UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

December 19, 2016

MEMORANDUM

SUBJECT: **Statistical Analysis of Human Studies for the Human Studies Review Board**: Meeting of January 25-26, 2017

FROM: Timothy F. McMahon, Ph.D.
Risk Assessment and Science Support Branch
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THRU: Timothy Leighton, Team Leader
Risk Assessment and Science Support Branch
Antimicrobials Division (7510P)

TO: Steven Weiss, Chief
Risk Assessment and Science Support Branch
Antimicrobials Division (7510P)

The attached memorandum from Dr. Jonathan Cohen, ICF International, discusses the statistical analysis of four scientific papers that the Agency identified as relevant for determining a point of departure for the chemical methylisothiazolinone. The Agency will present three of the four papers to the Human Studies Review Board (HSRB) for their review and recommendations. Based on EPA's review of the scientific and ethical conduct of one study discussed in the attached memo (Isaksson et al, *Contact Dermatitis*, 70, 238-260, 2014), EPA has chosen not to rely on this study; therefore, EPA will not present the research in the Isaksson article to the HSRB for consideration. EPA is presenting the information in the attached memo to the HSRB for use in its review of the three scientific papers that will be presented (Lundov et al., Yazar et al., Zachariae et al.).

The statistical analyses provided in the published papers were not able to be reproduced in their entirety as discussed in the attachment by Dr. Cohen; therefore, EPA is not relying on the statistical conclusions of the papers. Instead, EPA is proposing to use the results of the repeated open application test (ROAT) portion of the Lundov et al. paper to identify a No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) for an elicitation threshold for methylisothiazolinone, with results of Yazar et al. and Zachariae et al. providing a weight of evidence.

Memorandum

To:	Diana Hsieh, Tim Leighton, EPA
From:	Jonathan Cohen, ICF
Date:	November 22, 2016
Re:	EPA C140001, WA 3-98. Statistical Reviews of Four Repeat Open Application Test Papers

1. Introduction and Summary

ICF was asked to review the statistical methods used in four studies of contact allergies to methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI), as follows:

Lundov *et al,* 2011. Methylisothiazolinone contact allergy and dose-response relationships. *Contact Dermatitis,* 64, 330-336.

Isaksson *et al,* 2014. Repeat open application test with methylisothiazolinone in individuals sensitive to methylchloroisothiazolinone/ methylisothiazolinone. *Contact Dermatitis*, 70, 238-260.

Yazar *et al*, 2015. Methylisothiazolinone in rinse-off products causes allergic contact dermatitis: a repeated open-application study. *British Journal of Dermatology*, 173, 115-122.

Zachariae *et al*, 2006. An evaluation of dose/unit area and time as key factors influencing the elicitation capacity of methylchloroisothiazolinone/ methylisothiazolinone (MCI/MI) in MCI/MI-allergic patients. *Contact Dermatitis*, 55, 160-166

For each of these four papers, ICF reviewed and attempted to reproduce the statistical analyses. Each section of this memorandum summarizes the statistical review and includes the output of the SAS program used to evaluate the statistical methods. The SAS programs used are provided as attachments.

2. Lundov et al

Eleven MI-allergic individuals were patch tested with 12 different doses of MI without phenooxyethanol and with the same 12 doses of MI with phenooxyethanol. The doses ranged from 0.0105 µg/cm^2 MI to 60 µg/cm^2 MI. The same test subjects were tested using a repeated

open application test (ROAT) at doses of 0.0105, 0.105, and 0.21 μg/cm^2 MI twice daily for 21 days.

1. To model the patch test results without and with phenooxyethanol, logistic regression models were fitted. These models are of the form log {P(Response)/P(No Response)} = α + β log(dose), where log denotes the natural logarithm. The logistic regression models appear to have been fitted separately to the dose-response data without and with phenooxyethanol. The comparison of the two curves in their Figure 2 is graphical and does not take into account the fact that the data are likely to be correlated since the same test subjects were tested at multiple doses without or with phenooxyethanol. A preferred statistical comparison would be to use a model with a random subject effect to account for these possible correlations. This model would be of the form: log {P(Response)/P(No Response)} = α + β log(dose) + Subject, where "Subject" is the random subject effect (normally distributed with a mean of zero), and the intercept and/or the slope could be different for the tests without and with phenooxyethanol. This model cannot be fitted without access to the raw data since the detailed results for each subject are not shown.

2. A Wilcoxon rank(ed) sum test was used to compare the results of the patch tests without and with phenooxyethanol. The difference was not statistically significant. It is not obvious how this statistical test would have been conducted since it is not clear how to perform such a test to take into account the 12 different doses and also the possible correlations between the measurements on the same subjects. Alternative statistical tests cannot be applied without access to the raw data.

3. A better statistical test for comparing the patch tests without and with phenooxyethanol is to use a logistic regression model.of the form log {P(Response)/P(No Response)} = α + δ(phen) + β log(dose) + Subject, where phen = 1 for the tests with phenooxyethanol and phen = 0 for the tests without phenooxyethanol. This model cannot be fitted without access to the raw data since the detailed results for each subject are not shown. If the random subject effect can be ignored, then the fitted model shown in the SAS output (p. 26) gives an estimated value of δ = 0.0841, with a p-value of 0.8375, showing that the difference between the patch tests without and with phenooxyethanol is not statistically significant.

4. A Spearman ranked correlation test was used to test for correlations between the threshold doses from the patch tests without and with phenooxyethanol. The correlation was statistically significant (p = 0.002). This statistical test cannot be reproduced without access to the raw data and the threshold doses for each subject. The authors wrongly conclude that the strong ranked correlation implies that there are no differences in the threshold doses. In fact a strong correlation would also be found if the threshold dose without phenooxyethanol is approximately proportional to the threshold dose with phenooxyethanol, or if the differences were approximately constant, even if those threshold doses were not the same. A much better statistical approach would be to use a one-sample Wilcoxon rank sum test of the eleven differences between the thresholds for the same subject, testing if the median difference is zero.

5. Table 3 of the paper presents the eliciting doses for the patch tests without and with phenooxyethanol. For example, ED_{95} is the estimated dose such that the probability of a response is 95%, based on the fitted logistic regression model. The estimates for ED_{95} are 18 (95% confidence interval 6.3 - 362 without phenooxyethanol and 15 (5.6 - 227) with phenooxyethanol. Using SAS software and the data shown in their Table 2 I was unable to reproduce the estimates and confidence intervals. For example, as shown in the SAS output below (p. 23), the SAS estimates for ED_{95} are 22 (confidence interval 11.4 - 71.1 without phenooxyethanol and 19 (10.1 - 59.7) with phenooxyethanol (p. 18). These differences in the ED estimates are surprisingly large. It is not clear from the paper how the logistic regression models were fitted and how the confidence intervals for the eliciting doses were derived. SAS uses Fieller's method to compute Fiducial limits.

6. In their Table 4, the authors compare the patch and ROAT test results for the same dose per application and show that the response rates are significantly different (p-value 0.023) at doses of 0.21 and 0.105 $\mu g/cm^2$ but not significantly different (p-value 0.48) at a dose of 0.0105 $\mu g/cm^2$. Using SAS, the results given on pp 5, 6, and 8 for the same McNemar's test give similar but different p-values of 0.016, 0.016, and 0.50 using an exact two-sided test. The McNemar test is for the null hypothesis that the response rates for the two tests are the same. This statistical test is valid for cases where the same subject is given the same treatment so that the treatment results are not independent for the same subject.

7. Figures 3 and 4 of the paper comparing the patch and ROAT test logistic regressions are inconsistent because Figure 3 appears to show the patch tests without phenooxyethanol and Figure 4 appears to show the patch tests with phenooxyethanol. Since the ROAT tests used phenooxyethanol, the Figure 3 analyses are not relevant.

