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# Comparison of several test preparations with one standard in multivariate bioassays

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SUMMARY

In the paper we consider the problem of estimation of the relative efficiencies of several test preparations with respect to one standard preparation. We consider the case where several doses of each preparation are administered to units forming block designs. We assume that the effect of doses of preparations is measured by several measurable traits forming multivariate responses. We assume that responses can be described by a parallel-line model with independently and normally distributed vectors of errors with the same covariance matrix. The statistical method presented in the paper is applied to a comparison of the impact of different forms of nitrogen fertilizer on yield of winter wheat.

**Key words**: relative potency, multivariate bioassays, parallel-line assay, multivariate observations, block designs, testing hypotheses, estimation of parameters.

## 1. Introduction

In multivariate biological experiments, where the effect of new (test) preparations is compared with the effect of a standard preparation, the method of estimation of relative potency of preparations can be used. The relative potency of two preparations is defined as the ratio of such doses of preparations which give the same responses, i.e. $\rho = \frac{u_T}{u_S}$, where $u_S$ and $u_T$ denote the doses of standard and test preparations, respectively, producing similar responses. The estimate of the potency specifies the dose of test preparation which should be administered to produce the similar response to that produced by unit dose of the standard preparation.

The response of the experimental unit for the dose of preparation could be measured by one measurable trait (univariate bioassay) or by several traits (multivariate bioassay). In the paper we focus on the multivariate approach, which is more adequate to experimental researching. The method of estimation of the relative potency for multivariate observations is considered in many papers, namely, Rao (1954), Vølund (1980), Carter, Hubert (1985), Meisner et al. (1986). In the papers: Hanusz, Jędruszczak (1999), Hanusz (1999), Hanusz et al. (2003), the comparison of two test preparations with one standard preparation is considered. In this paper we generalize the results for several test preparations compared with one standard preparation.

## 2. The multivariate linear model for a parallel-line bioassay

Let us assume that $t$ test preparations: $T_1, T_2, \cdots, T_t$ are compared with one standard preparation, say, $S$. Let $\nu_0, \nu_1, \nu_2, \cdots, \nu_t$ denote the number of doses of the $j$th preparation, where $j = 0,1,\cdots,t$ and $\nu_0$ be the number of doses for the standard preparation. Let $u_{ij}$ denote the $i$th dose of the $j$th preparation, where $i = 1,2,\cdots,\nu_j$; $j = 0,1,\cdots,t$. Throughout the paper we assume that doses of the preparations are administered to units which form a block design containing $b$ blocks. Let $p$ be a number of measurable traits in the response and $\mathbf{y}_{ijkl}$ denote a $p$-variate response vector for the $i$th dose of the $j$th preparation applied in the $k$th block in the $l$th replication, where $i = 1,2,\cdots,\nu_j$; $j = 0, 1, 2, \cdots, t$; $k = 1,2,\cdots,b$; $l = 1,2,\cdots,n_{ij}$ and $n_{ij}$ is the number of plots where the dose $u_{ij}$ occurs in the experiment. We assume that each response can be expressed by the following linear model:

$$\mathbf{y}_{ijkl} = \boldsymbol{\tau}_k + \boldsymbol{\alpha}_j + x_{ij}\,\boldsymbol{\beta}_j + \mathbf{e}_{ijkl}, \tag{1}$$

where $x_{ij} = \log(u_{ij})$, $\boldsymbol{\tau}_k$, $\boldsymbol{\alpha}_j$ and $\boldsymbol{\beta}_j$ denote $p$-variate vectors of block effects, intercepts and slopes, respectively. We assume that each $p$ dimensional response described by the model (1) has $p$-variate normal distribution with common covariance matrix $\boldsymbol{\Sigma}$, i.e. $\mathbf{y}_{ijkl} \sim N_p(\boldsymbol{\tau}_k + \boldsymbol{\alpha}_j + x_{ij}\boldsymbol{\beta}_j, \boldsymbol{\Sigma})$ and that all responses are mutually independent.

