California Department of Pesticide Regulation
Environmental Monitoring and Pest Management
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PROTOCOL FOR THERMOGRAVIMETRY METHOD DEVELOPMENT FOR ESTIMATION OF VOLATILE ORGANIC COMPOUND EMISSION POTENTIAL OF PESTICIDES

I. INTRODUCTION

The California Clean Air Act of 1988 mandates that air pollution control districts and air quality management districts located in nonattainment areas for state ambient air quality standards maintain an *Air Quality Management Plan* to reduce nonattainment pollutant emission by five percent annually (averaged over a three-year period). Among these pollutants are those, termed reactive organic gases (ROGs), that react with nitrogen oxides (NO_x) in the atmosphere to produce ozone. California has the poorest air quality for ozone in the nation; in 90% of the air basins not in attainment of the ozone standards in 1989, pesticides were identified as contributing from <1% to a theoretical maximum of 10.7% of ROG emissions (Air Resources Board, 1991). Solvents are the main volatile organic compounds (VOCs) in pesticide formulations contributing to ROGs. A wide variety of pesticide formulations exist, ranging from liquids to pressurized dusts; emulsifiable concentrates contain the highest percentage of solvents and will probably be subject to the most restrictions.

The California Air Pollution Control Officers' Association (CAPCOA) formed a Pesticide Task Force in 1989 to study methods to decrease the impact of pesticide VOC emissions on ambient ozone levels. The Task Force has representatives drawn from the Air Resources Board (ARB), California Department of Pesticide Regulation (DPR), U.S. EPA Region IX, University of California, local air districts, the Farm Bureau, and the agricultural chemical industry. In 1991 DPR, ARB, and CAPCOA began investigating regulatory methods of reducing VOC emissions from pesticides. The initial step in this

process was selecting a test method to quantify the VOC emission potential of each agricultural pesticide product registered in California (~3,000 products). The CAPCOA Task Force compiled seven potential test methods and, in August, a public workshop was held to discuss the four with most promise. There was a general consensus that thermogravimetric analysis (TGA) is the best potential method for characterizing VOC emission potential of pesticides.

A thermogravimetric analyzer consists of a heating unit and an accurate microbalance housed in an enclosed chamber. Volatility is estimated from sample mass loss in a computer-controlled oven using a recording microbalance to determine the endpoint (when constant mass is achieved).

Advantages:
o   TGA provides information about the material's volatility and thermal stability, thus offering the greatest versatility.
o   A small amount of sample is required (10-20 mg).
o   Safety concerns are minimized by the enclosed atmosphere and small sample size.
o   Standard methods for compositional analysis and for estimating the volatility of coatings and automotive oils using TGA are available (ASTM; 1986b,1987; ITP, 1991).

Disadvantages:
o   No standard test method is currently available for pesticides.
o   A high initial outlay could be required for equipment, although commercial labs are available with TGA capability.

The next step is to develop the TGA experimental conditions for testing the VOC emission potential of pesticides. Existing ASTM Standard Test Methods (ASTM; 1987,1988) will be used as a basis for method development.

Analytical aspects to be addressed in developing the TGA experimental conditions include:
1) TGA instrument parameters
   a) sample mass
   b) analysis temperature

c) temperature ramping rate to constant temperature

d) analysis run time

e) purge gas composition and flow rate

f) effect of heating chamber configuration of various instruments

2) Statistical parameters

a) accuracy

b) precision

c) bias

d) repeatability

e) interferences

3) Suitability of TGA for each of the 16 pesticide formulation categories

4) Use of a standard(s)

a) identify possible standard materials (availability?)

b) validate accuracy, precision (see 2 above) under experimental conditions

5) Product water content determination

a) develop and validate two current methods for application to pesticides

i) titration with Karl Fischer reagent (ASTM, 1988a)

ii) direct injection into a gas chromatograph (ASTM, 1986a)

6) Conduct interlaboratory trial to ascertain variability between labs

7) Establishment of quality control procedures

a) instrument maintenance schedule

b) instrument calibration technique/frequency

c) relative difference in heating chamber temperature: expected and observed (measured with thermocouple)

d) use of a standard material for reference thermogram

8) Safety issues, including

a) whether hood effluent requires scrubbing?

9) Sampling factors

a) number of replicates that will be required per product when data call-in is implemented

b) sampling procedure for inhomogeneous products

Once the effective experimental conditions have been identified and validated, they will form the basis for a VOC data call-in. Regulations will be adopted

requiring registrants to submit results of TGA and water content analyses for certain pesticides registered in California. The water content will be subtracted from the total volatiles content (TGA) to yield the non-aqueous volatile fraction, or VOC. Registrants will be provided with a list of existing labs with TGA capabilities in the event that registrants are unable to perform the analyses in-house.

The TGA thermogram data and water content analysis for each product will then be reviewed and a *Volatility Index* will be assigned to the product. *Volatility Categories* will be established from the range of *Volatility Indices*. Regulations will then be proposed to reduce pesticide sources of VOCs based on the *Volatility Categories* and other possible factors, such as application method, that may influence the VOC emissions of pesticides.

One aspect of the VOC problem has not been addressed in this proposal: individual VOCs differ in reactivity with NO_x in the ozone-formation reaction. The experimental determination of a compound's reactivity is expensive and can only be accurately performed in an environmental chamber; these are only available at specialized research centers. At this time, there is no generally accepted modelling approach for estimating reactivity, although a plausible one is being developed at UC Riverside (Carter, 1990). When realistic reactivity estimates are available, they may be incorporated into the *Volatility Index* of a product.

II. OBJECTIVES

A) To establish effective experimental conditions for TGA analysis of pesticides; to validate that acceptable accuracy, precision, etc. are attainable under these conditions.

B) To confirm that these sample and instrumental parameters are appropriate for the wide range of pesticide formulation categories; establish sampling procedure for inhomogeneous products

C) To identify standard reference materials and establish that they are statistically acceptable under the proposed experimental conditions

D) To expand and validate two existing methods for determining product water content

E) To conduct an interlaboratory trial to establish the between-lab variance

F) To formulate effective quality control and safety policies

III. PERSONNEL

This study will be conducted under the supervision of Randall Segawa, Senior Environmental Research Scientist. Other key personnel include:

Project Leader	- Judy Pino
Senior Staff Scientist	- John Troiano
Statistics	- Terri Barry
Sample Preparation	-
Agency and Public Contact	- Mark Pepple (916-654-1141)

The experimental procedures described in this protocol will be carried out by contract lab(s).

IV. EXPERIMENTAL DESIGN AND DATA ANALYSIS   '

Five small-scale studies will be needed to validate the TGA methodology. Two can be conducted in parallel: a Pilot Study and Water Content Method Validation. The remaining three, Scope Investigation, Standard Identification and Validation, and Interlaboratory Trial, will follow sequentially after the first two studies.

A. Pilot Study

To find the effective combination of time, temperature and sample mass (predictor factors), we will employ a Path of Steepest Ascent Response Surface Methodology (RSM) (Figure 1). This approach will require a four step iterative sequence of designs. We will employ designs at each step that are both orthogonal and rotatable (Box and Hunter, 1957). Since the Path of Steepest Ascent RSM approach will require potentially a large number of sample runs, we plan to initially conduct this method on only one formulation, Goal™ 1.6E, an emulsifiable concentrate. This category contains products with the highest solvent concentrations and, thus, the most potential volatility. Goal™ 1.6E was chosen after considerations of composition, usage, safety, and availability.

The initial sample mass range to be evaluated will be 10-15 mg (exact mass to be determined in this experiment). The analysis temperature will be ramped at 5 °C/minute from ambient to 105-115 °C (exact temperature to be determined in this experiment). The analysis will be continued for 10-20 minutes (exact time period to be determined in this experiment) after the mass loss has stabilized at <0.05%/five minutes. The sample runs should be completed within one calibration period. The sequence of experimental runs is specified as follows:

1. First Order Model (12 sample runs required) - A planar surface is to be estimated at this stage of the experiments (Appendix 1). Fitting this surface will require a 3^2 factorial visualized as a cube arrangement shown in Figure 2a. Four replicate points are added in the center of the design to provide an estimate of the experimental error because each corner point of the factor combinations will be performed only once. To simplify the data analysis, the design matrix will be composed of coded values as shown in Appendix 1.

At the completion of this set of experimental runs we will use SAS (1987) Proc RSREG (response surface regression) to fit the planar surface and assess the fit of the equation. Most likely the surface will be planar and we will be some distance away from the region of the effective combination of predictor factors. In this case we need to perform experimental runs along the "Path of

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Steepest Ascent" in order to better locate the region of effective combination of the predictor factors. If the surface is curved, the following steps (Parts 2 and 3) may be omitted, and we can proceed directly to a central composite design (Part 4).
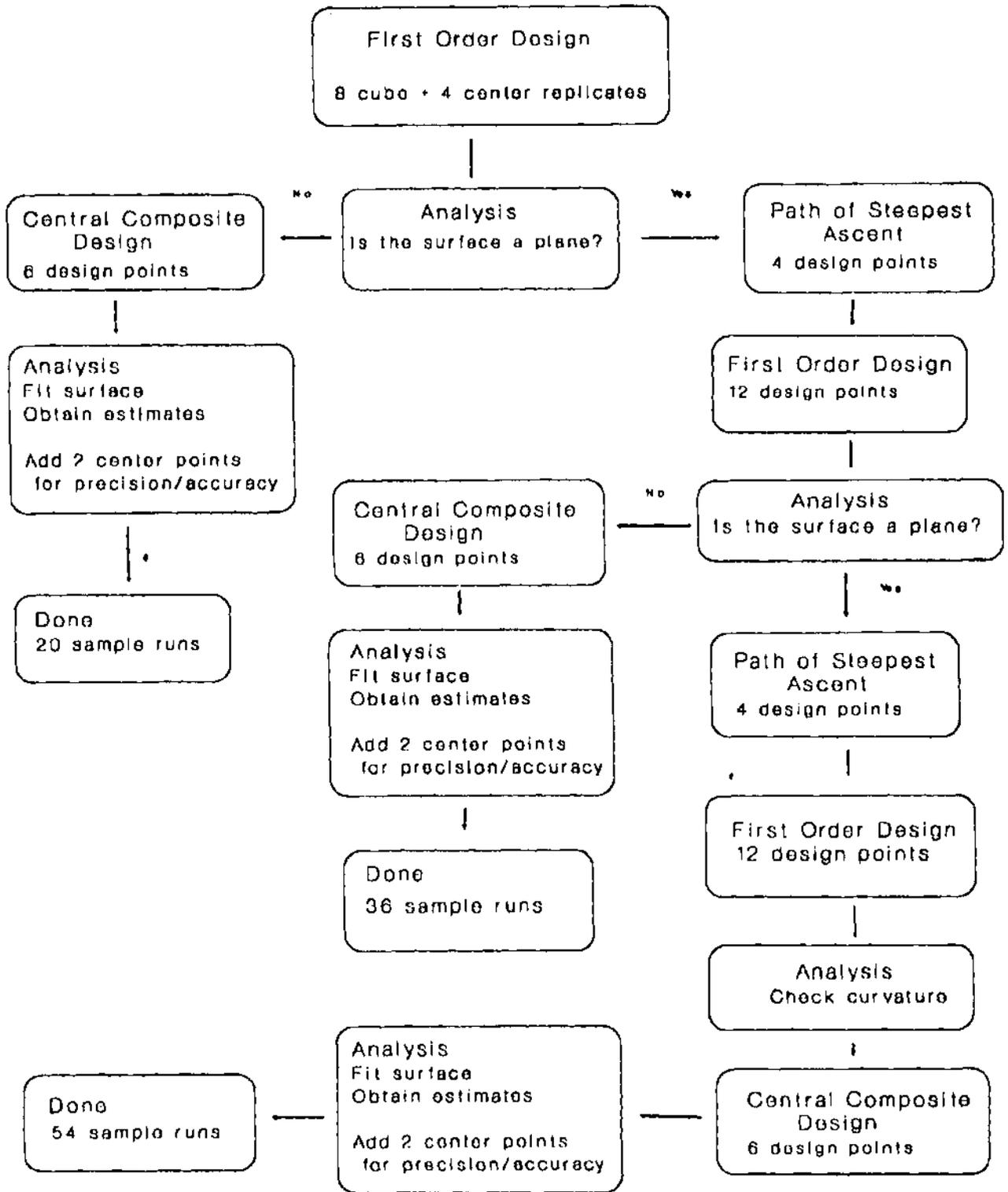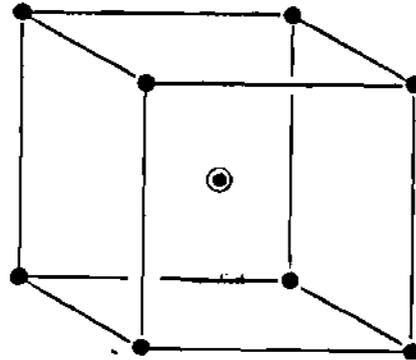
Figure 1. Flow chart of three alternative sequences of sample runs for the Response Surface Methodology experimental design.
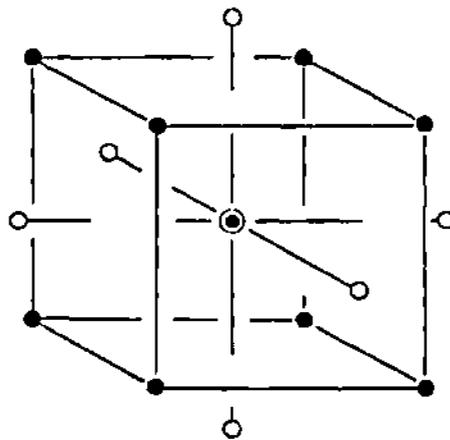
a)

◉ center point may
contain one or
more factorial points

● factorial with
added center points

b)

◉ center point may
contain one or
more factorial points
plus one or more
star points

● factorial with
added center points

○ star with added
center points

Central composite design for three variables.

Figure 2. Schematic of the experimental designs for three variables for the First Order Design (a) and the Central Composite Design (b).

2. **Path of Steepest Ascent** (4 sample runs) - The actual values of the predictor factors (time, temperature and mass) in this sequence of runs will be determined by the estimates, b_1, b_2, and b_3 (see Appendix 1). We plan to place four factor combinations (treatments) along the path of steepest ascent. The third set of experimental runs will be centered at the factor combination giving a stable volatility measurement obtained along the path of steepest ascent. We may need to add a few successive runs upward along the path of steepest ascent to locate a combination of factors giving a stable volatility.

3. **First Order Design** (12 sample runs) - The same experimental design, coded values and data analysis as listed in Part 1, will be employed at this stage. However, the actual level of the factor combinations will be shifted to the region of interest defined by the results of Parts 1 and 2. Therefore, although the codes in the design matrix are the same, the actual time, temperature, and sample masses will be different from the first experiment set. The presence of curvature in the first order polynomial model will indicate that the combination of factors is located within the region of maximum volatility, and we will proceed with the next step, the central composite design.

4. **Central Composite Design** (6 sample runs) - The composite design is built upon the previous First Order design (Part 3). This design has three components: 1) a two-level factorial, 2) an extra point at the center of the design to provide replicates, and 3) six extra points located at either extreme of each factor and at the center of all other factors (designated as "Star" points). The full experimental design at this stage of the research is shown in Figure 2b. The coded treatment combinations are listed in Appendix 1. This sequence of experimental runs will allow the fitting of the appropriate (first or second order) polynomial as shown in Appendix 1. The SAS (1987) Proc RSREG will be used to fit the appropriate surface, assess the goodness of fit of the polynomial and estimate an effective combination of time, temperature and sample mass.

The sequence of experimental runs listed above is the usual course of an RSM

study. There are two other possible outcomes, however. The first will in-
crease the total number of experimental runs and the second will decrease the
total number of experimental runs. They are both indicated on Figure 1.

The range of possible required experimental runs to arrive at a three factor
combination giving a maximum volatility for one formulation is therefore be-
tween 18 and 52. When a maximum is located we will add two experimental runs
to the center point to obtain a total of six replications. This would allow
both a precision and accuracy assessment; precision as estimated by the coef-
ficient of variation and accuracy confirmed by label information. This brings
the total required runs to between 20 and 54.

If it is possible to establish an effective combination of time, temperature,
and sample mass from less than 52 sample runs, then we will re-allocate the
remaining sample runs. For example, we need to verify that the same effective
combination of time, temperature and sample mass obtained in the RSM above is
effective for the other categories of formulations. If there are 18 sample
runs left over, we could perform a central composite design set of sample runs
on a formulation(s) from other categories.

B. Scope Investigation

Once an effective combination of time, temperature and sample mass is estab-
lished for EC formulations, it will be necessary to assess whether TGA is
practical for all of the formulation categories. A minimum of two replicates
for at least two products in the 16 formulation categories will be analyzed
(64 sample runs). If certain formulations require special pre-processing
(e.g. grinding), additional sample runs will be required to assess preparation
effectiveness.

C. Standard Identification and Validation

The different heating chamber configurations for instruments from various
manufacturers may lead to unavoidable discrepancies in predicting
volatilities. It will be more meaningful to compare thermograms from dif-
ferent instruments if a standard reference material is also run to assess the

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accuracy of the instruments. We will evaluate at least three candidate materials, preferably with a wide range of volatilities, that are available as documented reference standards from e.g. ASTM or NIST. Five replicates of each candidate material will be analyzed by TGA, and the results will be compared for accuracy, precision, bias, and repeatability.

D. Water Content Method Validation

Since water contained in a pesticide formulation will be vaporized along with the volatile organics, any mass loss method for determining volatility will require a correction for water content. The volatile organics will be equivalent to the difference between the total volatiles (mass loss as measured by TGA) and the aqueous fraction. There are two ASTM methods currently used for determining the water content of paint materials that may be amenable for pesticides:

1) *Karl Fischer Titration (ASTM, 1988)*: A sample is titrated with Karl Fischer reagent, which contains iodine, to an endpoint that is signalled by a color change.

2) *Gas Chromatography Direct Injection (ASTM, 1986a)*: A diluent and an internal standard are added to the sample which is then injected into a gas chromatography column containing a polymer packing that is capable of separating water from other volatiles.

Neither of these methods has been evaluated over the wide range of water contents that we expect to encounter during the course of measuring volatility of various pesticide formulations. A sample from each of the water content level categories will also be run by TGA. However, the data from these TGA runs will be used only for informational purposes, not for any statistical analysis.

We will use eleven solutions composed of mixtures of solvent (from 100% to 0% in increments) and water (from 0% to 100% in 10% increments) in an herbicide matrix. Analysis of Covariance methods will be employed to compare the performance of Karl Fisher verses Gas Chromatography method over the 0-100%

water content range. Regression equations will be fit separately for each method for the relationship of known water content to measured water content. Three statistical tests will be performed: 1) A test for heterogeneity of slopes will be made to detect possible interaction between method and water content. 2) Provided there is no heterogeneity of slopes; a test for whether one overall regression line, rather than two separate lines, is adequate. If this is true it would would indicate that the two methods give similar mean results. 3) a test for whether the slope(s) is different from one. A slope(s) different from one would indicate that there is significant systematic departure (bias) in the measured water content from actual water content. This test may be conducted regardless of the results for the heterogeneity of slopes. However, if heterogeneity of slopes exits, the two lines must be described and analyzed separately.

This experiment will require 33 sample runs for each method, to be allocated as indicated below:

Karl Fischer;   11 water content levels X 3 replicates = 33 sample runs
GC Direct Injection; 11 water content levels X 3 replicates = 33 sample runs
TGA: 11 water content levels X 3 replicates = 33 sample runs

E. Interlaboratory Trial

Once the Scope Investigation is completed, an interlaboratory study will be conducted as a partially nested three-way analysis of variance (ANOVA). The three factors included are laboratories, instrument calibration period (calibration includes calibrating the microbalance for mass against standard weights, and a temperature calibration utilizing the melting point of a pure metal or a Curie point metal), and formulation. Calibration period is nested within laboratories. We plan to include a minimum of five to 10 laboratories. One formulation from each of three categories will be included in order to detect possible laboratory by formulation category interactions (Wernimont, 1985). The laboratories will run two replicates of each of the three formulations (a total of six samples) during the same calibration period. Each laboratory will be instructed to perform a set of six sample runs, as specified above, during three different calibration periods. This arrangement will allow the estimation of within-laboratory variation. The calibration

periods should be separated by at least one day. It will also be specified that one operator perform all sample runs on the same instrument. If this is not possible, then we will need to include those factors in the ANOVA design.