8. The logistic regression of the ROAT test results has high uncertainty because the logistic regression was only fitted to three dose levels and so numerous curves with different shapes could be fit to the same data. Even if the dose-response model formulation is correct, the estimate parameters have wide confidence intervals. The SAS analysis (p. 11) shows that the estimated slope of log(dose) is 0.73 with a 95% confidence interval 0.097 to 1.366 (p-value 0.024).

9. A visual comparison was made between the logistic regression models for the patch and ROAT tests and the authors suggest that the slopes (coefficient of log dose) are similar. A quantitative statistical analysis is preferred. The ideal approach would use a logistic regression including a subject effect to take into account possible correlations between data from the same subject. Without access to the raw data, this comparison cannot be performed. In the SAS program we fitted a model of the form $\log\{P(\text{Response})/P(\text{No Response})\} = \alpha + \beta \log(\text{dose})$, where α and β are allowed to differ between the patch and ROAT tests, but the potential subject effect is ignored. The p-value for testing that the slopes are the same was 0.1152 (pp. 29-30), suggesting that the slopes are not statistically significantly different.

10. Under the assumption that the slopes are the same for the patch test (with phenooxyethanol) and ROAT tests, the authors derived the conversion formula $ED_{xx}(ROAT) = 0.0362 \times ED_{xx}$ (patch test). The ideal approach would use a logistic regression including a subject effect to take into account possible correlations between data from the same subject. In the SAS program we obtained a similar formula by fitting a logistic regression model and ignoring the potential subject effect. The fitted model was of the form log {P(Response)/P(No Response)} = α + δ(ROAT) + β log(dose), where ROAT = 1 for the ROAT test and ROAT = 0 for the patch test with phenooxyethanol. In particular this model assumes that the slopes β are the same for the patch and ROAT tests.The estimated values are α = −0.9172, β = 1.1996, and δ = 4.0120. Using this model, it follows that $ED_{xx}(ROAT) = F \times ED_{xx}$ (patch test), where F = exp (−δ/β) = 0.0353, which is close to the author's estimate of 0.0362.The authors also suggested that the conversion factor F is close to the value 0.0296 obtained from analyses of experiments with nickel and MDBGN. In the SAS program we test whether F = 0.0362 by testing if log(F) = (−δ/β) = log(0.0296). This is the same as testing if D = δ + β log(0.0296) = 0. From the fitted model, a 95% confidence interval for D is −0.779 to 1.222, so the hypothesis that F = 0.0362 is not rejected at the 5% level.

In summary, we were unable to reproduce several of the reported statistical analyses in the Lundov et al paper so the analysis of the study is not reliable. It would be best if the raw data could be obtained and analyzed so that potential correlations between data collected on the same subject could be accounted for.

2.1. Statistical analyses

Table of patch by roat			
patch	roat		
Frequency Percent Row Pct Col Pct	N	Y	Total
N	9 81.82 81.82 100.00	2 18.18 18.18 100.00	11 100.00
Y	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00
Total	9 81.82	2 18.18	11 100.00

Statistics for Table of patch by roat

McNemar's Test	
Statistic (S)	2.0000
DF	1
Asymptotic Pr > S	0.1573
Exact Pr >= S	0.5000

Simple Kappa Coefficient	
Kappa	0.0000
ASE	0.0000
95% Lower Conf Limit	0.0000
95% Upper Conf Limit	0.0000

Sample Size = 11

dose=0.105

Table of patch by roat			
patch	**roat**		
Frequency **Percent** **Row Pct** **Col Pct**	**N**	**Y**	**Total**
N	4 36.36 36.36 100.00	7 63.64 63.64 100.00	11 100.00
Y	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00
Total	4 36.36	7 63.64	11 100.00

Statistics for Table of patch by roat

McNemar's Test	
Statistic (S)	7.0000
DF	1
Asymptotic Pr > S	0.0082
Exact Pr >= S	0.0156

Statistics for Table of patch by roat

dose=0.105

Simple Kappa Coefficient	
Kappa	0.0000
ASE	0.0000
95% Lower Conf Limit	0.0000
95% Upper Conf Limit	0.0000

Sample Size = 11

dose=0.21

Table of patch by roat			
patch	**roat**		
Frequency **Percent** **Row Pct** **Col Pct**	**N**	**Y**	**Total**
N	4 36.36 36.36 100.00	7 63.64 63.64 100.00	11 100.00
Y	0 0.00 . 0.00	0 0.00 . 0.00	0 0.00
Total	4 36.36	7 63.64	11 100.00

Statistics for Table of patch by roat

McNemar's Test	
Statistic (S)	7.0000
DF	1
Asymptotic Pr > S	0.0082
Exact Pr >= S	0.0156

Statistics for Table of patch by roat

dose=0.21

Simple Kappa Coefficient	
Kappa	0.0000
ASE	0.0000
95% Lower Conf Limit	0.0000
95% Upper Conf Limit	0.0000

Sample Size = 11

type=roat

Model Information	
Data Set	WORK.A
Events Variable	responses
Trials Variable	n
Number of Observations	3
Number of Events	16
Number of Trials	33
Name of Distribution	Logistic
Log Likelihood	-19.81056912

Number of Observations Read	3
Number of Observations Used	3
Number of Events	16
Number of Trials	33

Algorithm converged.

Type III Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Ln(dose)	1	5.1097	0.0238

type=roat

Analysis of Maximum Likelihood Parameter Estimates							
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	1.9305	0.9257	0.1162	3.7448	4.35	0.0370
Ln(dose)	1	0.7318	0.3237	0.0973	1.3663	5.11	0.0238

Probit Model in Terms of Tolerance Distribution	
MU	**SIGMA**
-2.6380508	1.36650528

Estimated Covariance Matrix for Tolerance Parameters		
	MU	**SIGMA**
MU	0.274809	-0.009498
SIGMA	-0.009498	0.365448

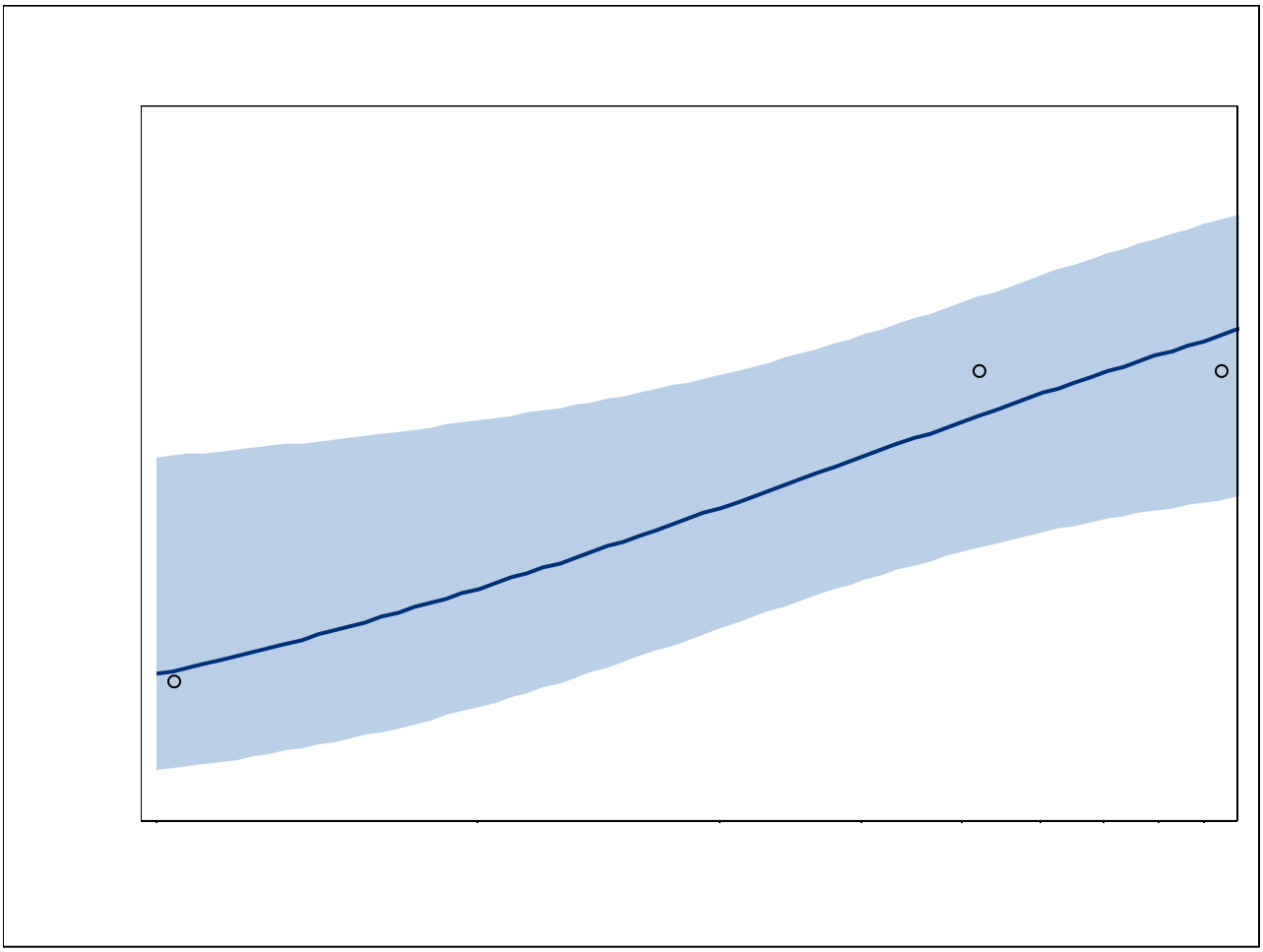
type=roat

Probit Analysis on Ln(dose)			
Probability	**Ln(dose)**	**95% Fiducial Limits**	
0.05	-6.6616	-33.2852	-4.6275
0.10	-5.6406	-25.6537	-4.0314
0.25	-4.1393	-14.5447	-3.0435
0.50	-2.6381	-4.8108	-0.6805
0.75	-1.1368	-2.2169	8.8225
0.90	0.3645	-1.2164	19.9190
0.95	1.3855	-0.6182	27.5484

type=roat

Probit Analysis on dose			
Probability	**dose**	**95% Fiducial Limits**	
0.05	0.00128	3.503E-15	0.00978
0.10	0.00355	7.2234E-12	0.01775
0.25	0.01593	4.82306E-7	0.04767
0.50	0.07150	0.00814	0.50637
0.75	0.32085	0.10895	6785
0.90	1.43975	0.29629	447411061
0.95	3.99699	0.53891	9.20716E11

type=roat



type=with

Model Information	
Data Set	WORK.A
Events Variable	responses
Trials Variable	n
Number of Observations	12
Number of Events	62
Number of Trials	132
Name of Distribution	Logistic
Log Likelihood	-37.88198782

Number of Observations Read	12
Number of Observations Used	12
Number of Events	62
Number of Trials	132

Algorithm converged.

Type III Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Ln(dose)	1	34.1056	<.0001

type=with

Analysis of Maximum Likelihood Parameter Estimates							
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	-1.0629	0.3640	-1.7764	-0.3494	8.52	0.0035
Ln(dose)	1	1.3599	0.2329	0.9035	1.8163	34.11	<.0001

Probit Model in Terms of Tolerance Distribution	
MU	**SIGMA**
0.78160315	0.73534068

Estimated Covariance Matrix for Tolerance Parameters		
	MU	**SIGMA**
MU	0.047086	-0.003135
SIGMA	-0.003135	0.015854

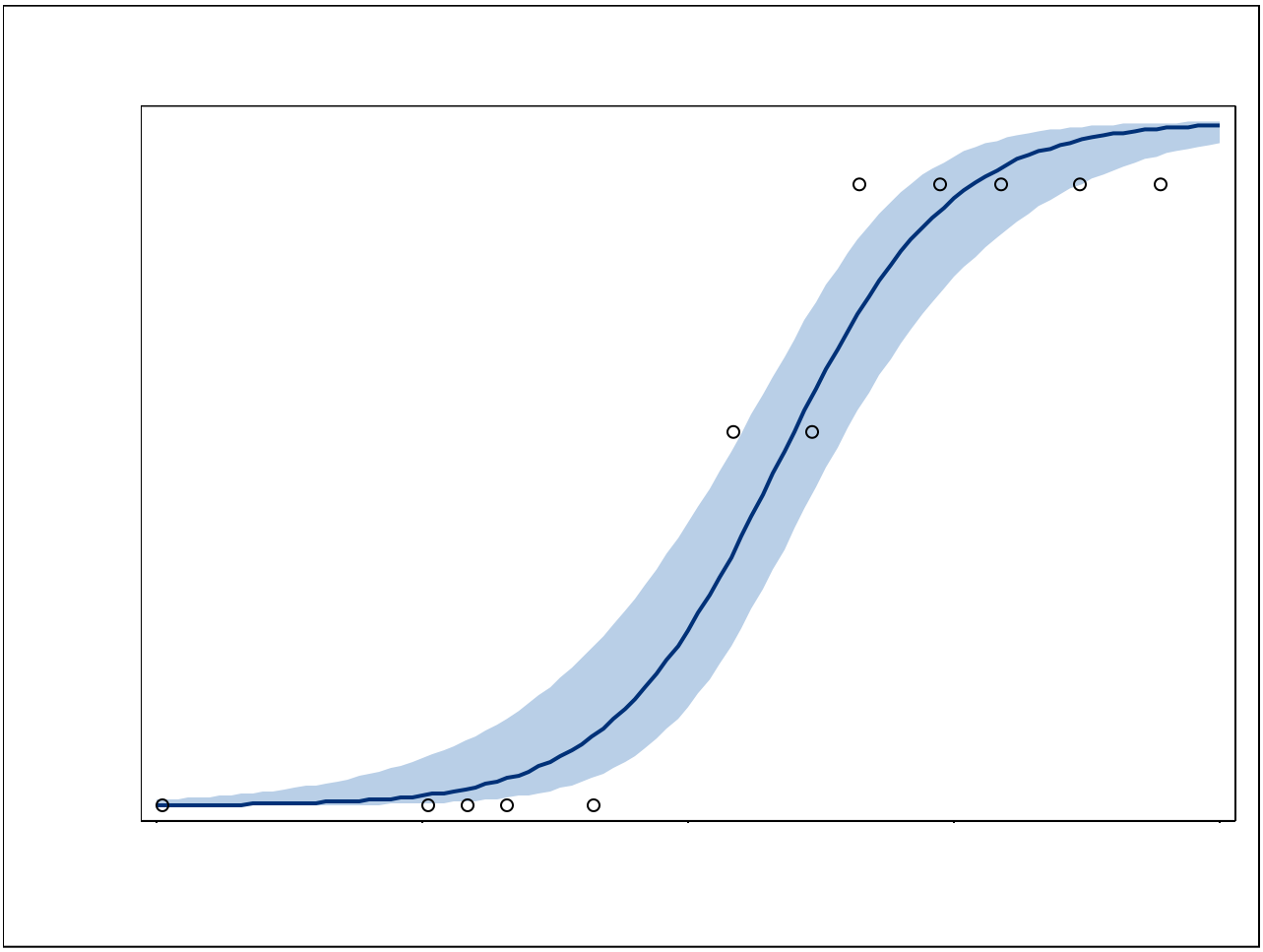
type=with

Probit Analysis on Ln(dose)			
Probability	**Ln(dose)**	**95% Fiducial Limits**	
0.05	-1.38356	-2.65910	-0.69459
0.10	-0.83411	-1.86065	-0.25465
0.25	-0.02625	-0.72270	0.42820
0.50	0.78160	0.31128	1.21501
0.75	1.58946	1.15981	2.18728
0.90	2.39731	1.86953	3.29834
0.95	2.94677	2.31732	4.08896

type=with

Probit Analysis on dose			
Probability	**dose**	**95% Fiducial Limits**	
0.05	0.25068	0.07001	0.49928
0.10	0.43426	0.15557	0.77519
0.25	0.97409	0.48544	1.53449
0.50	2.18497	1.36518	3.37032
0.75	4.90109	3.18931	8.91092
0.90	10.99358	6.48525	27.06780
0.95	19.04432	10.14840	59.67777

type=with



type=without

Model Information	
Data Set	WORK.A
Events Variable	responses
Trials Variable	n
Number of Observations	12
Number of Events	61
Number of Trials	132
Name of Distribution	Logistic
Log Likelihood	-39.32244176

Number of Observations Read	12
Number of Observations Used	12
Number of Events	61
Number of Trials	132

Algorithm converged.

