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MEMORANDUM

HSM-03011

TO: Dave Johnson, Task Force Manager
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FROM: Joseph P. Frank, Senior Toxicologist
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DATE: April 28, 2003

SUBJECT: COMMENTS BY THE REGULATORY AGENCIES ON THE EXPOSURE ALGORITHM PROPOSED BY THE OUTDOOR RESIDENTIAL EXPOSURE TASK FORCE

At the March 4, 2003 meeting of the Outdoor Residential Exposure Task Force (ORETF) and Joint Regulatory Committee (JRC), Doug Baugher gave a presentation on the ORETF "exposure algorithm", i.e., the specific mathematical curve ORETF has chosen to describe the relationship between total dermal exposure (TDE) and transferable turf residue (TTR). The written report on the exposure algorithm is not expected until May 12, 2003. Nonetheless, the regulatory agencies would like to provide comments for consideration by the ORETF when drafting the final report. ORETF is strongly encouraged to submit the final report to the regulatory agencies as soon as possible as regulatory decisions are being impacted by the delay..

The attached document, written by DPR and U.S. EPA staff, reflects the views of the regulatory agencies.

Attachment

cc: Jeff Evans
Jeff Dawson
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Nicolle Tulve
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Mary Mitchell
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Attachment to HSM-03011

Comments on the ORETF exposure algorithm for turf

Sally Powell, CA DPR
Jeff Evans, David Miller and Nicolle Tulve, US EPA

April 28, 2003

At the March 4, 2003 meeting of the Outdoor Residential Exposure Task Force (ORETF), Doug Baugher gave a presentation on the ORETF "exposure algorithm" (i.e., the specific mathematical curve ORETF has chosen to describe the relationship between total dermal exposure (TDE) and transferable turf residue (TTR)). The JRC has not yet seen the written report on the exposure algorithm. Nonetheless, we would like to make the following comments at this preliminary stage, and suggest that the task force consider them in preparing the written report.

Comparability of residue sampling methods

The report on the exposure algorithm must address the effect of the different TTR sampling methods used in these studies. The data in Table 1 show that the TTR value is influencing the TDE value. How is ORETF going to take into account the fact that a PUF roller and a CA roller have different capabilities? This is critical for the interpretation of the data relating TDE to TTR. How will the model include this information?

Comparability of formulations

The validity of combining the liquid and granular data has not been established, nor can it be with the current data, which include only two granular studies that are in a lower TTR range than the liquid studies. The data are consistent with a model fit to the combined points, but they are also consistent with separate lines fit to the granular and liquid studies. There are good reasons to suspect that the relationship of exposure to transferable residue might differ by formulation, including the different natures of granular and liquid turf residues and the differential ability of the roller method to measure them.

The Moses Lake study provides a limited test of the hypothesis of a common relationship between TDE and TTR for granular and liquid formulations. Since all other experimental factors are identical, the effect of formulation can be isolated. A regression model of the form

$$\log TDE = A + B*\log TTR + C*\text{Indicator variable} + D*\text{Indicator variable}*\log TTR$$

can be used to test whether one line describes both granular and liquid data points. The indicator variable equals 0 for granular data points, 1 for liquid. Thus, the parameter C represents the difference in intercepts, and the parameter D the difference in slopes, between the formulations. We fit this model to the arithmetic means of the four granular and four liquid data sets from Moses Lake. Both the intercepts and slopes differ significantly (Fig.1). The granular regression slope is virtually zero, which is not surprising given that the four data points are nearly identical. In other words, these data do not provide a good basis to test the hypothesis.

Means *vs.* individual data points

We support fitting models to the arithmetic means of studies rather than to individual observations because: 1) it is not desirable to let any study dominate the fit just because it has a lot of observations, and 2) observations from the same study cannot be considered independent. (Although if the studies were essentially comparable, it might be desirable to give more weight to larger studies, the studies in this case represent different chemicals, application methods, TTR dislodging techniques, exposure measurement methods, etc., and it was considered undesirable to give greater weight to any specific scenarios.)

On the other hand, we must be concerned with the exposures of individuals, and not just the mean exposure of a group of individuals. Therefore, in the end, we will want to see where all the *individual* observations lie in relation to a proposed model. Any submission on the part of the Task Force should thus certainly include not just the average exposures, but the individual exposure measurements which produce that average. In addition, the report should give, in addition to the arithmetic mean, the sample size, standard deviation, minimum and maximum for each dataset used in the model.

Empirical model-fitting

Empirical model-fitting in the absence of a theoretical model is not a hard-and-fast science. A theoretical model must describe the mechanism(s) producing the relationship in a way that can be translated into a specific mathematical equation. ORETF is engaged in empirical model-fitting. As Doug Baugher noted in his presentation, many different equations may fit a data set equally well and there are no fixed rules for choosing between them.