The resulting ANOVA table, based on five laboratories, is shown below:

Source	df	Mean Squares
Laboratory	4	MSL
Calib (w/in lab)	10	MSC(L)
Formulation	2	MSF
L X F Interaction	8	MSLF
F X Calib (w/in Lab)	20	MSFC(L)
Error	45	MSE
Total	89	

Three hypothesis tests will be performed: 1) $F = MSLF/MSFC(L)$, testing whether the differences observed between formulations are independent of the differences observed between laboratories. If this F-test is significant, it indicates that the differences observed in volatility between the three formulations are dependent upon which laboratory performed the analysis. If interaction between formulations and laboratories is present, then the formulation results cannot be averaged over laboratories and vice versa. Provided this test is insignificant, the following F-tests will be performed: 2) $F = MSL/MSC(L)$, testing whether the between-laboratory variation is larger than the random variation; 3) $F = MSF/MSFC(L)$, testing whether the between-formulation variation is larger than the random variation.

From the Mean Square results obtained in this trial we will estimate repeatability and reproducibility (Caulcutt and Boddy, 1983). The repeatability provides an estimate of the size of the expected difference, on average, between sample run determinations on the same formulation at the same laboratory under uniform conditions. Reproducibility gives an estimate of the

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size of the expected difference, on average, between sample run determinations on the same formulation at different laboratories.

VII. TIMETABLE

Prepare and send out Request for Proposals for Pilot Study and Water Content Validation:	Jan 1992
(Bid presentation workshop - optional):	(Feb 1992)
Pilot Study/Water Content Validation:	15 March - 30 April 1992
Pilot Study/Water Validation final report due:	30 April 1992
Prepare and send out Request for Proposals for Method Validation, Standard Identification, and Interlaboratory Trial:	May 1992
Method Validation, Standard Identification, and Interlaboratory Trial:	June - Aug 1992
Method Validation, Standard Identification, and Interlaboratory Trial final reports due:	31 Aug 1992
Propose regulations for VOC data call-in:	September 1992

VIII. REFERENCES

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APPENDIX 1

RESPONSE SURFACE METHODOLOGY

We are interested in the combination(s) of time, temperature and sample mass that will yield a stable, maximum volatility measure for the formulations. Since there are no existing recommendations on either the reasonable range or the combination of these factors to use, we must use a sequential set of experiments. It is important that each step be predicated on the results of the previous step. We need to characterize the four dimensional surface of volatility that results from the possible combinations of the three factors listed above. It should be noted that the region of interest in terms of the factor combinations on the volatility response surface is relatively small and may change as the sequence of experiments proceed. This objective specifies that the major potential expenditure of sample runs be made within a sequential set of experiments defined by a Response Surface Methodology (RSM) approach (Box et al., 1978; Box and Draper, 1987). The endpoint response surface of interest will most likely be some nonlinear function approximated by a quadratic polynomial in only a small region near the optimum conditions.

RSM is actually a group of statistical techniques used in the building of empirical models. The techniques are necessarily iterative and the whole process insures that it is possible to assess a) the number of replications needed for the required precision, b) the location of the experimental region of most interest, c) the proper scaling and transformation for the response and predictor variables, and d) the order of the surface function (Box et al., 1978). The structure of the sets of experimental runs used are critical to the success of the overall RSM results. We will use a sequential set of Variance-Optimal designs (Box and Draper, 1975) with the following characteristics: 1) requiring a minimum number of experimental runs, 2) providing an internal estimate of error, 3) giving good detectability of lack of fit of the model, 4) allowance for designs of increasing order to be built up sequentially, 5) ensuring that the predicted value of the response variable (y) at a given point will be as close as possible to the true value, 6) behaving well when errors occur in the settings of the predictor variables (x's), and

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7) giving a satisfactory distribution of information throughout the region of interest.

We will employ the Path of Steepest Ascent RSM (Figure 1) giving a four step iterative sequence of designs. We will specify that the designs employed at each step in this process be both orthogonal and rotatable (Box and Hunter, 1957). The design being orthogonal ensures that all the polynomial coefficients in the model are uncorrelated. The design being rotatable insures that the estimated response variable (volatility) has constant variance at all points the same distance from the center of the design. This means that if the design was rotated about the center point and experimental runs conducted at those new points, that the information obtained from those runs would be consistent with the information previously collected.

Since the Path of Steepest Ascent RSM approach will require potentially a large number of sample runs, we plan to initially conduct this method on only one formulation. The sequence of experimental runs is specified as follows:

A. __First Order Model__ experimental sample runs (12 sample runs required)

A planar surface is to be estimated at this stage of the experiments:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3$$

Fitting this surface will require a 3^2 factorial visualized as a cube arrangement shown in Figure 2.

Additional points must be added in the center of the design to provide an estimate of the experimental error because each corner point of the factor combinations will be replicated only once. We decided on 4 replications at the center based on the recommendation in Box and Draper (1984) for the minimum number of center points, given the number of factors.

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To simplify the data analysis, the design matrix will be composed of coded values such that

$$\text{Coded value} = (\text{original value} - M)/S$$

Where M = average of highest and lowest and S = half their difference

For the first experiment the coded values are shown below:

	Coded Values			Actual units		
	Time	Temp	Mass	Time (min.)	Temp (°C)	Mass (mg)
Run #	X_1	X_2	X_3			
First Order Cube Design Points:						
1	-1	-1	-1	10	105	10
2	1	-1	-1	20	105	10
3	-1	1	-1	10	115	10
4	1	1	-1	20	115	10
5	-1	-1	1	10	105	20
6	1	-1	1	20	105	20
7	-1	1	1	10	115	20
8	1	1	1	20	115	20
Center Replication Points:						
9	0	0	0	15	110	15
10	0	0	0	15	110	15
11	0	0	0	15	110	15
12	0	0	0	15	110	15

This design is both orthogonal and rotatable. The advantage of this design over the usual factorial is that it provides the same information while requiring fewer experimental runs. If, instead, we replicated each factor combination 4 times and eliminated the center points we would need 32 runs total. Even if we reduced the replication at each factor combination to the absolute minimum of 2 runs and eliminated the center points we would still need 16 total runs. Instead, because of the characteristics of the design we need only 12. It should be noted that the actual sequence in which the runs are performed at the lab <u>must</u> be randomized.

At the completion of this set of experimental runs we will use SAS (1987) Proc RSREG (response surface regression) to perform the following analysis before the laboratory is instructed to proceed to the next step:

1) A least squares fit of the parameters for the planar polynomial model.
2) A check for interaction between the three factors. This would indicate that the effects of the factors are not additive.
3) A check for curvature in the plane. Presence of curvature would indicate that we are already close to the optimal operating region.

The outcome of the above analysis will determine which of two alternative sets of experimental runs will be ordered (Figure 1). We will discuss the usual progression of an RSM study first and then follow with the alternative outcomes at each step.

Usually at this stage, in exploratory studies, the planar model is adequate. This indicates that we are still some distance away from the region of the optimal combination of predictor factors. This is because there is insufficient information to make a first guess at the factor combinations that will be in the region of a maximum yield. In this case we need to perform experimental runs along the "Path of Steepest Ascent" in order to better locate the region of effective combination of the predictor factors.

B. **Path of Steepest Ascent** (four sample runs)

The actual values of the predictor factors (time, temperature and mass) in this sequence of runs will be designated by the estimates, b_1, b_2, and b_3, respectively. The factor combinations used in the experiment must be configured to lie along the steepest upward change in volatility for each relative unit change in the factors. We plan to place four factor combinations (treatments) along this path (runs 13, 14, 15, 16). The volatility measures from these runs, along with the average of the center points from the first order design, will provide five volatility measures with which to find the factor combinations for the location of the center for a third set of treatment (factor) combinations. We will expect to see increasing volatility as we travel up the path of steepest ascent followed by, most likely, a

plateau in volatility. The third set of experimental runs will be centered at the first factor combination giving the maximum volatility measurement obtained along the path of steepest ascent. If a maximum is not found we may want to add a few successive runs until a plateau is found before we proceed to the next step.