Type III Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Ln(dose)	1	34.5089	<.0001

type=without

Analysis of Maximum Likelihood Parameter Estimates							
Parameter	**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept	1	-1.1007	0.3602	-1.8067	-0.3948	9.34	0.0022
Ln(dose)	1	1.3111	0.2232	0.8737	1.7486	34.51	<.0001

Probit Model in Terms of Tolerance Distribution	
MU	**SIGMA**
0.83950969	0.7626936

Estimated Covariance Matrix for Tolerance Parameters		
	MU	**SIGMA**
MU	0.048487	-0.002978
SIGMA	-0.002978	0.016857

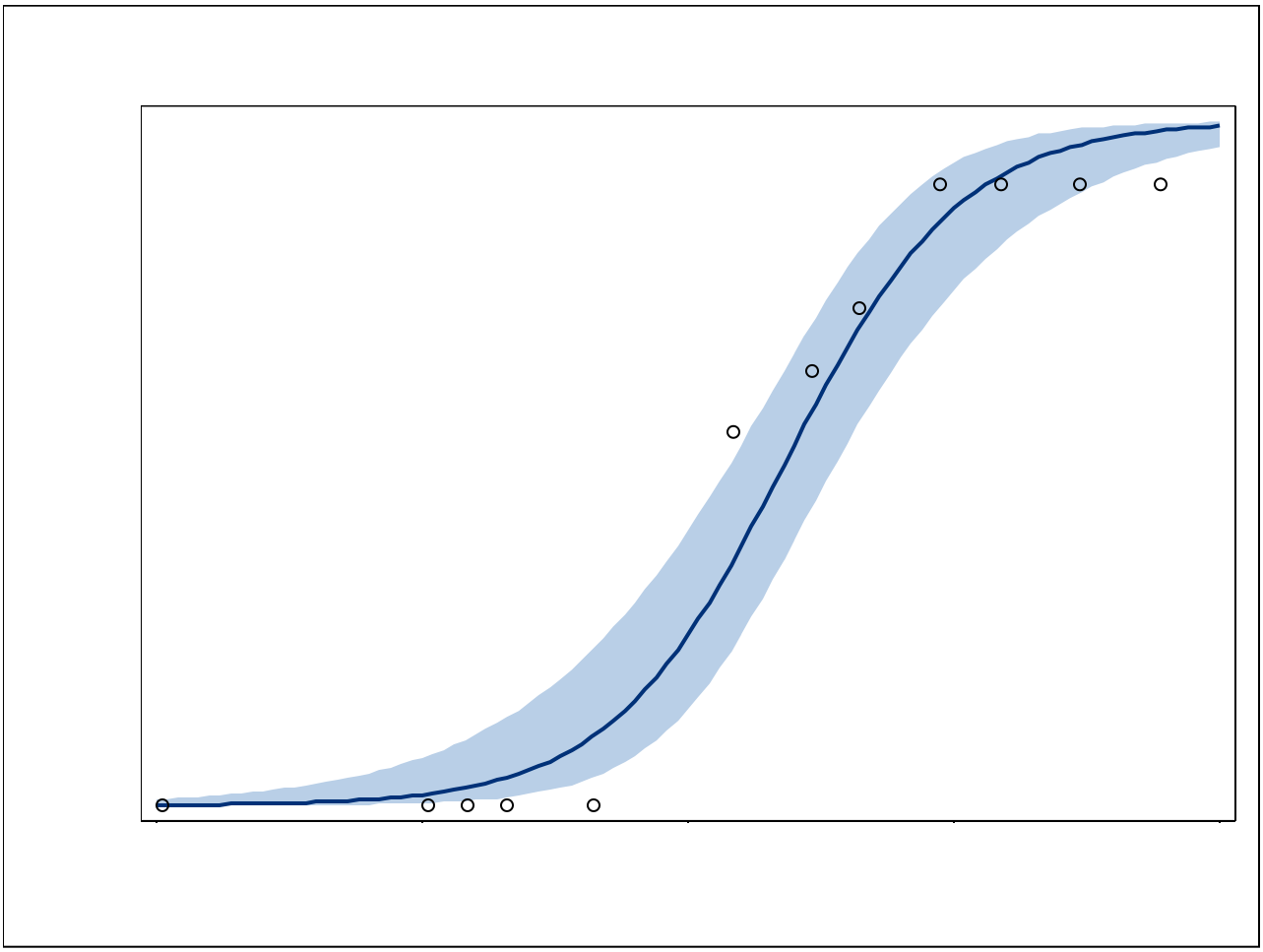
type=without

Probit Analysis on Ln(dose)			
Probability	**Ln(dose)**	**95% Fiducial Limits**	
0.05	-1.40620	-2.70739	-0.70136
0.10	-0.83630	-1.88125	-0.24494
0.25	0.00161	-0.70390	0.46344
0.50	0.83951	0.36450	1.28075
0.75	1.67741	1.23918	2.29181
0.90	2.51532	1.97211	3.44460
0.95	3.08521	2.43563	4.26364

type=without

Probit Analysis on dose			
Probability	**dose**	**95% Fiducial Limits**	
0.05	0.24507	0.06671	0.49591
0.10	0.43331	0.15240	0.78275
0.25	1.00161	0.49465	1.58953
0.50	2.31523	1.43980	3.59936
0.75	5.35170	3.45277	9.89279
0.90	12.37055	7.18581	31.33068
0.95	21.87216	11.42296	71.06853

type=without



Model Information	
Data Set	WORK.A
Events Variable	responses
Trials Variable	n
Number of Observations	24
Number of Events	123
Number of Trials	264
Name of Distribution	Logistic
Log Likelihood	-77.21587102

Number of Observations Read	24
Number of Observations Used	24
Number of Events	123
Number of Trials	264

Class Level Information		
Name	**Levels**	**Values**
type	2	with without

Algorithm converged.

Type III Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Ln(dose)	1	68.6378	<.0001
type	1	0.0420	0.8375

Analysis of Maximum Likelihood Parameter Estimates								
Parameter		**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept		1	-1.1241	0.3297	-1.7704	-0.4778	11.62	0.0007
Ln(dose)		1	1.3351	0.1611	1.0192	1.6509	68.64	<.0001
type	with	1	0.0841	0.4103	-0.7201	0.8884	0.04	0.8375
type	without	0	0.0000	.	.	.	.	.

The Probit Procedure

Model Information	
Data Set	WORK.A
Events Variable	responses
Trials Variable	n
Number of Observations	15
Number of Events	78
Number of Trials	165
Name of Distribution	Logistic
Log Likelihood	-58.84664328

Number of Observations Read	15
Number of Observations Used	15
Number of Events	78
Number of Trials	165

Class Level Information		
Name	**Levels**	**Values**
type	2	roat with

Algorithm converged.

The Probit Procedure

Type III Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Ln(dose)	1	44.2801	<.0001
type	1	26.5649	<.0001

Analysis of Maximum Likelihood Parameter Estimates								
Parameter		**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept		1	-0.9172	0.3198	-1.5439	-0.2905	8.23	0.0041
Ln(dose)		1	1.1996	0.1803	0.8462	1.5529	44.28	<.0001
type	roat	1	4.0120	0.7784	2.4863	5.5376	26.56	<.0001
type	with	0	0.0000	.	.	.	.	.