The general linear model of all observations then has the following form:

$$\mathbf{Y} = \mathbf{D}_\tau \boldsymbol{\tau} + \boldsymbol{\Delta}_\alpha \boldsymbol{\alpha} + \boldsymbol{\Delta}_\beta \boldsymbol{\beta} + \mathbf{E}, \tag{2}$$

where $\mathbf{Y} = [\mathbf{Y}_S', \mathbf{Y}_{T_1}', \cdots, \mathbf{Y}_{T_t}']'$ is an $(n \times p)$ matrix of all responses in (1) allocated as rows of $\mathbf{Y}$, $\mathbf{D}_\tau$ is the $(n \times b)$ binary matrix of the experimental plan, $\mathbf{D}_\alpha = diag(\mathbf{1}_{n_0}, \mathbf{1}_{n_1}, \cdots, \mathbf{1}_{n_t})$ is the $(n \times (t+1))$ block diagonal matrix with the

vectors $\mathbf{1}_{n_j}$ of $n_j$ ones on the diagonal, $n_j$ denotes the total number of units in experiments with the $j$th preparation $(j=0,1,\cdots,t)$, $n=\sum_{j=0}^{t} n_j$, $\mathbf{D}_{\beta}=diag\left(\mathbf{x}_S,\mathbf{x}_{T_1},\cdots,\mathbf{x}_{T_t}\right)$ is the $\left(n\times(t+1)\right)$ block diagonal matrix with the vectors $\mathbf{x}_i$ of size $(n_i\times 1)$ including logarithms of all applied doses for $i$th preparation with replications, and $\boldsymbol{\tau}=\left[\tau_1,\tau_2,\cdots,\tau_b\right]$, $\boldsymbol{\alpha}=\left[\alpha_S,\alpha_{T_1},\cdots,\alpha_{T_t}\right]$, $\boldsymbol{\beta}=\left[\beta_S,\beta_{T_1},\cdots,\beta_{T_t}\right]$ are matrices of block effects, intercepts and slopes, respectively. The matrix of observation, $\mathbf{Y}$, has multivariate normal distribution as $\mathbf{Y}\sim N_{n,p}\left(\mathbf{D}_{\tau}\boldsymbol{\tau}+\boldsymbol{\Delta}_{\alpha}\boldsymbol{\alpha}+\boldsymbol{\Delta}_{\beta}\boldsymbol{\beta},\mathbf{I}_n\otimes\boldsymbol{\Sigma}\right)$, where $\mathbf{I}_n$ denotes a unit matrix of size $n$, and $\otimes$ denotes the Kronecker product of matrices.

## 3. Estimation of relative potencies of test preparations relative to a standard

In this section we present the method of estimation of the potencies of all test preparations relative to the same standard preparation. Let us denote the known matrices and unknown parameters in the model (2) in the following forms:

$$\mathbf{X}=\left[\mathbf{D}_{\tau},\boldsymbol{\Delta}_{\alpha},\boldsymbol{\Delta}_{\beta}\right],\quad \boldsymbol{\Theta}=\begin{bmatrix}\boldsymbol{\tau}\\ \boldsymbol{\alpha}\\ \boldsymbol{\beta}\end{bmatrix}.$$

Maximum likelihood estimates of parameters' matrix and covariance matrix have the forms (see, Muirhaed, 1982, Krzyśko, 2000):

$$\hat{\boldsymbol{\Theta}}=\left(\mathbf{X}'\mathbf{X}\right)^{-}\mathbf{X}'\mathbf{Y},\qquad \hat{\boldsymbol{\Sigma}}=\frac{1}{n}\left(\mathbf{Y}-\mathbf{X}\hat{\boldsymbol{\Theta}}\right)'\left(\mathbf{Y}-\mathbf{X}\hat{\boldsymbol{\Theta}}\right),$$

where $\left(\mathbf{X}'\mathbf{X}\right)^{-}$ denotes the generalized inverse of the matrix $\mathbf{X}'\mathbf{X}$.

### 3.1. Testing a hypothesis about similarity of preparations

Test preparations could be compared with the standard one by the relative potency if vectors of slopes are parallel to the vector of slopes for the standard preparation (parallel-line assays). This similarity can be described as a hypothesis $H_{\beta}^{0}$ of the form:

$$H_{\beta}^{0}:\begin{cases}\boldsymbol{\beta}_{T_1}-\boldsymbol{\beta}_S=\mathbf{0}\\ \boldsymbol{\beta}_{T_2}-\boldsymbol{\beta}_S=\mathbf{0}\\ \quad\vdots\\ \boldsymbol{\beta}_{T_t}-\boldsymbol{\beta}_S=\mathbf{0}\end{cases}$$

or in matrix notation as follows:

$$H_\beta^0 : \mathbf{C\Theta} = \mathbf{0},\ \underset{t\times(b+2t+2)}{\mathbf{C}} = \left[\underset{t\times b}{\mathbf{0}},\ \underset{t\times(t+1)}{\mathbf{0}},\ \underset{t\times(t+1)}{\mathbf{C}_1}\right],\ \mathbf{C}_1 = \begin{bmatrix} -1 & 1 & 0 & \cdots & 0 \\ -1 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ -1 & 0 & 0 & & 1 \end{bmatrix},$$

where $\underset{n\times m}{\mathbf{0}}$ denote null matrix of size $(n\times m)$. The hypothesis $H_\beta^0$ can be tested, versus the alternative that at least one equality $\boldsymbol{\beta}_{T_i} - \boldsymbol{\beta}_S = \mathbf{0}$ is not fulfilled $(i = 1, 2, \cdots, t)$, by using the *Wilks lambda* test of the form (Meisner et al., 1986):

$$\Lambda = \frac{1}{\left|\mathbf{I}_t + \left[\mathbf{C}(\mathbf{X}'\mathbf{X})^- \mathbf{C}'\right]^{-1}\left(\mathbf{C}\hat{\mathbf{B}}\right)\hat{\boldsymbol{\Sigma}}^{-1}\left(\mathbf{C}\hat{\mathbf{B}}\right)' / n\right|}. \tag{3}$$

The hypothesis $H_\beta^0$ is not rejected if $-\left[n - r(\mathbf{X}) - \frac{p-t+1}{2}\right] ln\Lambda < \chi^2_{pt,\alpha}$, where $r(\mathbf{X})$ denotes the rank of the matrix $\mathbf{X}$ and $\alpha$ is a known significant level. The test preparations are similar to the test preparation if $H_\beta^0$ is accepted. However, if the general hypothesis $H_\beta^0$ is rejected then we can to check which detailed hypothesis: $H_{\beta i}^0 : \boldsymbol{\beta}_{T_i} - \boldsymbol{\beta}_S = \mathbf{0}, i = 1, 2, \cdots, t$ is rejected. To test the hypotheses $H_{\beta i}^0$ we can use the test given in (3), putting the *i*th row of **C**, namely, $\mathbf{c}_i = row(\mathbf{C}, i)$, instead of **C** $(i = 1, 2, \cdots, t)$. Then

$$\Lambda_i = \frac{1}{1 + \left(\mathbf{c}_i'\hat{\mathbf{B}}\right)\hat{\boldsymbol{\Sigma}}^{-1}\left(\mathbf{c}_i'\hat{\mathbf{B}}\right)' / \left[n\mathbf{c}_i'(\mathbf{X}'\mathbf{X})^- \mathbf{c}_i\right]},$$

and the hypothesis $H_{\beta i}^0$ is not rejected if $-\left[n - r(\mathbf{X}) - \frac{p}{2}\right] ln\Lambda_i < \chi^2_{pt,\alpha/t}$. Only the test preparations for which the hypothesis $H_{\beta i}^0$ is accepted can be compared with the standard by the relative potency.

### 3.2. Testing a hypothesis about the relative potencies

Let us suppose that $r$ test preparations $(r \le t)$ are similar to the standard preparation, which means that the hypotheses $H_{\beta i}^0 : \boldsymbol{\beta}_{T_i} - \boldsymbol{\beta}_S = \mathbf{0}$, $i = 1, 2, \cdots, r$ have not been rejected. Then we can take in model (2) the same vector of slopes for $r$ test preparations as for the standard one. As a consequence we can create

a new model, removing the test preparations which are not similar to the standard preparation. The model has the following form:

$$\tilde{\mathbf{Y}} = \tilde{\mathbf{D}}_{\tau}\boldsymbol{\tau} + \tilde{\boldsymbol{\Delta}}_{\alpha}\tilde{\boldsymbol{\alpha}} + \tilde{\mathbf{x}}\boldsymbol{\beta}' + \tilde{\mathbf{E}}, \tag{4}$$

where $\tilde{\mathbf{Y}}$, $\tilde{\mathbf{D}}_{\tau}$ and $\tilde{\boldsymbol{\Delta}}_{\alpha}$ are submatrices of $\mathbf{Y}$, $\mathbf{D}_{\tau}$ and $\boldsymbol{\Delta}_{\alpha}$, respectively, containing the rows corresponding to responses for applied doses of $r$ test preparations and the standard preparation. Similarly, $\tilde{\boldsymbol{\alpha}}$ denotes the matrix of unknown intercepts for $r$ test preparations and the standard preparation, $\tilde{\mathbf{x}}$ is a vector of all logarithms of doses for $r$ test preparations and the standard preparation and $\boldsymbol{\beta}$ is the only one vector of slopes, the same for $r$ test preparations and the standard preparation. To estimate the potencies of test preparations to standard, the following hypothesis has to be true:

$$H_{\mu}^{0}: \begin{cases} \boldsymbol{\alpha}_{T_1} - \boldsymbol{\alpha}_{S} = \mu_1\boldsymbol{\beta} \\ \boldsymbol{\alpha}_{T_2} - \boldsymbol{\alpha}_{S} = \mu_2\boldsymbol{\beta} \\ \quad\vdots \\ \boldsymbol{\alpha}_{T_r} - \boldsymbol{\alpha}_{S} = \mu_r\boldsymbol{\beta} \end{cases},$$

where $\mu_1, \mu_2, \cdots, \mu_r$ denote the logarithms of potencies of the corresponding test preparations to the same standard preparation, $\mu_i = \log(\rho_i)$. To test the hypothesis $H_{\mu}^{0}$ the *Wilks lambda* statistic should be also used (Meisner et al., 1986). This statistic has the following form:

$$\Lambda(\boldsymbol{\mu}) = \frac{1}{\left|\mathbf{I}_r + \left[\mathbf{C}(\boldsymbol{\mu})\left(\tilde{\mathbf{X}}'\tilde{\mathbf{X}}\right)^{-}\mathbf{C}'(\boldsymbol{\mu})\right]^{-1}\left[\mathbf{C}(\boldsymbol{\mu})\hat{\tilde{\boldsymbol{\Theta}}}\right]\hat{\boldsymbol{\Sigma}}^{-1}\left[\mathbf{C}(\boldsymbol{\mu})\hat{\tilde{\boldsymbol{\Theta}}}\right]'/n\right|},$$

where $\boldsymbol{\mu} = [\mu_1, \mu_2, \cdots, \mu_r]'$, $\mathbf{C}(\boldsymbol{\mu}) = [\mathbf{0}, \mathbf{C}_1, -\boldsymbol{\mu}]$, $\underset{r\times(r+1)}{\mathbf{C}_1} = \begin{bmatrix} -1 & 1 & 0 & \cdots & 0 \\ -1 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \cdots & \vdots \\ -1 & 0 & 0 & \cdots & 1 \end{bmatrix}$,

$\tilde{\mathbf{X}} = \left[\tilde{\mathbf{D}}_{\tau}, \tilde{\boldsymbol{\Delta}}_{\alpha}, \tilde{\mathbf{x}}\right]$ and $\hat{\tilde{\boldsymbol{\Theta}}} = \left(\tilde{\mathbf{X}}'\tilde{\mathbf{X}}\right)^{-}\tilde{\mathbf{X}}'\tilde{\mathbf{Y}}$. The maximum likelihood estimator of $\boldsymbol{\mu}$ is such a $\hat{\boldsymbol{\mu}}$ which minimizes $\Lambda(\boldsymbol{\mu})$ and for which the hypothesis $H_{\mu}^{0}$ is not rejected. $H_{\mu}^{0}$ is not rejected if

$$-\left[n - r(\tilde{\mathbf{X}}) - \frac{p-r+1}{2} - \frac{1}{\min\Lambda(\boldsymbol{\mu})}\right] ln\Lambda(\hat{\boldsymbol{\mu}}) < \chi^2_{pr,\alpha}.$$

Remark. In the case where the number of tests is greater then two, there exists the problem of numerical calculation of extremes of $\Lambda(\boldsymbol{\mu})$. In such a case we can use iterative methods to find the maximum and minimum of $\Lambda(\boldsymbol{\mu})$. Thus, we can describe the general hypothesis as a system of the hypotheses:

$$\begin{cases} H^0_{\mu_1} : \boldsymbol{\alpha}_{T_1} - \boldsymbol{\alpha}_S = \mu_1 \boldsymbol{\beta} \\ H^0_{\mu_2} : \boldsymbol{\alpha}_{T_2} - \boldsymbol{\alpha}_S = \mu_2 \boldsymbol{\beta} \\ \vdots \\ H^0_{\mu_r} : \boldsymbol{\alpha}_{T_r} - \boldsymbol{\alpha}_S = \mu_r \boldsymbol{\beta} \end{cases}.$$