Empirical model-fitting is essentially data smoothing. The goal of model-fitting is to smooth out the noise in the data, but not the underlying relationship. Any XY data set without multiple Y values for the same X value can be fit perfectly, i.e., a function can be found that goes through every data point, by putting enough parameters into the model. This represents no smoothing at all. This model describes the current data perfectly, but is unlikely to predict any future observation well; such a model is "over fit." A straight line represents the greatest possible smoothing.

When the form of the underlying relationship is not posited, you cannot know when you've done the right amount of smoothing. The approach generally used, therefore, is to find the simplest model that describes the data "adequately." Typically, this means starting with a linear model and adding parameters if they significantly improve the fit and are "consistent" with scientific judgment about the underlying relationship. For the relationship of exposure to transferable residue, it is natural to start with the zero-intercept linear model that defines the conventional transfer coefficient (TC), then see whether the fit is improved significantly by first adding a non-zero intercept, then adding higher-order terms.

In any case, we would expect the chosen model to be tested "afresh" with newly collected data (or at least data that was not used in the model development process) before we could be convinced that the algorithmic model had potential validity. It is not difficult to take a set of data and develop a model that fits those data well. What is difficult is to take a set of data and develop a model that speaks to more general truths and is useful in fitting other sets of data. It is for this reason that "hold-back" samples are simultaneously collected and used to test the generated model.

Alternate models

At the March 4 meeting, Doug Baugher provided to the JRC the data he used to develop this algorithm. The data were provided as a table of arithmetic mean TTR (μg cm^{-2}) and TDE (μg hr^{-1}) for 15 turf data sets (Table 1). Since his presentation gave little information about how the chosen model was selected, we did some analyses of these data to compare the fit of the ORETF model with other possible models.

Methods

The 15 ORETF data sets were first collapsed into nine (Table 2) by averaging the four granular and the four liquid data sets from the ORETF Moses Lake study. This was done because the four granular data points (and similarly, the four liquid points) are all from the same application and day, and therefore should not be treated as replicates. Logarithms of both TTR and TDE were analyzed because both are believed to be lognormally distributed (this is consistent with the ORETF analysis).

Four models were considered:

I. Linear model with slope = 1: log(TDE) = a + log(TTR)
  Equivalent to $DE = 10^a \cdot TTR$, the conventional zero-intercept linear model.
  TC = 10^a for any TTR.

II. Linear model: log(TDE) = a + b•log(TTR)
  Equivalent to $TDE = 10^a \cdot TTR^b$.
  Transfer ratio is dependent on TTR.

III. Alternate model: log(TDE) = a + b•log(TTR) + c•$(\log TTR)^2$
  Equivalent to $TDE = 10^a \cdot TTR^b \cdot 10^{c\cdot(\log(TTR))^2}$.
  Transfer ratio is dependent on TTR.

IV. ORETF model: $(\log TDE)^2$ = a + b•log(TTR)
  Equivalent to $TDE = 10^{(a+b\cdot\log(TTR))^{1/2}}$.
  Transfer ratio is dependent on TTR.

The models were compared by testing the significance of the parameters added going from Model I to II, and from II to III. Model IV, the ORETF model, cannot be directly compared to the others because it has a different structure. Model III is proposed as a surrogate for the ORETF model. Model III has a similar R^2 to the ORETF model and reflects the nonlinearity in approximately the same way within the range of the observed data (Figs. 2 and 3). Model III also has narrower confidence and prediction intervals[1]. Figures 4 and 5 show the same information for Models II and I.

SAS PROC REG and PROC GENMOD were used to fit and compare the models. The SAS program is included in an appendix to this document.

Results

Model I was fit using SAS PROC REG with the slope parameter restricted to equal 1 (Fig. 6). R^2 is 0.85. The significance of the RESTRICT parameter ($p = 0.0488$) indicates that restricting the slope has a significant effect, i.e., that the slope is significantly different from 1.

Models II and III were compared using SAS PROC REG (Fig. 6) to fit an unrestricted model in two steps: 1) with log TTR only, and 2) with log TTR and $(\log TTR)^2$. The linear model has $R^2 = 0.918$ (summary information at the bottom of Fig.6) Adding $(\log TTR)^2$ increases R^2 by only 0.023, a nonsignificant improvement ($p = 0.175$). Figures 8a and 8b present an alternate statistical test of the same comparison. SAS PROC GENMOD was used to fit Models III (Fig. 8a) and II (Fig. 8b). The "deviance" associated with each model represents the lack-of-fit of that model. The deviance associated with Model II (0.711) is higher than that of Model III (0.510) because Model III, having an additional parameter, accounts for more variability. The significance of the additional variability accounted for is tested using the difference between the two model deviances ($0.711 – 0.510 = 0.201$), which is distributed as chi-square with $7 – 6 = 1$ degree of freedom, showing that the addition of $(\log TTR)^2$ is nonsignificant ($p = 0.65$).

Dermal exposures predicted by the ORETF (Model IV) and linear (Model II) models are compared in Fig. 9. Figure 10 compares the transfer ratios (model-predicted TDE divided by TTR) for the two models.

Conclusion

The statistical evidence indicates that the conventional constant-TC model (Model I) does not adequately describe the ORETF data; transfer rate does vary by TTR level. The statistical evidence also indicates that the data are described adequately by a linear model (Model II), with no significant improvement in fit by going to a curvilinear model (Model III). The fact that the curvilinear model is not significantly better than the linear model does not prove that it is incorrect. It means that the ORETF data do not provide statistical support for moving from a simpler to a more complex model.

General conclusions

We have concerns with the methodology used to determine a model structure. There are also concerns about direct quantitative comparisons of exposures estimated by means of a jazzercise scenario and those estimated by other scenarios simulating actual exposures. In addition, combining granular and liquid formulations to determine TCs may not be valid.

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[1] See endnote on calculation of intervals.

Notes

Calculation of confidence and prediction intervals.

There was some discussion at the ORETF meeting about how TableCurve 2D calculates confidence and prediction intervals. Appendix D of the User's Manual gives the formulas

Confidence Interval $\hat{y} \pm t\sqrt{MSE\,l'\left(X'X\right)^{-1} l}$, and

Prediction Interval $\hat{y} \pm t\sqrt{MSE\left(1 + l'\left(X'X\right)^{-1} l\right)}$.

These are the standard textbook formulae, except for the definition of the vector *l*. In the standard formulae, *l* is the vector of values of the predictor variables for a specific observation. The TableCurve manual defines *l* as the "coefficient partial derivative vector evaluated at x_i". I do not know the reason for defining it that way, but for the models we are considering, the two definitions are equivalent. For example, the ORETF model is the model

$$y^2 = a + bx$$

fit to the logs of X and Y. The coefficient partial derivative vector evaluated at x_i is

$$\begin{bmatrix} \dfrac{\partial y^2}{\partial a} = 1 \\ \dfrac{\partial y^2}{\partial b} = x_i \end{bmatrix},$$

which is the vector of values of the predictor variables for an observation at x_i (1 being the "data value" corresponding to the intercept term).

Software.

The plots in this document were produced using TableCurve 2D® V5.01. Statistical analyses were done with SAS® V8.01, with reference to the On-Line Documentation for SAS V8.

Table 1. Arithmetic mean TTR and TDE for turf data sets used to develop ORETF exposure algorithm (data provided by Doug Baugher).

Study	TTR $\mu g\ cm^{-2}$	TDE $\mu g\ hr^{-1}$
CHAPs 2--Granular	0.000162	37
CHAPs 1--Granular	0.000196	39
Jazz 2--Granular	0.000206	30
Jazz 1 --Granular	0.000318	40
CHAPs 2--Liquid	0.00237	820
Jazz 2--Liquid	0.00285	749
Vaccaro--Granular	0.00286	962
CHAPs 1--Liquid	0.006	2,328
Jazz 1 --Liquid	0.0106	2,743
Vaccaro--Liquid	0.02081	7,001
Jazz Imidacloprid--Liquid	0.074	6,690
Bernard--Liquid	0.085	4,800
Jazz Triadimefon--Liquid	0.502	75,597
Jazz Vinclozolin--Liquid	1.01	74,208
Jazz Oxadiazon--Liquid	1.22	27,457

Table 2. Arithmetic mean TTR and TDE for turf studies used in DPR analysis.

Study	TTR $\mu g\ cm^{-2}$	TDE $\mu g\ hr^{-1}$
Moses Lake--Granular	0.000221	36.5
Vaccaro--Granular	0.00286	962
Moses Lake--Liquid	0.005455	1660
Vaccaro--Liquid	0.02081	7,001
Jazz Imidacloprid--Liquid	0.074	6,690
Bernard--Liquid	0.085	4,800
Jazz Triadimefon--Liquid	0.502	75,597
Jazz Vinclozolin--Liquid	1.01	74,208
Jazz Oxadiazon--Liquid	1.22	27,457

Fig. 1. SAS PROC REG output (edited to fit on page): Comparison of slopes and intercepts for granular and liquid product in Moses Lake study.

Stepwise Selection: Step 1
Variable logttr Entered: R-Square = 0.9819 and C(p) = 8.4441

Source	DF	SS	MS	F Value	Pr > F
Model	1	27.69585	27.69585	326.17	<.0001
Error	6	0.50947	0.08491		
Corrected Total	7	28.20532			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	13.48518	0.45829	73.52036	865.84	<.0001
logttr	1.16514	0.06451	27.69585	326.17	<.0001

Stepwise Selection: Step 2
Variable indicator Entered: R-Square = 0.9895 and C(p) = 5.2617

Source	DF	SS	MS	F Value	Pr > F
Model	2	27.90802	13.95401	234.68	<.0001
Error	5	0.29730	0.05946		
Corrected Total	7	28.20532			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	10.56085	1.59487	2.60718	43.85	0.0012
logttr	0.82466	0.18815	1.14222	19.21	0.0071
indicator	1.13517	0.60093	0.21217	3.57	0.1175

Stepwise Selection: Step 3
Variable slope_diff Entered: R-Square = 0.9942 and C(p) = 4.0000

Source	DF	SS	MS	F Value	Pr > F
Model	3	28.04155	9.34718	228.31	<.0001
Error	4	0.16376	0.04094		
Corrected Total	7	28.20532			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	4.77390	3.46680	0.07763	1.90	0.2405
logttr	0.13995	0.41002	0.00477	0.12	0.7500
indicator	7.54822	3.58578	0.18142	4.43	0.1031
slope_diff	0.80083	0.44343	0.13354	3.26	0.1452

Stepwise Selection: Step 4
Variable logttr Removed: R-Square = 0.9940 and C(p) = 2.1165

Source	DF	SS	MS	F Value	Pr > F
Model	2	28.03678	14.01839	415.90	<.0001
Error	5	0.16853	0.03371		
Corrected Total	7	28.20532			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	3.59114	0.09180	51.58512	1530.43	<.0001
indicator	8.73098	0.83623	3.67442	109.01	0.0001
slope_diff	0.94078	0.15320	1.27098	37.71	0.0017

All variables left in the model are significant at the 0.1500 level.
No other variable met the 0.1500 significance level for entry into the model.

Fig. 2. ORETF exposure model (Model IV) fit to arithmetic means of turf studies (with 95% confidence and prediction limits).

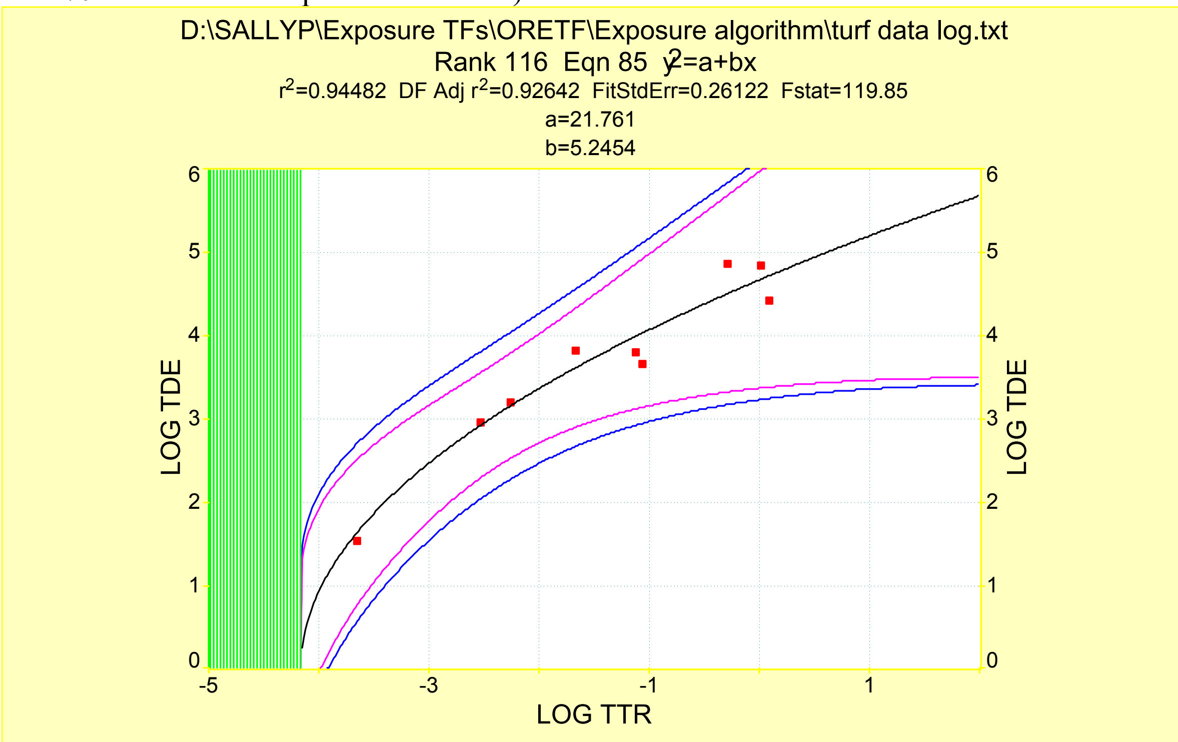


Fig. 3. Alternate curvilinear model (Model III) fit to arithmetic means of turf studies (with 95% confidence and prediction limits).

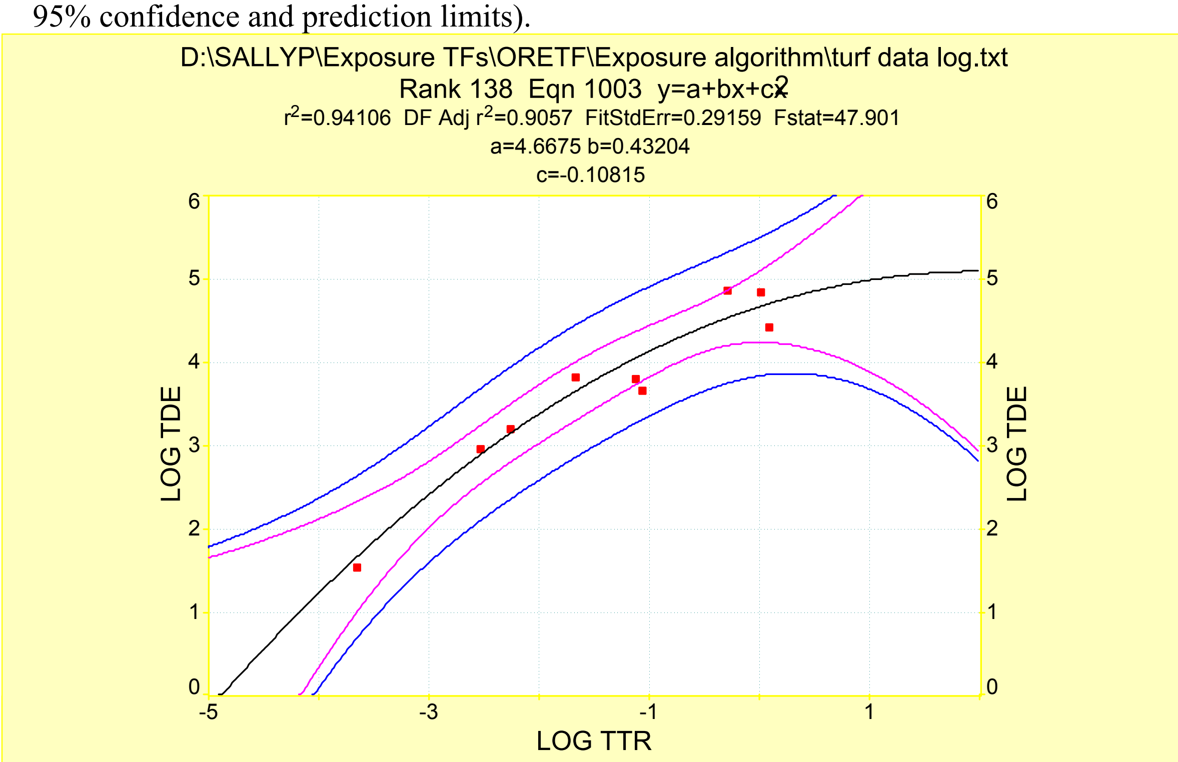


Fig. 4. Linear model (Model II) fit to arithmetic means of turf studies (with 95% confidence and prediction limits).

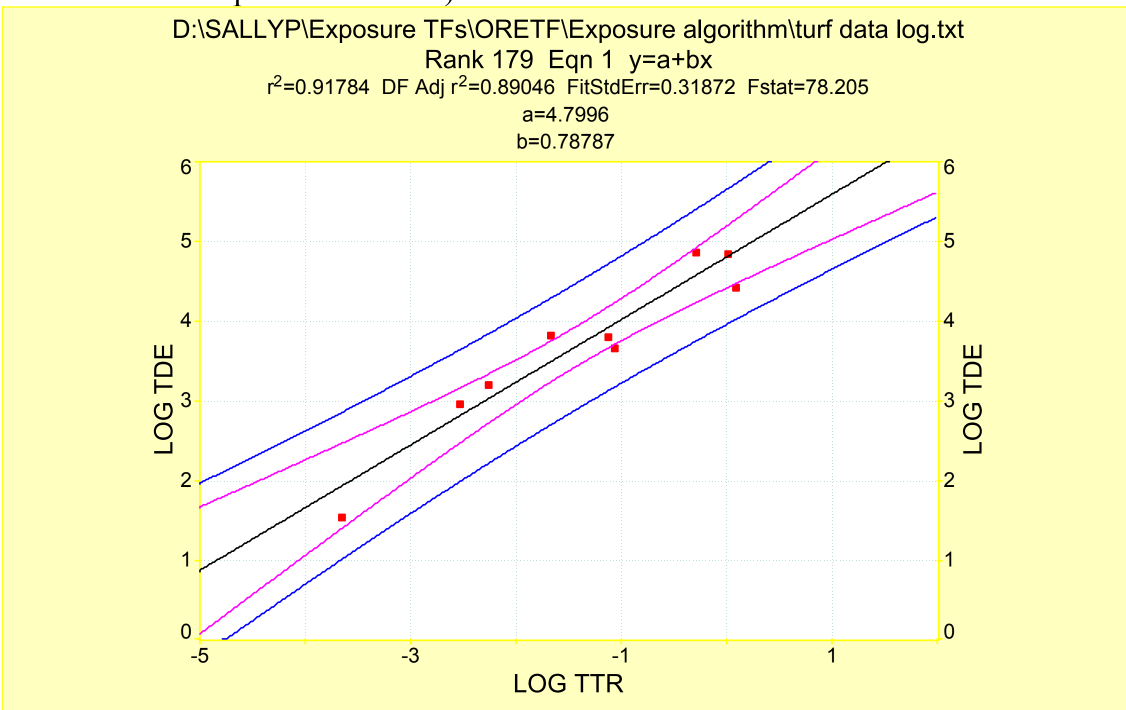


Fig. 5. Constrained linear model (Model I) fit to arithmetic means of turf studies (with 95% confidence and prediction limits).

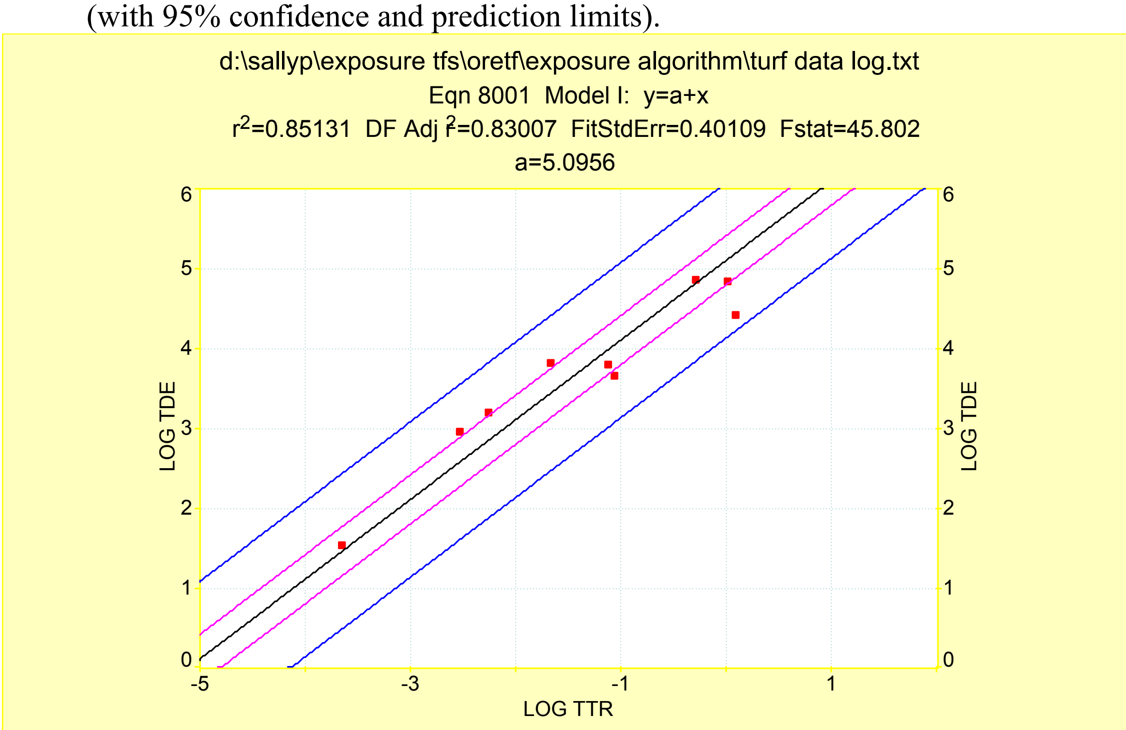


Fig. 6. SAS PROC REG output: Linear model with slope constrained to equal 1.

The REG Procedure

Model: MODEL1

Dependent Variable: logTDE

NOTE: Restrictions have been applied to parameter estimates.

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	0	7.36851	.	.	.
Error	8	1.28701	0.16088		
Corrected Total	8	8.65551			

Root MSE	0.40109	R-Square	0.8513
Dependent Mean	3.70056	Adj R-Sq	0.8513
Coeff Var	10.83873		

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	5.09557	0.13370	38.11	<.0001
logTTR	1	1.00000	0	Infty	<.0001
RESTRICT	-1	-2.71490	1.43490	-1.89	0.0488*

* Probability computed using beta distribution.

Fig. 7. SAS PROC REG output: Linear and quadratic terms entered sequentially to compare Models II and III – slope unconstrained.

The REG Procedure

Dependent Variable: logTDE

Forward Selection: Step 1

Variable logTTR Entered: R-Square = 0.9178 and C(p) = 3.3636

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	7.94442	7.94442	78.20	<.0001
Error	7	0.71110	0.10159		
Corrected Total	8	8.65551			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	4.79965	0.16351	87.53596	861.70	<.0001
logTTR	0.78787	0.08909	7.94442	78.20	<.0001

Forward Selection: Step 2

Variable logTTR2 Entered: R-Square = 0.9411 and C(p) = 3.0000

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	8.14538	4.07269	47.90	0.0002
Error	6	0.51014	0.08502		
Corrected Total	8	8.65551			

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	4.66751	0.17252	62.23531	731.98	<.0001
logTTR	0.43204	0.24538	0.26356	3.10	0.1288
logTTR2	-0.10815	0.07035	0.20096	2.36	0.1751

Summary of Forward Selection

Step	Variable Entered	Number Vars In	Partial R-Square	Model R-Square	C(p)	F Value	Pr > F
1	logTTR	1	0.9178	0.9178	3.3636	78.20	<.0001
2	logTTR2	2	0.0232	0.9411	3.0000	2.36	0.1751

Fig. 8a. SAS PROC GENMOD output: Model III.

GENMOD Procedure

Model Information

Data Set	WORK.ALL
Distribution	Normal
Link Function	Identity
Dependent Variable	logTDE
Observations Used	9

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	6	0.5101	0.0850
Scaled Deviance	6	9.0000	1.5000
Pearson Chi-Square	6	0.5101	0.0850
Scaled Pearson X2	6	9.0000	1.5000
Log Likelihood		0.1459	

Algorithm converged.

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	4.6675	0.1409	4.3914	4.9436	1097.98	<.0001
logTTR	1	0.4320	0.2004	0.0393	0.8247	4.65	0.0311
logTTR2	1	-0.1081	0.0574	-0.2207	0.0044	3.55	0.0597
Scale	1	0.2381	0.0561	0.1500	0.3779		

NOTE: The scale parameter was estimated by maximum likelihood.

Fig. 8b. SAS PROC GENMOD output: Model II.

The GENMOD Procedure

Model Information

Data Set	WORK.ALL
Distribution	Normal
Link Function	Identity
Dependent Variable	logTDE
Observations Used	9

Criteria For Assessing Goodness Of Fit

Criterion	DF	Value	Value/DF
Deviance	7	0.7111	0.1016
Scaled Deviance	7	9.0000	1.2857
Pearson Chi-Square	7	0.7111	0.1016
Scaled Pearson X2	7	9.0000	1.2857
Log Likelihood		-1.3487	

Algorithm converged.

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	4.7996	0.1442	4.5170	5.0823	1107.90	<.0001
logTTR	1	0.7879	0.0786	0.6339	0.9419	100.55	<.0001
Scale	1	0.2811	0.0663	0.1771	0.4461		

NOTE: The scale parameter was estimated by maximum likelihood.

Fig. 9. Dermal exposures (TDE) predicted by the linear and ORETF models.

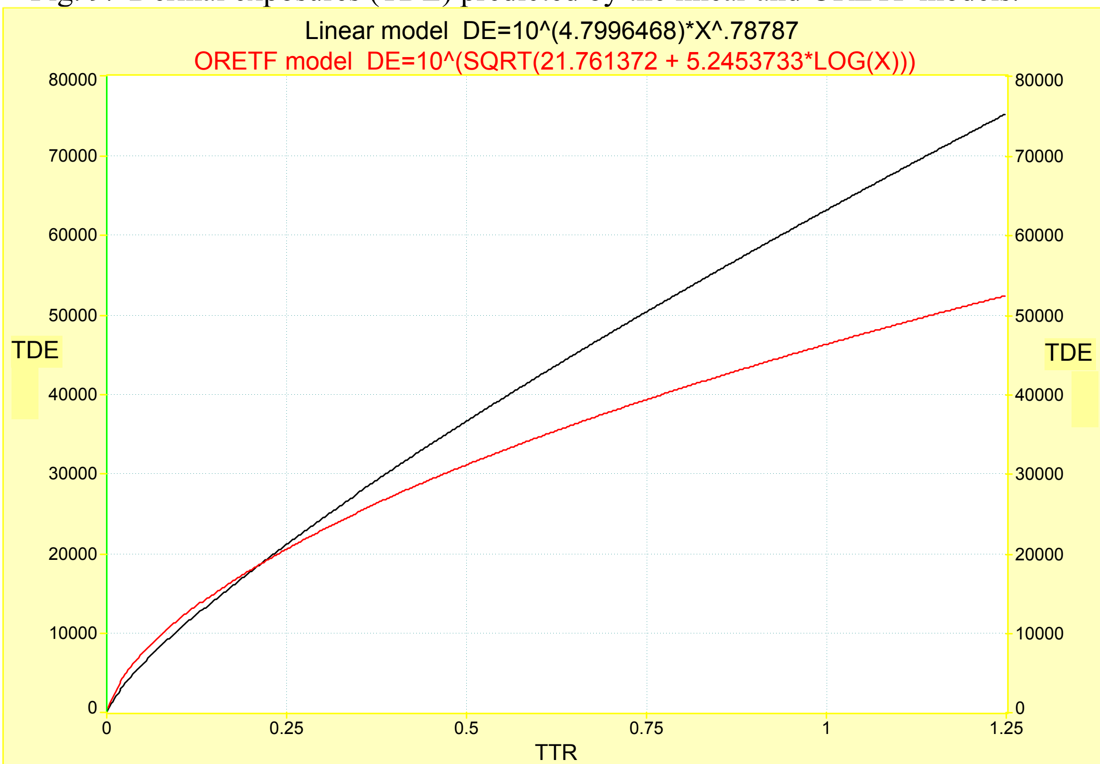
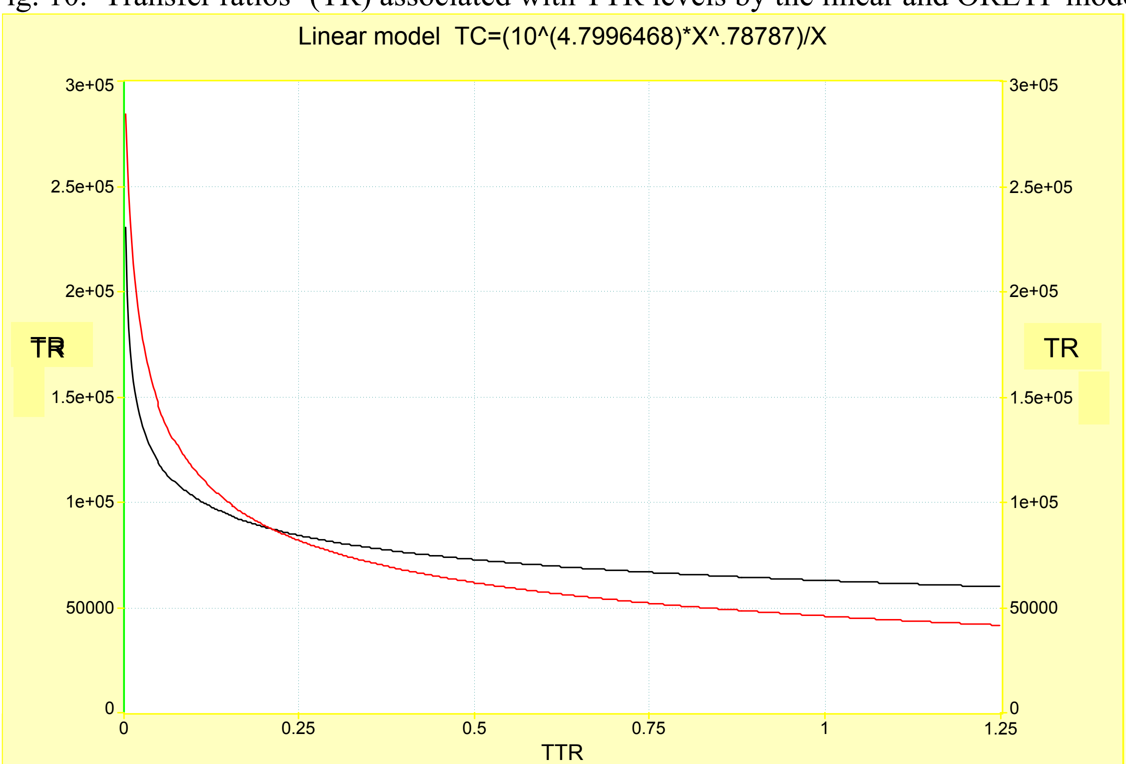