Estimate							
Label	**Estimate**	**Standard Error**	**z Value**	**Pr > |z|**	**Alpha**	**Lower**	**Upper**
deltatest	0.2214	0.5106	0.43	0.6646	0.05	-0.7793	1.2221

Model Information	
Data Set	WORK.A
Events Variable	responses
Trials Variable	n
Number of Observations	15
Number of Events	78
Number of Trials	165
Name of Distribution	Logistic
Log Likelihood	-57.69255694

McNemar tests
All subjects
Divide p-values by 2

The FREQ Procedure

Number of Observations Read	15
Number of Observations Used	15
Number of Events	78
Number of Trials	165

Class Level Information		
Name	**Levels**	**Values**
type	2	roat with

Algorithm converged.

Type III Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
Ln(dose)	1	27.5122	<.0001
type	1	9.0563	0.0026
Ln(dose)*type	1	2.4809	0.1152

McNemar tests
All subjects
Divide p-values by 2

The FREQ Procedure

Analysis of Maximum Likelihood Parameter Estimates								
Parameter		**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept		1	-1.0629	0.3640	-1.7764	-0.3494	8.52	0.0035
Ln(dose)		1	1.3599	0.2329	0.9035	1.8163	34.11	<.0001
type	roat	1	2.9934	0.9947	1.0438	4.9430	9.06	0.0026
type	with	0	0.0000	.	.	.	.	.
Ln(dose)*type	roat	1	-0.6281	0.3988	-1.4097	0.1535	2.48	0.1152
Ln(dose)*type	with	0	0.0000	.	.	.	.	.

3. Isaksson et al

Fifteen test subjects were tested with two sets of creams using a repeated open application test (ROAT). One of the creams contained parabens. The other cream contained MI. Each cream was applied (on different arms) twice daily for 2 weeks. Of the 15 subjects, 9 were found to have contact allergy to MI based on a patch test and 6 were found to have contact allergy to MCI/MI based on a patch test. The paper is not clear about whether any of the subjects reacted to the cream containing parabens. According to the paper “”a positive ROAT result is equivalent to dermatitis on skin exposed to MI” and “McNemar’s test was used to compare the ROAT outcome between the MI-treated area and the paraben-treated area.” For the statistical analyses we assume that there were no reactions to the paraben cream.

1. McNemar’s test was applied to test if the probability of a reaction on the ROAT using MI is higher than the probability of a reaction on the ROAT using paraben. The proportion of subjects reacting to the ROAT with MI were 8/15 for all subjects, 5/9 for MI-allergic subjects, and 6/9 for MCI/MI-allergic subjects. The one-sided p-values reported in the paper were 0.004, 0.031, and 0.016, respectively. These p-values agree with the results calculated using the SAS program (see pp. 31, 35, and 33). (One-sided p-values are the reported two-sided p-values divided by 2).

For this paper we were able to reproduce the statistical analyses by assuming no reaction to the paraben ROAT..

McNemar tests
All subjects
Divide p-values by 2

The FREQ Procedure

3.1. Statistical Results

Table of roatmi by roatparaben			
roatmi	**roatparaben**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
0	7 46.67 100.00 46.67	0 0.00 0.00 .	7 46.67
1	8 53.33 100.00 53.33	0 0.00 0.00 .	8 53.33
Total	15 100.00	0 0.00	15 100.00

Statistics for Table of roatmi by roatparaben

McNemar tests
All subjects
Divide p-values by 2

The FREQ Procedure

Statistics for Table of roatmi by roatparaben

McNemar's Test	
Statistic (S)	8.0000
DF	1
Asymptotic Pr > S	0.0047
Exact Pr >= S	0.0078

Simple Kappa Coefficient	
Kappa	0.0000
ASE	0.0000
95% Lower Conf Limit	0.0000
95% Upper Conf Limit	0.0000

Sample Size = 15

McNemar tests
MCIMI allergic subjects
Divide p-values by 2

The FREQ Procedure

Table of roatmi by roatparaben			
roatmi	**roatparaben**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
0	3 33.33 100.00 33.33	0 0.00 0.00 .	3 33.33
1	6 66.67 100.00 66.67	0 0.00 0.00 .	6 66.67
Total	9 100.00	0 0.00	9 100.00

Statistics for Table of roatmi by roatparaben

McNemar's Test	
Statistic (S)	6.0000
DF	1
Asymptotic Pr > S	0.0143
Exact Pr >= S	0.0313

McNemar tests
MCIMI allergic subjects
Divide p-values by 2

The FREQ Procedure

Statistics for Table of roatmi by roatparaben

Simple Kappa Coefficient	
Kappa	0.0000
ASE	0.0000
95% Lower Conf Limit	0.0000
95% Upper Conf Limit	0.0000

Sample Size = 9

McNemar tests
MI allergic subjects
Divide p-values by 2

The FREQ Procedure

Table of roatmi by roatparaben			
roatmi	**roatparaben**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
0	4 44.44 100.00 44.44	0 0.00 0.00 .	4 44.44
1	5 55.56 100.00 55.56	0 0.00 0.00 .	5 55.56
Total	9 100.00	0 0.00	9 100.00

Statistics for Table of roatmi by roatparaben

McNemar's Test	
Statistic (S)	5.0000
DF	1
Asymptotic Pr > S	0.0253
Exact Pr >= S	0.0625

4. Yazar et al

Nineteen MI-allergic subjects and nineteen controls without MI-allergy were tested for their reactions to a liquid soap on each of their arms using a ROAT for 21 days. The soap was applied five times a day. !0 of the MI-allergic subjects used 1liquid soap with 100 ppm MI on one arm and a non-MI soap on the other arm. 9 of the MI-allergic subjects used a liquid soap with 50 ppm MI on one arm and a non-MI soap on the other arm. All 19 controls used a liquid soap with 100 ppm MI on one arm and a non-MI soap on the other arm. The ROAT tests were performed after confirmatory patch testing to ensure that the MI-allergic subjects responded to the MI patch and the controls did not.

1. Fisher's exact test was used to test whether the proportions of MI-allergic subjects reacting to 100 ppm MI was the same as the proportion of control subjects reacting to 100 ppm MI. The response rates were 10/10 for the MI-allergic subjects and 0/19 for the control subjects. The reported p-value was 5×10^{-8}, which agrees with the results calculated using the SAS program (p. 44).
2. Fisher's exact test was used to test whether the proportions of MI-allergic subjects reacting to 50 ppm MI was the same as the proportion of control subjects reacting to 50 ppm MI. Although the control subjects were not tested using 50 ppm MI, the analysis in the paper must have assumed that the control subjects did not react to 50 ppm MI since they failed to react to 100 ppm MI. On that basis, the response rates were 7/9 for the MI-allergic subjects and 0/19 for the control subjects. The reported p-value was 0.00003, which agrees with the results calculated using the SAS program (p. 44).
3. McNemar's test was used to test whether the probability of a reaction to the patch test for the MI-allergic subjects exposed to a dose of 0.48 μg/cm^2 in both the patch and ROAT tests is the same as the probability of a reaction to the ROAT test for the same dose. For several of the subjects using 100 ppm MI, the calculated dose per application in the ROAT was a little lower than the nominal 0.48 μg/cm^2 MI. The reported p-value was 0.00195. The paper reports the McNemar test as showing that the higher reactivity to the ROAT was statistically significant. However, if the McNemar test is properly performed as a one-sided test, the p-value is 0.0010. The results for the two-sided test agree with the results calculated using the SAS program (p. 45)..
4. McNemar's test was used to test whether the probability of a reaction to the patch test for the MI-allergic subjects is the same as the probability of a reaction to the ROAT test for a dose of at most 0.48 μg/cm^2 which is the same as 100 ppm MI. For several of the subjects using 100 ppm MI, the calculated dose per application in the ROAT was a little lower than the nominal 0.48 μg/cm^2 MI. The reported p-value was 0.000122. The paper reports the McNemar test as showing that the higher reactivity to the ROAT was statistically significant. However, if the McNemar test is properly performed as a one-

sided test, the p-value is 0.000061. The results for the two-sided test agree with the results calculated using the SAS program (p. 47).