C. First Order Design (12 sample runs)

The same experimental design, coded values and data analysis as listed in part A. will be employed at this stage (This sequence of experimental runs will be runs 17 through 28). However, the actual level of the factor combinations will be shifted to the region of interest defined by the results of parts A and B. Therefore, although the codes in the design matrix are the same, the actual time, temperature and sample masses will be different from the first experiment set. Once the data analysis is completed and it is verified that the correct factor combination region is chosen (as indicated by the presence of curvature in tests conducted during the first degree design), we will proceed with the next step, the Central Composite Design.

D. Central Composite Design (six sample runs)

The composite design is built upon the previous First Order design (part C). This design has three components, 1) a two-level factorial, 2) an extra point at the center of the design to provide replicates and 3) 2k (k = number of factors) extra points at either extreme of each factor and at the center of all other factors (designated as "Star" points). The full experimental design (Central Composite Design: a two-level 3 factor factorial plus the star points) at this stage of the research is shown in Figure 2b. In this design there are (2^k+2k+1) total required treatment combinations.

In order for the design to be orthogonal and rotatable, the treatment combinations must be certain specified distances from the center of the design. As indicated above, the original two-level factorial design experimental runs may be used as a base on which to add the Star points (The data from runs 17 through 28). This is because the original design is already

orthogonal and rotatable. The added Star Points (runs 29 through 34) must be located the <u>same</u> distance from the center as the factorial points if the design is to remain orthogonal and rotatable. For the 3 factor experiment the coded distance for the star points is 1.68 standardized units from the center.

The coded treatment combinations are listed below:

Run #	Time X_1	Temp X_2	Mass X_3
First order two-level factorial cube design points:[a]			
17	-1	-1	-1
18	1	-1	-1
19	-1	1	-1
20	1	1	-1
21	-1	-1	1
22	1	-1	1
23	-1	1	1
24	1	1	1
Center replication points:[a]			
25	0	0	0
26	0	0	0
27	0	0	0
28	0	0	0
Composite design star points:			
29	-1.68	0	0
30	1.68	0	0
31	0	-1.68	0
32	0	1.68	0
33	0	0	-1.68
34	0	0	1.68

[a]Runs 17-28 were previously done in Part C; only runs 29-34 need to be done for Part D.

This sequence of experimental runs will allow the fitting of the second order polynomial, if necessary, as shown below:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{11}X_1{}^2 + b_{22}X_2{}^2 + b_{33}X_3{}^2 +$$

$$b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3$$

The SAS (1987) Proc RSREG will be used to perform the following data analysis:

1) Least squares estimation of the polynomial coefficients in the model listed above.
2) Check for lack of fit of the appropriate model.
3) Plotting of the surface contours and the location of the factor combination(s) that give(s) the maximum volatility.
4) Calculation of confidence interval for both predicted maximum volatility and the polynomial coefficients.

The sequence of experimental runs listed above is the usual course of a RSM study. There are two alternative outcomes, however. The first will increase the total number of experimental runs and the second will decrease the total number of experimental runs. They are both indicated on Figure 1.

It is possible that the first guess at the location of the first order design is actually quite far from where the optimum combination lies. In that case steps I and II may need to be completed twice before we could add the star points to complete the study. If this was the case then the total number of experimental runs required to characterize the response surface would be 52. This is because we would need an additional first order design (12 experimental runs) and an additional set of runs along the path of steepest ascent (four additional runs). There is no way of knowing whether this is the case at this time.

Alternatively, if we find that there is significant curvature in the surface at the first design region then we will know that the factor combinations are already in the region of interest (the region of maximum volatility). If this is the case then we will not need to perform runs 13 through 28. This is because we will not need to shift the design to another region on the response surface. Then we can simply add the star point runs (runs 29 through 34) to

form a composite design immediately after the first first-order design is completed. In this case we would require only 18 total experimental runs to find the optimum combination of factors for stable volatility.

The range of possible required experimental runs to arrive at a three factor combination giving a stable volatility for one formulation is therefore between 18 and 52. Additionally, when a stable volatility is located we will add 2 experimental runs to the center point to obtain a total of 6 replications. This would allow both a precision and accuracy assessment; precision as estimated by the coefficient of variation and accuracy confirmed by product composition. This brings the total required runs to between 20 and 54.

REFERENCES

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