Each hypothesis $H^0_{\mu_i}$ $(i = 1, 2, \cdots, r)$ can be tested separately by using the *Wilks lambda* statistic of the form:

$$\Lambda(\mu_i) = \frac{1}{1 + \left[\mathbf{c}'(\mu_i)\hat{\boldsymbol{\Theta}}\right]\hat{\boldsymbol{\Sigma}}^{-1}\left[\mathbf{c}'(\mu_i)\hat{\boldsymbol{\Theta}}\right]' \Big/ \left[n\mathbf{c}'(\mu_i)(\tilde{\mathbf{X}}'\tilde{\mathbf{X}})^{-}\mathbf{c}(\mu_i)\right]},$$

where $\mathbf{c}(\mu_i)$ is the $i$th row of $\mathbf{C}(\boldsymbol{\mu})$ $(i = 1, 2, \cdots, r)$. Moreover, each hypothesis should be tested at a significant level $\alpha^* = \frac{\alpha}{r}$.

## 4. Example

We apply the theoretical results presented in the previous sections we apply to compare the efficiency of different rates of nitrogen fertilizer on winter wheat of the Korweta variety. The experiment was carried out at the Agricultural Experimental Station in Grabow in 2003 (Rutkowska, 2005). The first factor in the experiment was basic nitrogen fertilization in doses of multiplicities of 40 $kg\,N \cdot ha^{-1}$ in the form of ammonium sulphate. These were applied during the early period of the plants' vegetation: the first dose at the beginning of spring vegetation and then: 14, 28 and 42 days after the start of vegetation. The experiment included control treatment without nitrogen fertilization. The second factor was late nitrogen top-dressing of 40 $kg\,N \cdot ha^{-1}$ administered in two phases – at tillering and/or after anthesis. As nitrogen content in the soil in the early spring was also examined, these quantities were treated as part of a given dose of preparations. The differently administered doses are given in Table 1.

**Table 1.** Doses of nitrogen and time of administration

| **Factor I** Basic nitrogen rate $[kg\ N \cdot ha^{-1}]$ | **Factor II** - Nitrogen top-dressing | | | |
|---|---|---|---|---|
| | $0\ kg\ N \cdot ha^{-1}$ | $40\ kg\ N \cdot ha^{-1}$ at tillering | $40\ kg\ N \cdot ha^{-1}$ after anthesis | $80\ kg\ N \cdot ha^{-1}$ 40 at tillering+40 after anthesis |
| 0+40 | - | 40 | 40 | 80 |
| 40+40 | 40 | 80 | 80 | 120 |
| 80+40 | 80 | 120 | 120 | 160 |
| 120+40 | 120 | 160 | 160 | 200 |
| 160+40 | 160 | 200 | 200 | 240 |

In the experiment, nine traits were measured. The names of traits and boxplots of all traits from four blocks are given in Fig. 1. These boxes inform us that some of the traits are characterized by asymmetrical distribution and there exist outstanding observations.

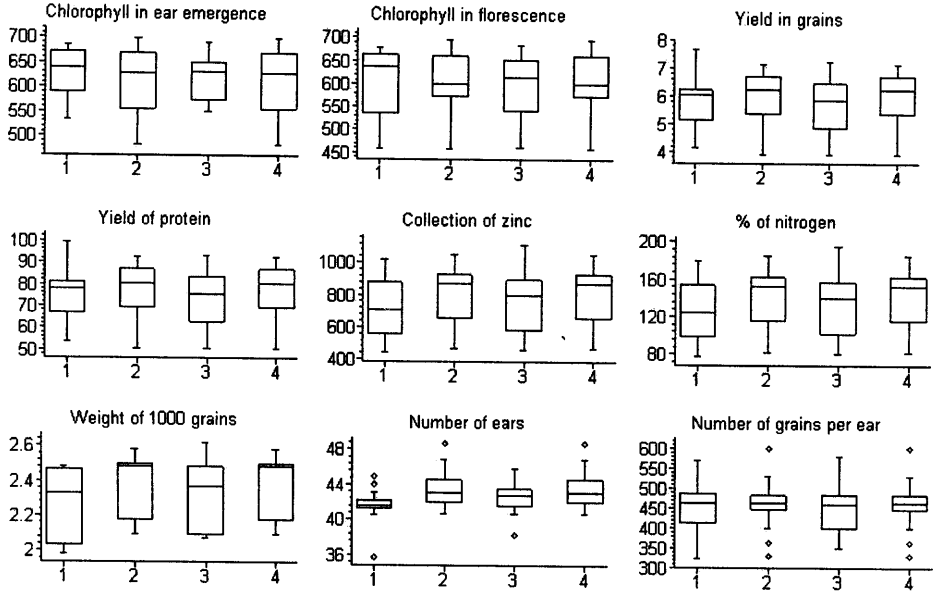


**Fig. 1.** Boxplots for the data of nine traits obtained in four blocks in 2003

The test functions, critical values of tests and maximum likelihood estimates of relative potency are given in Table 2.

**Table 2.** Test function, critical values and estimates of relative potencies for experimental data

| Hypotheses | Test statistics | Critical values | Estimates of potency |
|---|---|---|---|
| $H_{\beta}^{0}: \mathbf{C\Theta = 0}$ | $\chi_0^2 = 116.48$ | $\chi^2_{0,05;27} = 40.11$ | - |
| **Detailed hypotheses:** | | | |
| $H_{\beta 1}^{0}: \beta_{T_1} - \beta_S = 0$ | $\chi_1^2 = 53.38$ | | |
| $H_{\beta 2}^{0}: \beta_{T_2} - \beta_S = 0$ | $\chi_2^2 = 26.91$ | $\chi^2_{0,05/3;9} = 20.21$ | - |
| $H_{\beta 3}^{0}: \beta_{T_3} - \beta_S = 0$ | $\chi_3^2 = 55.61$ | | |
| $H_{\mu_1}^{0}: \alpha_{T_1} - \alpha_S = \mu_1 \beta$ | $\chi_1^2 = 53.38$ | | $\hat{\rho}_1 = 1.24$ |
| $H_{\mu_2}^{0}: \alpha_{T_2} - \alpha_S = \mu_2 \beta$ | $\chi_2^2 = 26.91$ | $\chi^2_{0,05/3;9} = 20.21$ | $\hat{\rho}_2 = 1.39$ |
| $H_{\mu_3}^{0}: \alpha_{T_3} - \alpha_S = \mu_3 \beta$ | $\chi_3^2 = 55.61$ | | $\hat{\rho}_3 = 1.46$ |

The results contained in Table 2 show that for all traits in the response, both the general hypotheses $H_{\beta}^{0}$ and $H_{\mu}^{0}$ as well as the detailed hypotheses: $H_{\beta i}^{0}$ $(i = 1, 2, 3)$ should be rejected at a significance level $\alpha = 0.05$. Thus, we should not calculate the estimates of relative potencies. However, taking into account only two traits in the response, namely, $x_3$ (yield of grains) and $x_9$ (number of grains per ear) we get the results contained in Table 3.

**Table 3.** Test function, critical values and estimates of relative potencies for two traits

| Hypotheses | Test statistics | Critical values | Estimate of potency |
|---|---|---|---|
| $H_{\beta}^{0}: \mathbf{C\Theta = 0}$ | $\chi_0^2 = 12.19$ | $\chi^2_{0,05;6} = 12.59$ | - |
| $H_{\mu_1}^{0}: \alpha_{T_1} - \alpha_S = \mu_1 \beta$ | $\chi_1^2 = 1.36$ | | $\hat{\rho}_1 = 1.21$ |
| $H_{\mu_2}^{0}: \alpha_{T_2} - \alpha_S = \mu_2 \beta$ | $\chi_2^2 = 1.87$ | $\chi^2_{0,05/3;2} = 8.19$ | $\hat{\rho}_2 = 1.43$ |
| $H_{\mu_3}^{0}: \alpha_{T_3} - \alpha_S = \mu_3 \beta$ | $\chi_3^2 = 5.59$ | | $\hat{\rho}_3 = 1.38$ |

In the case of two traits both hypotheses are not rejected and we are allowed to calculate the estimates of relative potencies. When we compare the estimates of potencies given in Table 2 and Table 3 we can notice the very similar results.

## 5. Conclusion

In experiments where the impact of dose preparations on experimental unit is measured by several traits, the estimation of relative potency with multidimensional responses can be used. However, when many traits (in the response) are measured then the assumption about the similarity of preparations (hypothesis $H_{\beta}^{0}$) could not be fulfilled. In that case the experimenter should decide which traits are the most important in the estimation of potency. The calculation should then be performed for the chosen traits.

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