5. The Kendall's tau-b was used to measure the correlation between the threshold for the patch test and threshold for the ROAT test among the 17 MI-allergic subjects that reacted to the ROAT. The correlation coefficient was 0.381 (exact p-value 0.062, approximate p-value 0.036). The estimated correlation coefficient calculated in the SAS program (p. 48) was the same value, but the p-value was different (0.0569), likely due to different algorithms used to compute the p-value. The SAS program also gives the Spearman correlation coefficient, which has a similar value.
6. In the SAS program, we also calculated the Kendall's tau-b was used to measure the correlation between the threshold for the patch test and threshold for the ROAT test among all 19 MI-allergic subjects. For this purpose we assumed a very high value (999) for the ROAT threshold of the two subjects that did not react during the 21 days. The estimated correlation coefficient calculated in the SAS program was 0.317, and the p-value was 0.094 (p. 50). The SAS program also gives the Spearman correlation coefficient, which has a similar value.

For this paper we were able to reproduce the statistical analyses reasonably well. For the Fisher exact tests, we had to assume that the controls did not respond to 50 ppm since they did not respond to 100 ppm, a reasonable assumption. For the McNemar tests the text implied that a one-sided test was performed but the reported results were for a two-sided test.

4.1. Statistical Results

Simple Kappa Coefficient	
Kappa	0.0000
ASE	0.0000
95% Lower Cof Limit	0.0000
95% Upper Conf Limit	0.0000

Sample Size = 9

Table of group by response			
group	**response**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
allergic	2 7.14 22.22 9.52	7 25.00 77.78 100.00	9 32.14
control	19 67.86 100.00 90.48	0 0.00 0.00 0.00	19 67.86
Total	21 75.00	7 25.00	28 100.00

Statistics for Table of group by response

Statistic	DF	Value	Prob
Chi-Square	1	19.7037	<.0001
Likelihood Ratio Chi-Square	1	21.9561	<.0001
Continuity Adj. Chi-Square	1	15.7739	<.0001
Mantel-Haenszel Chi-Square	1	19.0000	<.0001
Phi Coefficient		-0.8389	
Contingency Coefficient		0.6427	
Cramer's V		-0.8389	
WARNING: 50% of the cells have expected counts less than 5. (Asymptotic) Chi-Square may not be a valid test.			

The FREQ Procedure

Statistics for Table of group by response

dose=50

Pearson Chi-Square Test	
Chi-Square	19.7037
DF	1
Asymptotic Pr > ChiSq	<.0001
Exact Pr >= ChiSq	<.0001

Likelihood Ratio Chi-Square Test	
Chi-Square	21.9561
DF	1
Asymptotic Pr > ChiSq	<.0001
Exact Pr >= ChiSq	<.0001

Mantel-Haenszel Chi-Square Test	
Chi-Square	19.0000
DF	1
Asymptotic Pr > ChiSq	<.0001
Exact Pr >= ChiSq	<.0001

The FREQ Procedure

Statistics for Table of group by response

dose=50

Fisher's Exact Test	
Cell (1,1) Frequency (F)	2
Left-sided Pr <= F	<.0001
Right-sided Pr >= F	1.0000
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 28

The FREQ Procedure

dose=100

Table of group by response			
group	**response**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
allergic	0 0.00 0.00 0.00	10 34.48 100.00 100.00	10 34.48
control	19 65.52 100.00 100.00	0 0.00 0.00 0.00	19 65.52
Total	19 65.52	10 34.48	29 100.00

Statistics for Table of group by response

Statistic	DF	Value	Prob
Chi-Square	1	29.0000	<.0001
Likelihood Ratio Chi-Square	1	37.3628	<.0001
Continuity Adj. Chi-Square	1	24.7426	<.0001
Mantel-Haenszel Chi-Square	1	28.0000	<.0001
Phi Coefficient		-1.0000	
Contingency Coefficient		0.7071	

The FREQ Procedure

Statistics for Table of group by response

dose=100

Statistic	DF	Value	Prob
Cramer's V		-1.0000	
WARNING: 25% of the cells have expected counts less than 5. (Asymptotic) Chi-Square may not be a valid test.			

Pearson Chi-Square Test	
Chi-Square	29.0000
DF	1
Asymptotic Pr > ChiSq	<.0001
Exact Pr >= ChiSq	<.0001

Likelihood Ratio Chi-Square Test	
Chi-Square	37.3628
DF	1
Asymptotic Pr > ChiSq	<.0001
Exact Pr >= ChiSq	<.0001

The FREQ Procedure

Statistics for Table of group by response

dose=100

Mantel-Haenszel Chi-Square Test	
Chi-Square	28.0000
DF	1
Asymptotic Pr > ChiSq	<.0001
Exact Pr >= ChiSq	<.0001

Fisher's Exact Test	
Cell (1,1) Frequency (F)	0
Left-sided Pr <= F	<.0001
Right-sided Pr >= F	1.0000
Table Probability (P)	<.0001
Two-sided Pr <= P	<.0001

Sample Size = 29

Obs	dose	Table	Name1	Label1	cValue1	nValue1
1	50	Table group * response	Cell1_FREQ	Cell (1,1) Frequency (F)	2	2.000000
2	50	Table group * response	XPL_FISH	Left-sided Pr <= F	<.0001	0.000030404
3	50	Table group * response	XPR_FISH	Right-sided Pr >= F	1.0000	1.000000
4	50	Table group * response				.
5	50	Table group * response	P_TABLE	Table Probability (P)	<.0001	0.000030404
6	50	Table group * response	XP2_FISH	Two-sided Pr <= P	<.0001	0.000030404
7	100	Table group * response	Cell1_FREQ	Cell (1,1) Frequency (F)	0	0
8	100	Table group * response	XPL_FISH	Left-sided Pr <= F	<.0001	4.9925087E-8
9	100	Table group * response	XPR_FISH	Right-sided Pr >= F	1.0000	1.000000
10	100	Table group * response				.
11	100	Table group * response	P_TABLE	Table Probability (P)	<.0001	4.9925087E-8
12	100	Table group * response	XP2_FISH	Two-sided Pr <= P	<.0001	4.9925087E-8

McNemar tests
Doses =0.48 ug/cm2
Divide p-values by 2

The FREQ Procedure

Table of roat by patch			
roat	**patch**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
0	0 0.00 . 0.00	0 0.00 . .	0 0.00
1	10 100.00 100.00 100.00	0 0.00 0.00 .	10 100.00
Total	10 100.00	0 0.00	10 100.00

Statistics for Table of roat by patch

McNemar's Test	
Statistic (S)	10.0000
DF	1
Asymptotic Pr > S	0.0016
Exact Pr >= S	0.0020

McNemar tests
Doses =0.48 ug/cm2
Divide p-values by 2

The FREQ Procedure

Statistics for Table of roat by patch

Simple Kappa Coefficient	
Kappa	0.0000
ASE	0.0000
95% Lower Conf Limit	0.0000
95% Upper Conf Limit	0.0000

Sample Size = 10

McNemar tests
Doses <= 0.48 ug/cm2
Divide p-values by 2

The FREQ Procedure

Table of roat by patch			
roat	**patch**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
0	2 10.53 100.00 12.50	0 0.00 0.00 0.00	2 10.53
1	14 73.68 82.35 87.50	3 15.79 17.65 100.00	17 89.47
Total	16 84.21	3 15.79	19 100.00

Statistics for Table of roat by patch

McNemar's Test	
Statistic (S)	14.0000
DF	1
Asymptotic Pr > S	0.0002
Exact Pr >= S	0.0001

McNemar tests
Doses <= 0.48 ug/cm2
Divide p-values by 2

The FREQ Procedure

Statistics for Table of roat by patch

Simple Kappa Coefficient	
Kappa	0.0432
ASE	0.0381
95% Lower Conf Limit	-0.0316
95% Upper Conf Limit	0.1179

Sample Size = 19

2 Variables:	patch roat

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Median**	**Minimum**	**Maximum**
patch	17	4.23176	4.34100	3.00000	0.48000	15.00000
roat	17	13.86529	5.55615	14.00000	6.60000	25.43000

Spearman Correlation Coefficients, N = 17 Prob > |r| under H0: Rho=0		
	patch	**roat**
patch	1.00000	0.45216 0.0684
roat	0.45216 0.0684	1.00000

Kendall Tau b Correlation Coefficients, N = 17 Prob > |tau| under H0: Tau=0		
	patch	**roat**
patch	1.00000	0.38111 0.0569
roat	0.38111 0.0569	1.00000

2 Variables:	patch roat

Simple Statistics						
Variable	**N**	**Mean**	**Std Dev**	**Median**	**Minimum**	**Maximum**
patch	19	4.10211	4.11112	3.00000	0.48000	15.00000
roat	19	117.56368	310.65888	14.60000	6.60000	999.00000

Spearman Correlation Coefficients, N = 19 Prob > |r| under H0: Rho=0		
	patch	**roat**
patch	1.00000	0.38416 0.1044
roat	0.38416 0.1044	1.00000

Kendall Tau b Correlation Coefficients, N = 19 Prob > |tau| under H0: Tau=0		
	patch	**roat**
patch	1.00000	0.31706 0.0942
roat	0.31706 0.0942	1.00000

5. Zachariae et al

Twenty-five MCI/MI-allergic patients and 10 control subjects were tested using a ROAT test for their reaction to MCI/MI. Each subject was exposed to a dose of 0.025 µg/cm^2 per day for 4 weeks (ROAT1), followed by a wash-out period of at least four weeks, and then were exposed to a dose of 0.094 µg/cm^2 per day for 4 weeks (ROAT2).

1. The reactions to the ROAT1 for the MCI/MI allergic patients and control group were compared using Fisher's exact test. The p-value for a difference in the probability of a reaction was 0.0835, agreeing with the calculations in the SAS program (p. 53).

2. The reactions to the ROAT2 for the MCI/MI allergic patients and control group were compared using Fisher's exact test. The p-value for a difference in the probability of a reaction was 0.00022, agreeing with the calculations in the SAS program (p. 57).

3. A logistic regression model including a random subject effect was used to compare the proportions of reactions to the ROAT1 and ROAT2 doses among MCI/MI-allergic patients. The observed proportions were 7/25 for ROAT1 and 14/25 for ROAT2. The reported p-value was < 0.0001. The details of the fitted logistic regression model were not given. A suitable model used in the SAS program is of the form log {P(Response)/P(No Response}} = a + b × dose + Subject, where Subject is assumed to be a random subject effect that is normally distributed with a mean of zero. This takes into account the fact that the same subjects were tested with each dose. A logistic regression without including a subject effect gave a p-value of 0.0484 for the difference between the two doses (p. 61). Adding in a random subject effect to the model and using the SAS GLIMMIX procedure gave very different p-values depending upon the method used to fit the model. The Laplace method is often recommended for cases of binomial sampling where the number of measurements per subject is small; here we have 2 measurements per subject. The p-value using the Laplace method was 0.4936 (p. 65). The default method in SAS is the "Residual Pseudo-likelihood" method, which gives a p-value of 0.0407 (p. 69). The statistical literature does not make clear recommendations as to the preferred method. The fact that the standard error of the estimated variance between subjects was 3 times larger than the estimate for the Laplace method but about 70% of the estimated variance for the "Residual Pseudo-likelihood" method suggests that the estimates from the default method are more stable.

4. As an alternative approach to compare ROAT1 and ROAT2, the SAS program includes a McNemar test. The p-value was 0.0078 for testing that a reaction to the ROAT is more likely with the higher dose (p. 58, a one-sided test).

For this paper, we were able to reproduce the Fisher exact tests, but could not reproduce the logistic regression analysis comparing the two doses, taking into account a possible subject effect. Differences between statistical software and methods used to fit generalized linear models with random effects can explain the large differences in those p-values.

5.1. Statistical Analyses

Table of group by response			
group	**response**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
allergic	18 51.43 72.00 64.29	7 20.00 28.00 100.00	25 71.43
control	10 28.57 100.00 35.71	0 0.00 0.00 0.00	10 28.57
Total	28 80.00	7 20.00	35 100.00

Statistics for Table of group by response

Statistic	DF	Value	Prob
Chi-Square	1	3.5000	0.0614
Likelihood Ratio Chi-Square	1	5.3805	0.0204
Continuity Adj. Chi-Square	1	1.9688	0.1606
Mantel-Haenszel Chi-Square	1	3.4000	0.0652
Phi Coefficient		-0.3162	
Contingency Coefficient		0.3015	
Cramer's V		-0.3162	
WARNING: 25% of the cells have expected counts less than 5. (Asymptotic) Chi-Square may not be a valid test.			

Statistics for Table of group by response

dose=ROAT1

Pearson Chi-Square Test	
Chi-Square	3.5000
DF	1
Asymptotic Pr > ChiSq	0.0614
Exact Pr >= ChiSq	0.1554

Likelihood Ratio Chi-Square Test	
Chi-Square	5.3805
DF	1
Asymptotic Pr > ChiSq	0.0204
Exact Pr >= ChiSq	0.0835

Mantel-Haenszel Chi-Square Test	
Chi-Square	3.4000
DF	1
Asymptotic Pr > ChiSq	0.0652
Exact Pr >= ChiSq	0.1554

Statistics for Table of group by response

dose=ROAT1

Fisher's Exact Test	
Cell (1,1) Frequency (F)	18
Left-sided Pr <= F	0.0715
Right-sided Pr >= F	1.0000
Table Probability (P)	0.0715
Two-sided Pr <= P	0.0835

Sample Size = 35

Test for differences between allergic vs control group

The FREQ Procedure 11:36 Tuesday, December 20, 2016 **55**

dose=ROAT2

Table of group by response			
group	**response**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
allergic	11 31.43 44.00 52.38	14 40.00 56.00 100.00	25 71.43
control	10 28.57 100.00 47.62	0 0.00 0.00 0.00	10 28.57
Total	21 60.00	14 40.00	35 100.00

Statistics for Table of group by response

Statistic	DF	Value	Prob
Chi-Square	1	9.3333	0.0023
Likelihood Ratio Chi-Square	1	12.8143	0.0003
Continuity Adj. Chi-Square	1	7.1458	0.0075
Mantel-Haenszel Chi-Square	1	9.0667	0.0026
Phi Coefficient		-0.5164	
Contingency Coefficient		0.4588	
Cramer's V		-0.5164	
WARNING: 25% of the cells have expected counts less than 5. (Asymptotic) Chi-Square may not be a valid test.			

Statistics for Table of group by response

dose=ROAT2

Pearson Chi-Square Test	
Chi-Square	9.3333
DF	1
Asymptotic Pr > ChiSq	0.0023
Exact Pr >= ChiSq	0.0056

Likelihood Ratio Chi-Square Test	
Chi-Square	12.8143
DF	1
Asymptotic Pr > ChiSq	0.0003
Exact Pr >= ChiSq	0.0022

Mantel-Haenszel Chi-Square Test	
Chi-Square	9.0667
DF	1
Asymptotic Pr > ChiSq	0.0026
Exact Pr >= ChiSq	0.0056

Statistics for Table of group by response

dose=ROAT2

Fisher's Exact Test	
Cell (1,1) Frequency (F)	11
Left-sided Pr <= F	0.0019
Right-sided Pr >= F	1.0000
Table Probability (P)	0.0019
Two-sided Pr <= P	0.0022

Sample Size = 35

McNemar test
ROAT1 vs ROAT2
Divide p-values by 2

The FREQ Procedure

Table of roat1 by roat2			
roat1	**roat2**		
Frequency **Percent** **Row Pct** **Col Pct**	**0**	**1**	**Total**
0	11 44.00 61.11 100.00	7 28.00 38.89 50.00	18 72.00
1	0 0.00 0.00 0.00	7 28.00 100.00 50.00	7 28.00
Total	11 44.00	14 56.00	25 100.00

Statistics for Table of roat1 by roat2

McNemar's Test	
Statistic (S)	7.0000
DF	1
Asymptotic Pr > S	0.0082
Exact Pr >= S	0.0156

McNemar test
ROAT1 vs ROAT2
Divide p-values by 2

The FREQ Procedure

Statistics for Table of roat1 by roat2

Simple Kappa Coefficient	
Kappa	0.4681
ASE	0.1445
95% Lower Conf Limit	0.1850
95% Upper Conf Limit	0.7512

Sample Size = 25

The Probit Procedure

Model Information	
Data Set	WORK.C
Dependent Variable	response
Number of Observations	50
Name of Distribution	Logistic
Log Likelihood	-31.97207794

Number of Observations Read	50
Number of Observations Used	50

Class Level Information		
Name	**Levels**	**Values**
dose	2	ROAT1 ROAT2
response	2	0 1

Response Profile		
Ordered Value	**response**	**Total Frequency**
1	1	21
2	0	29

PROC PROBIT is modeling the probabilities of levels of response having LOWER Ordered Values in the respon profile table.

Algorithm converged.

The Probit Procedure

Type III Analysis of Effects			
Effect	**DF**	**Wald Chi-Square**	**Pr > ChiSq**
dose	1	3.8966	0.0484

Analysis of Maximum Likelihood Parameter Estimates								
Parameter		**DF**	**Estimate**	**Standard Error**	**95% Confidence Limits**		**Chi-Square**	**Pr > ChiSq**
Intercept		1	0.2412	0.4029	-0.5485	1.0309	0.36	0.5495
dose	ROAT1	1	-1.1856	0.6006	-2.3628	-0.0084	3.90	0.0484
dose	ROAT2	0	0.0000	.	.	.	.	.

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Model Information	
Data Set	WORK.C
Response Variable	response
Response Distribution	Binary
Link Function	Logit
Variance Function	Default
Variance Matrix Blocked By	id
Estimation Technique	Maximum Likelihood
Likelihood Approximation	Laplace
Degrees of Freedom Method	Containment

Class Level Information		
Class	**Levels**	**Values**
dose	2	ROAT1 ROAT2
id	25	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

Number of Observations Read	50
Number of Observations Used	50

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Response Profile		
Ordered Value	**response**	**Total Frequency**
1	0	29
2	1	21
The GLIMMIX procedure is modeling the probability that response='1'.		

Dimensions	
G-side Cov. Parameters	1
Columns in X	3
Columns in Z per Subject	1
Subjects (Blocks in V)	25
Max Obs per Subject	2

Optimization Information	
Optimization Technique	Dual Quasi-Newton
Parameters in Optimization	3
Lower Boundaries	1
Upper Boundaries	0
Fixed Effects	Not Profiled
Starting From	GLM estimates

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Iteration History					
Iteration	**Restarts**	**Evaluations**	**Objective Function**	**Change**	**Max Gradient**
0	**0**	4	59.300818288	.	3.388366
1	**0**	2	58.418341539	0.88247675	1.592952
2	**0**	3	58.020991027	0.39735051	0.459968
3	**0**	4	57.428023719	0.59296731	0.50658
4	**0**	4	57.137327381	0.29069634	0.22089
5	**0**	4	57.049248702	0.08807868	0.100402
6	**0**	3	57.034843311	0.01440539	0.083062
7	**0**	3	57.030966223	0.00387709	0.024051
8	**0**	3	57.030726845	0.00023938	0.015686
9	**0**	3	57.030656278	0.00007057	0.000694
10	**0**	3	57.030655655	0.00000062	0.000255
11	**0**	3	57.030655563	0.00000009	0.000032

Convergence criterion (GCONV=1E-8) satisfied.

Fit Statistics	
-2 Log Likelihood	57.03
AIC (smaller is better)	63.03
AICC (smaller is better)	63.55
BIC (smaller is better)	66.69

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Fit Statistics	
CAIC (smaller is better)	69.69
HQIC (smaller is better)	64.04

Fit Statistics for Conditional Distribution	
-2 log L(response | r. effects)	12.22
Pearson Chi-Square	6.76
Pearson Chi-Square / DF	0.14

Covariance Parameter Estimates			
Cov Parm	**Subject**	**Estimate**	**Standard Error**
Intercept	id	15.9480	47.1381

Solutions for Fixed Effects						
Effect	**dose**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		0.6103	1.3913	24	0.44	0.6648
dose	ROAT1	-3.4471	4.9580	24	-0.70	0.4936
dose	ROAT2	0	.	.	.	.

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Type III Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
dose	1	24	0.48	0.4936

Model Information	
Data Set	WORK.C
Response Variable	response
Response Distribution	Binary
Link Function	Logit
Variance Function	Default
Variance Matrix Blocked By	id
Estimation Technique	Residual PL
Degrees of Freedom Method	Containment

Class Level Information		
Class	Levels	Values
dose	2	ROAT1 ROAT2
id	25	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25

Number of Observations Read	50
Number of Observations Used	50

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Response Profile		
Ordered Value	**response**	**Total Frequency**
1	0	29
2	1	21
The GLIMMIX procedure is modeling the probability that response='1'.		

Dimensions	
G-side Cov. Parameters	1
Columns in X	3
Columns in Z per Subject	1
Subjects (Blocks in V)	25
Max Obs per Subject	2

Optimization Information	
Optimization Technique	Newton-Raphson with Ridging
Parameters in Optimization	1
Lower Boundaries	1
Upper Boundaries	0
Fixed Effects	Profiled
Starting From	Data

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Iteration History					
Iteration	**Restarts**	**Subiterations**	**Objective Function**	**Change**	**Max Gradient**
0	**0**	**3**	219.79173881	0.18508021	2.875E-7
1	**0**	**3**	222.72612978	0.07948512	5.36E-10
2	**0**	**2**	223.87340697	0.02690526	5.194E-7
3	**0**	**2**	224.26111426	0.00865697	5.774E-9
4	**0**	**2**	224.38511647	0.00272487	5.74E-11
5	**0**	**1**	224.4240467	0.00085056	1.115E-6
6	**0**	**1**	224.43618802	0.00026557	1.086E-7
7	**0**	**1**	224.43997787	0.00008274	1.054E-8
8	**0**	**1**	224.44115851	0.00002576	1.022E-9
9	**0**	**1**	224.44152609	0.00000802	9.9E-11
10	**0**	**0**	224.44164051	0.00000000	4.662E-6

Convergence criterion (PCONV=1.11022E-8) satisfied.

Fit Statistics	
-2 Res Log Pseudo-Likelihood	224.44
Generalized Chi-Square	31.66
Gener. Chi-Square / DF	0.66

Covariance Parameter Estimates			
Cov Parm	**Subject**	**Estimate**	**Standard Error**
Intercept	id	2.1853	1.5297

Logistic regressions
With subject effect
Laplace

The GLIMMIX Procedure

Solutions for Fixed Effects						
Effect	**dose**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**
Intercept		0.3156	0.5362	24	0.59	0.5616
dose	ROAT1	-1.4534	0.6720	24	-2.16	0.0407
dose	ROAT2	0	.	.	.	.

Type III Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
dose	1	24	4.68	0.0407

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