UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

November 16, 2012

MEMORANDUM:

Subject: Accelerated Storage Stability and Corrosion Characteristics Study Protocol

From: Richard Keigwin, Director
Pesticide Re-evaluation Division

Joan Harrigan-Farrelly, Director
Antimicrobials Division

Lois Rossi, Director
Registration Division

Jack Housenger, Director
Health Effects Division

To: Office of Pesticide Programs

OPP is providing guidance (Attachment A) to registrants identifying that a non-guideline accelerated storage stability and corrosion characteristics study can be used, at the registrant's discretion, to fulfill these data requirements. OPP has determined that this study, conducted for 14 days at an elevated temperature (54° C), provides adequate data in certain circumstances to allow EPA to make a regulatory finding regarding the stability of the product and the effect of the formulation on the product packaging.

To determine the scientific soundness of this approach, OPP initiated a pilot study in 2010, whereby registrants were allowed to use an elevated temperature (40-54°C) for 14 days when conducting the storage stability and corrosion characteristics study for product reregistration. OPP conducted a retrospective analysis of these data, comparing the results from substantially similar formulations that were produced using the traditional 1-year, ambient temperature study protocol. The data show there were no significant differences in the results from these two test protocols (Attachment B).

Subsequent to this pilot, the protocol was modified to specify the test temperature of 54°C±2°C. This temperature is consistent with the Organisation for Economic Co-operation and Development (OECD) and the World Health Organization/Collaborative International Pesticides Analytical Council (WHO/CIPAC) approach to accelerated testing. This protocol was reviewed by the OPP Science Policy Council and found to provide high-quality data in the circumstances identified in the protocol.

Registrants are encouraged to consider this protocol as an alternative to the guideline study protocols specified in 830.6317 Storage Stability and 830.6320 Corrosion Characteristics. If there are any questions, please contact Patricia Parrott, at 703 305-0744 or by e-mail at parrott.patricia@epa .gov.

**Attachment A**

September 24, 2012

# GUIDANCE

## Accelerated Storage Stability and Corrosion Characteristics Study Protocol

EPA has determined that studies using this protocol will, in certain circumstances, provide the Agency with all the information it needs to make a determination on the storage stability of pesticides. For that reason, EPA believes registrants may, if they desire, follow this protocol in generating data to fulfill the Storage Stability and Corrosion Characteristics data requirements (Guidelines 830.6317 and 830.6320) for registration and product reregistration for certain conventional and antimicrobial manufacturing-use and end-use products. The study uses a 14-day test duration at elevated temperatures to determine product stability and corrosion characteristics. However, the Agency does not consider all products/materials appropriate for this protocol. Registrants must make the determination, based on their knowledge of the physical and chemical properties of their products (such as thermal properties, volatility, packaging, and whether any incidents related to product instability are known), whether or not their products are suitable for this study or whether the one-year study is more appropriate.

If a 14-day study submitted to the Agency is found acceptable, then storage stability testing is complete. If a 14-day study submitted to the Agency demonstrates product instability or is performed with a product deemed unsuitable for this protocol, then a 1-year study will be required.

Below are the details of the test protocol that the Agency has determined will, for some products, provide an adequate study for purposes of fulfilling the Storage Stability and Corrosion Characteristics data requirements. Registrants are not obligated to follow any particular protocol, but registrants should be aware that if they conduct a study that does not follow the protocol below or Guidelines 830.6317 or 830.6320, they may need to demonstrate to the Agency that the study conducted is sufficient to support the regulatory conclusions the Agency needs to make with respect to storage stability and corrosion.

**Test Details:**

1) The test should be conducted with the product in its commercial package or in smaller packages of the same construction and materials.

2) The test shall be conducted in compliance with the Good Laboratory Practice standards (GLP) under 40 CFR Part 160.135(b).

3) The test shall be conducted at 54°C ± 2°C for 14 days.

4) The product to be used in the test must be taken from a batch that has passed quality control analysis. The active ingredient concentration of the product must be the same as

the label claim or meet the certified limits requirements under 40 CFR 158.350(b)(2). [See also item #5 under "Additional considerations"]

5) The concentration(s) of the active ingredient(s) in the product shall be determined at the beginning of the test period and after 14 days, using a validated analytical method.

6) Deterioration or degradation of the product during the test period should be determined. At the end of the test period, the product should be examined for physical changes, such as phase separation or clumping, and, in particular, any changes that would interfere with the usefulness or safe handling of the product if used according to label directions.

7) The product should be quantitatively analyzed for active ingredient content and changes in impurities as a result of degradation or packaging deterioration over the test period. Results should be reported as concentration in weight percent.

8) The product and container should be observed for any physical changes at the beginning and end of the test, recording all observations in the raw data.

9) