \theta_1 = \cdots = \theta_k$ versus $H_1 : \theta_0 \leqq \theta_1 \leqq \cdots \leqq \theta_k$ (with at least one strict inequality).

In addition to binary responses, we consider a case that response variables are measured with a set of ordered categories and we propose a nonparametric testing procedure for identifying the MED with binary or categorical responses.

In Section 2, we propose how to construct a test for ordinal responses. In Section 3, we present the Monte Carlo study results to compare the proposed test with Williams' test for binary responses. We also examine the simulation results when responses are ordered categorical. The final section contains some conclusion and remark.

2. The proposed test

Chen (1999) proposed a test procedure for identifying the MED with continuous response. The test is used the Mann-Whitney statistic and the step-down closed testing scheme suggested by Tamhane et al. (1996). Appling this test we propose a nonparametric procedure for identifying the MED with ordinal responses.

Let k denote the number of treatments with the exception of a control, and let c denote the number of categories of the response variable, which is denoted by Y_i. Let x_{ij} $(i = 0, 1, \cdots, k,$ $j = 1, 2, \cdots, c)$ denote the number of individuals in the ith treatment group whose response falls in the jth category. Let $n_i = \sum_{j=1}^{c} x_{ij}$ denote the number of subjects in that group, and $N_i = \sum_{l=0}^{i} n_l, i = 1, 2, \cdots, k$. We treat the counts in separate rows as independent multinomial samples (when c=2, binomial samples). We arrange the k treatment groups from the lowest to the highest dose group, and the response categories from the least favourable to the most favourable. Note that a test for binary responses can be viewed as a special case of the c is 2. Therefore this test can be used when responses are involved in a set of binary or ordered categories. Let Y_i denote a response at dose i with $F_{ij} = P(Y_i \leqq j)$ and independent multinomial variables from the probability mass function defined by p_{i1} through p_{ic} with

$\sum_{j=1}^{c} p_{ij} = 1$ $(i = 0, 1, ..., ; j = 1, 2, ..., c)$. The hypothesis for identifying the MED is as follows :

$$H_{i,0} : F_{0j} = F_{1j} = \cdots = F_{ij},$$
$$H_{i,1} : F_{0j} = F_{1j} = \cdots = F_{i-1j} > F_{ij}, \text{ for all } j$$

We consider using the Mann-Whitney statistic incorporated into the step-down closed testing scheme to estimate the MED. This statistic can be applied to situations in which no numerical responses are observed but the subjects are divided into ordered categories, and it is observed how many subjects in the treatment and control groups fall into each of theses categories. The two-sample statistic comparing the ith dose group with the combined groups of all lower dose levels is

$$T_i = x_{i1}(\frac{1}{2}s_{i1}) + x_{i2}(s_{i1} + \frac{1}{2}s_{i2}) + \cdots + x_{ij}(s_{i1} + s_{i2} + \cdots + \frac{1}{2}s_{ij})$$
$$+ \cdots + x_{ic}(s_{i1} + s_{i2} + \cdots + \frac{1}{2}s_{ic}),$$

where $i = 1, 2, \cdots, k$; $j = 1, \cdots, c$; $s_{ij} = \sum_{l=0}^{i-1} x_{lj}$. And then, let

$$T_i^* = \frac{[T_i - \mu(T_i)]}{\sqrt{\sigma^2(T_i)}}, \quad i = 1, 2, \cdots, k,$$

where $\mu(T_i) = \frac{n_i N_{i-1}}{2}$, $\sigma^2(T_i) = \frac{n_i N_{i-1}(N_i + 1)}{12} - \frac{n_i N_{i-1} \sum_{j=1}^{c} (t_j^3 - t_j)}{12 N_i (N_i - 1)}$ and $t_j = s_{i+1,j}$ is the size of tied group j. Under the null hypothesis $T_1^*, T_2^*, \cdots, T_k^*$ are asymptotically independent and identically distributed standard normal by the results in Terpstra (1952) and the projection theorem (Randles and Wolfe, 1979).

We describe Chen's test procedure applying step-down closed testing scheme proposed by Tamhane et al. (1996) as follows : Let $k_1 = k$ and find $T_{(k_1)}^*$. $T_{(k_1)}^*$ is the maximum of $T_1^*, T_2^*, \cdots, T_{k_1}^*$. Let $\alpha(k_1) = 1 - (1 - \alpha)^{\frac{1}{k_1}}$ and $z(\alpha)$ is the upper αth percentile of the standard normal distribution. Define $d(k_1)$ to be the antirank of $T_{(k_1)}^*$, i. e., $T_{(k_1)}^* = T_{d(k_1)}^*$. If

$T^*_{(k_1)} \geqq z(\alpha(k_1))$, reject $H_{j,0}, j = d(k_1), \cdots, k_1$, and go to the second step with $k_2 = d(k_1) - 1$; otherwise, stop testing and declare no dose level as the MED. Generally, at the ith step, set $k_i = d(k_{i-1}) - 1$ and $\alpha(k_i) = 1 - (1-\alpha)^{\frac{1}{k_i}}$. Let $d(k_i)$ be the antirank of $T^*_{(k_i)}$, where $T^*_{(k_i)}$ is the maximum of $T^*_1, T^*_2, \cdots, T^*_{k_i}$. If $T^*_{(k_i)}$ or $T^*_{d(k_i)} \geqq z(\alpha(k_i))$, then reject $H_{j,0}$, $j = d(k_i), \cdots, k_i$ and go to the $(i+1)$th step; otherwise, stop testing and declare MED= $d(k_i) - 1$. When testing stops at the mth step, estimate the MED as $d(k_{m-1})$.

3. An example

We consider the data set in a table in order to calculate statistic in the proposed procedure. Table 1 illustrates the type of data observed that response variables are measured with a set of ordered categories. In Table 1, five ordered categories ranging from 'death' to 'good recovery' describe the clinical outcome of patients who experienced trauma. In literature on clinical care, these five categories are often called the Glasgow Outcome Scale (GOS). It includes four treat groups, that is, a control and three treatment doses. The three intravenous doses for the investigational medication are labelled as low, medium and high. The original data have been modified somewhat to protect the identity of the trial (Chuang-stein & Agresti, 1997).

Table 1. Responses on the Glasgow Outcome Scale from a clinical trial with a placebo and three treatment groups labelled as low dose, medium dose and high dose

Treatment dose	Glasgow Outcome Scale					Total
	Death	Vegetative state	Major disability	Minor disability	Good recovery	
Placebo	59	25	46	48	32	210
Low	48	21	44	47	30	190
Medium	44	14	54	64	31	207
High	43	4	49	58	41	195

The statistics for this test are obtained in the following : T_1 = 20683.5, T_2 = 45827, T_3 = 66019, $\mu(T_1)$ = 19950, $\mu(T_2)$ = 41400, $\mu(T_3)$ = 59182.5, $\sigma(T_1)$ = 1125.953, $\sigma(T_2)$ = 1995.013, $\sigma(T_3)$ = 2738.66, T^*_1 = 0.651, T^*_2 = 2.219, T^*_3 = 2.496. First of all, k_1=3, the

maximum of T_1^*, T_2^*, T_3^* is T_3^* and $d(3)$=3. As $T_3^* = 2.496 \geqq z(0.017) = 2.12$ $(0.017 \approx 1-(1-0.05)^{\frac{1}{3}})$ at the level $\alpha = 0.05$, we go to the second step with k_2=2. Note that $d(2)$=2 and $T_2^* = 2.219 \geqq z(0.025) = 1.96$ $(0.025 \approx 1-(1-0.05)^{\frac{1}{2}})$, but $T_3^* = 0.651$ $< z(0.05) = 1.645$ $(0.05 \approx 1-(1-0.05)^{\frac{1}{1}})$. Consequently, we conclude that, at the level $\alpha = 0.05$, the MED is the second dose level.

4. Simulation

4.1 Design of the simulation study

We compare powers of two procedures, Williams' test and the proposed test. Empirical FWE and powers were considered for comparing two procedures, defined as follows :

$$FWE = \frac{\{number\ of\ rejecting\ true\ H_{i,0}\}}{replications},$$

$$Power = \frac{\{number\ of\ (MED = \widehat{MED})\}}{replications}$$

This study was conducted for k=3 and 5 treatments with a zero-dose control, with $n_0 = n_1 = \cdots = n_k = n =$ 10, 20, 30, 50 and 70 observations per sample in case. And what is more, we performed for c=3 and 5 response categories per each treatment. In each case, we used 10,000 replications in obtaining the various power estimates and employed the 5% significant level.

In order to obtain data for the simulation study, appropriate binomial and multinomial deviates were derived by using the SAS routines RANBIN and RANTBL, respectively.

4.2 Simulation results

In the simulation results for powers of binary responses (Table 2 - Table 4), they are different as the configurations of the treatment effects; step-type, linear-type and umbrella patterned configurations. Here, we describe only the case of k=5 treatments with a control because simulation results are similar to the case of k=3. First, for step-type ordered configurations, the better result is given in the proposed test when MED=2 and 3. Note that, as compared with k=3, powers is strong in cases of MED=3 although n is small. Second, we consider linear-type ordered configurations. When the treatment effects have a monotonic

ordering of equal differences, Williams' test provides the excellent power like k=3 treatments, because it makes explicit use of the monotonicity assumption. However, the proposed test always is more powerful for MED=3. Under this type configuration, however, no powers of two procedures are superior. Third, the proposed test has excellent power when the treatment effect difference between a control and the treatment with MED for umbrella patterned configurations is large. On the other hand, Williams' test has high power in the case that the treatment effect difference between p and $p+1$ is small, where p is the peak of the umbrella.

We discuss briefly the simulation results obtained for the cases of ordered categorical responses (Table 5 - Table 8). The powers become decreasing when MED = 4 and 5 like cases for binary responses. As a whole, they maintain surprisingly high power. Generally the FWE of proposed test is well controlled. In the cases of k=3, however, the FWE of two procedures is low (< 0.01) for n=10 and MED=2 and the FWE for MED=4 and 5 has high values (> 0.06) in the cases of k=5.

5. Discussion

We comment the problem of the FWE. Contrary to our expectations, the FWE for Williams' test and the proposed test are not entirely controlled. We guess that the reason is caused by normal approximation. Typically, the normal approximation is not as close in the presence of ties as it is for the same group sizes without ties. Hence we are in need of studies for a better approximation to the null distribution than the normal approximation. This problem is left for future study.

In conclusion, the proposed test for binary or ordered categorical responses has several important advantages. First, the proposed test involves only the two-sample Mann-Whitney statistics, which are very easy to compute in terms of the established nonparametric procedures. Second, this test has an appreciable power performance compared to Williams' test. Finally, the proposed test could be extended to take into account ordered categorical responses.

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Table 2. Estimated power and FWE[3)]
for α=.05, k=5, step-type configurations

							True	power		FWE	
n	Θ_0	Θ_1	Θ_2	Θ_3	Θ_4	Θ_5	MED	WILM	PROT	WILM	PROT
10	0.1	0.6	0.6	0.6	0.6	0.6	1	0.6560	0.5546	-	-
	0.1	0.1	0.6	0.6	0.6	0.6	2	0.6737	0.7824	0.0250	0.0193
	0.1	0.1	0.1	0.6	0.6	0.6	3	0.6830	0.8268	0.0696	0.0432
	0.1	0.1	0.1	0.1	0.6	0.6	4	0.7731	0.8349	0.0322	0.0512
	0.1	0.1	0.1	0.1	0.1	0.6	5	0.8071	0.6219	0.0436	0.0621
30	0.1	0.6	0.6	0.6	0.6	0.6	1	0.9969	0.9919	-	-
	0.1	0.1	0.6	0.6	0.6	0.6	2	0.9452	0.9470	0.0520	0.0517
	0.1	0.1	0.1	0.6	0.6	0.6	3	0.9381	0.9487	0.0590	0.0506
	0.1	0.1	0.1	0.1	0.6	0.6	4	0.9529	0.9100	0.0461	0.0899
	0.1	0.1	0.1	0.1	0.1	0.6	5	0.9499	0.9400	0.0481	0.0890
50	0.1	0.6	0.6	0.6	0.6	0.6	1	1.0000	1.0000	-	-
	0.1	0.1	0.6	0.6	0.6	0.6	2	0.9518	0.9523	0.0482	0.0477
	0.1	0.1	0.1	0.6	0.6	0.6	3	0.9356	0.9481	0.0644	0.0519
	0.1	0.1	0.1	0.1	0.6	0.6	4	0.9576	0.8906	0.0424	0.0920
	0.1	0.1	0.1	0.1	0.1	0.6	5	0.9500	0.9061	0.0500	0.0809

WILM : Williams' test, PROT : proposed test

Table 3. Estimated power and FWE
for α=.05, k=5, linear-type configurations

							True	power		FWE	
n	Θ_0	Θ_1	Θ_2	Θ_3	Θ_4	Θ_5	MED	WILM	PROT	WILM	PROT
10	0.1	0.2	0.3	0.4	0.5	0.6	1	0.0440	0.1254	-	-
	0.1	0.1	0.3	0.4	0.5	0.6	2	0.2067	0.2455	0.0079	0.0081
	0.1	0.1	0.1	0.4	0.5	0.6	3	0.3818	0.4838	0.0450	0.0358
	0.1	0.1	0.1	0.1	0.5	0.6	4	0.6464	0.5877	0.0328	0.0515
30	0.1	0.2	0.3	0.4	0.5	0.6	1	0.2554	0.2171	-	-
	0.1	0.1	0.3	0.4	0.5	0.6	2	0.5610	0.5670	0.0494	0.0435
	0.1	0.1	0.1	0.4	0.5	0.6	3	0.8467	0.8719	0.0428	0.0490
	0.1	0.1	0.1	0.1	0.5	0.6	4	0.9372	0.9230	0.0455	0.0718
50	0.1	0.2	0.3	0.4	0.5	0.6	1	0.3766	0.3027	-	-
	0.1	0.1	0.3	0.4	0.5	0.6	2	0.7749	0.7423	0.0495	0.0407
	0.1	0.1	0.1	0.4	0.5	0.6	3	0.9345	0.9417	0.0477	0.0508
	0.1	0.1	0.1	0.1	0.5	0.6	4	0.9493	0.7535	0.0500	0.0716

3) For MED=1, the FWE entry equals .0000 for all procedures, and is hence omitted.

Table 4. Estimated power and FWE
for α=.05, k=5, umbrella patterned configurations

							True	power		FWE	
n	Θ_0	Θ_1	Θ_2	Θ_3	Θ_4	Θ_5	MED	WILM	PROT	WILM	PROT
10	0.1	0.1	0.4	0.5	0.6	0.5	2	0.3781	0.4342	0.0192	0.0096
	0.1	0.1	0.4	0.5	0.6	0.1	2	0.1749	0.4281	0.0128	0.0095
	0.1	0.1	0.5	0.6	0.5	0.4	2	0.4568	0.6292	0.0178	0.0113
	0.1	0.1	0.5	0.6	0.1	0.1	2	0.2136	0.6180	0.0133	0.0119
	0.1	0.1	0.1	0.5	0.6	0.5	3	0.5283	0.6912	0.0670	0.0419
	0.1	0.1	0.1	0.5	0.6	0.1	3	0.2158	0.6812	0.0779	0.0402
30	0.1	0.1	0.4	0.5	0.6	0.5	2	0.8248	0.8596	0.0552	0.0513
	0.1	0.1	0.4	0.5	0.6	0.1	2	0.6607	0.8567	0.0546	0.0521
	0.1	0.1	0.5	0.6	0.5	0.4	2	0.9161	0.9348	0.0533	0.0528
	0.1	0.1	0.5	0.6	0.1	0.1	2	0.2990	0.9352	0.0477	0.0515
	0.1	0.1	0.1	0.5	0.6	0.5	3	0.9176	0.9407	0.0599	0.0524
	0.1	0.1	0.1	0.5	0.6	0.1	3	0.7369	0.9399	0.0737	0.0519
50	0.1	0.1	0.4	0.5	0.6	0.5	2	0.9289	0.9374	0.0517	0.0498
	0.1	0.1	0.4	0.5	0.6	0.1	2	0.8857	0.9381	0.0543	0.0512
	0.1	0.1	0.5	0.6	0.5	0.4	2	0.9466	0.9494	0.0522	0.0503
	0.1	0.1	0.5	0.6	0.1	0.1	2	0.5662	0.9495	0.0498	0.0502
	0.1	0.1	0.1	0.5	0.6	0.5	3	0.9398	0.9521	0.0594	0.0477
	0.1	0.1	0.1	0.5	0.6	0.1	3	0.8946	0.9475	0.0653	0.0522

Table 5. Estimated power and FWE for α=.05, k=3, c=3

true MED	Dose level	p_1	p_2	p_3	n	Power	FWE
1	zero-dose	0.6	0.3	0.1	30	0.9997	-
	dose1	0.1	0.3	0.6	50	1.0000	-
	dose2	0.1	0.3	0.6	70	1.0000	-
	dose3	0.1	0.3	0.6			
2	zero-dose	0.6	0.3	0.1	30	0.9494	0.0506
	dose1	0.6	0.3	0.1	50	0.9506	0.0494
	dose2	0.1	0.3	0.6	70	0.9497	0.0503
	dose3	0.1	0.3	0.6			
3	zero-dose	0.6	0.3	0.1	30	0.9521	0.0479
	dose1	0.6	0.3	0.1	50	0.9498	0.0502
	dose2	0.6	0.3	0.1	70	0.9481	0.0519
	dose3	0.1	0.3	0.6			

Table 6. Estimated power and FWE for α=.05, k=5, c=3

true MED	Dose level	p_1	p_2	p_3	n	Power	FWE
1	zero-dose	0.6	0.3	0.1	30	0.9993	-
	dose1	0.1	0.3	0.6	50	1.0000	-
	dose2	0.1	0.3	0.6	70	1.0000	-
	dose3	0.1	0.3	0.6			
	dose4	0.1	0.3	0.6			
	dose5	0.1	0.3	0.6			
2	zero-dose	0.6	0.3	0.1	30	0.9489	0.0510
	dose1	0.6	0.3	0.1	50	0.9495	0.0505
	dose2	0.1	0.3	0.6	70	0.9513	0.0487
	dose3	0.1	0.3	0.6			
	dose4	0.1	0.3	0.6			
	dose5	0.1	0.3	0.6			
3	zero-dose	0.6	0.3	0.1	30	0.9486	0.0514
	dose1	0.6	0.3	0.1	50	0.9523	0.0477
	dose2	0.6	0.3	0.1	70	0.9496	0.0504
	dose3	0.1	0.3	0.6			
	dose4	0.1	0.3	0.6			
	dose5	0.1	0.3	0.6			
4	zero-dose	0.6	0.3	0.1	30	0.9243	0.0757
	dose1	0.6	0.3	0.1	50	0.9268	0.0732
	dose2	0.6	0.3	0.1	70	0.9228	0.0772
	dose3	0.6	0.3	0.1			
	dose4	0.1	0.3	0.6			
	dose5	0.1	0.3	0.6			
5	zero-dose	0.6	0.3	0.1	30	0.9149	0.0851
	dose1	0.6	0.3	0.1	50	0.9150	0.0850
	dose2	0.6	0.3	0.1	70	0.9159	0.0841
	dose3	0.6	0.3	0.1			
	dose4	0.6	0.3	0.1			
	dose5	0.1	0.3	0.6			

Table 7. Estimated power and FWE for α=.05, k=3, c=5

true MED	Dose level	p_1	p_2	p_3	p_4	p_5	n	Power	FWE
1	zero-dose	0.4	0.3	0.2	0.05	0.05	30	1.0000	-
	dose1	0.05	0.05	0.2	0.3	0.4	50	1.0000	-
	dose2	0.05	0.05	0.2	0.3	0.4	70	1.0000	-
	dose3	0.05	0.05	0.2	0.3	0.4			
2	zero-dose	0.4	0.3	0.2	0.05	0.05	30	0.9512	0.0488
	dose1	0.4	0.3	0.2	0.05	0.05	50	0.9504	0.0496
	dose2	0.05	0.05	0.2	0.3	0.4	70	0.9505	0.0495
	dose3	0.05	0.05	0.2	0.3	0.4			
3	zero-dose	0.4	0.3	0.2	0.05	0.05	30	0.9500	0.0500
	dose1	0.4	0.3	0.2	0.05	0.05	50	0.9505	0.0495
	dose2	0.4	0.3	0.2	0.05	0.05	70	0.9496	0.0504
	dose3	0.05	0.05	0.2	0.3	0.4			

Table 8. Estimated power and FWE for α=.05, k=5, c=5

true MED	Dose level	p_1	p_2	p_3	p_4	p_5	n	Power	FWE
1	zero-dose	0.4	0.3	0.2	0.05	0.05	30	0.9998	
	dose1	0.05	0.05	0.2	0.3	0.4	50	1.0000	-
	dose2	0.05	0.05	0.2	0.3	0.4	70	1.0000	-
	dose3	0.05	0.05	0.2	0.3	0.4			
	dose4	0.05	0.05	0.2	0.3	0.4			
	dose5	0.05	0.05	0.2	0.3	0.4			
2	zero-dose	0.4	0.3	0.2	0.05	0.05	30	0.9516	0.0482
	dose1	0.4	0.3	0.2	0.05	0.05	50	0.9548	0.0452
	dose2	0.05	0.05	0.2	0.3	0.4	70	0.9496	0.0504
	dose3	0.05	0.05	0.2	0.3	0.4			
	dose4	0.05	0.05	0.2	0.3	0.4			
	dose5	0.05	0.05	0.2	0.3	0.4			
3	zero-dose	0.4	0.3	0.2	0.05	0.05	30	0.9488	0.0512
	dose1	0.4	0.3	0.2	0.05	0.05	50	0.9484	0.0516
	dose2	0.4	0.3	0.2	0.05	0.05	70	0.9508	0.0492
	dose3	0.05	0.05	0.2	0.3	0.4			
	dose4	0.05	0.05	0.2	0.3	0.4			
	dose5	0.05	0.05	0.2	0.3	0.4			
4	zero-dose	0.4	0.3	0.2	0.05	0.05	30	0.9257	0.0743
	dose1	0.4	0.3	0.2	0.05	0.05	50	0.9254	0.0746
	dose2	0.4	0.3	0.2	0.05	0.05	70	0.9254	0.0746
	dose3	0.4	0.3	0.2	0.05	0.05			
	dose4	0.05	0.05	0.2	0.3	0.4			
	dose5	0.05	0.05	0.2	0.3	0.4			
5	zero-dose	0.4	0.3	0.2	0.05	0.05	30	0.9151	0.0849
	dose1	0.4	0.3	0.2	0.05	0.05	50	0.9168	0.0832
	dose2	0.4	0.3	0.2	0.05	0.05	70	0.9185	0.0815
	dose3	0.4	0.3	0.2	0.05	0.05			
	dose4	0.4	0.3	0.2	0.05	0.05			
	dose5	0.05	0.05	0.2	0.3	0.4			