Fig. 10. Transfer ratios[a] (TR) associated with TTR levels by the linear and ORETF models.



[a] TR = TDE predicted by the model for a given TTR value, divided by the TTR value.

APPENDIX
SAS programs used for data analyses

```
****** Compare intercepts and slopes of lines fit to
   granular and liquid data sets ***************************;
title 'Moses Lake data on TTR and TDE';
data one;
input set $ form $ ttr tde;
logttr=log(ttr); logtde=log(tde);
indicator=0; if form='Liquid' then indicator=1;
slope_diff=indicator*logttr;
cards;
CHAPs2  Granular  0.000162    37
CHAPs1  Granular  0.000196    39
Jazz2  Granular    0.000206   30
Jazz1   Granular  0.000318    40
CHAPs2  Liquid    0.00237     820
Jazz2  Liquid     0.00285     749
CHAPs1  Liquid    0.006      2328
Jazz1   Liquid    0.0106      2743
;
run;
proc reg;
model logtde=logttr indicator slope_diff/selection=stepwise;
run;

****** Fit and compare 4 models ******************************;
title 'ORETF data on TTR and TDE';
data logs;
input TTR TDE logTTR logTDE;
logTTR2=logTTR**2;
cards;
0.0002205  36.5   -3.656591406      1.562292864
0.00286      962  -2.543633967      2.983175072
0.005455    1660  -2.263205245      3.220108088
0.02081     7001  -1.68172792       3.845160078
0.074       6690  -1.13076828       3.825426118
0.085       4800  -1.070581074      3.681241237
0.502      75597  -0.299296283      4.878504561
1.01       74208   0.004321374      4.870450727
1.22       27457   0.086359831      4.438653084
;
run;

title2 'Linear model with slope constrained to equal 1';
proc reg;
model logTDE=logTTR;
restrict logTTR=1;
run;

title2 'Linear and quadratic models with slope unconstrained';
title3'Linear and quadratic terms entered sequentially';
proc reg ;
model logTDE=logTTR logTTR2/selection=forward;
run;
```

```
title2'Two GENMOD runs to test significance of quadratic term';
proc genmod;
model logTDE=logTTR logTTR2;
run;
proc genmod;
model logTDE=logTTR ;
run;
```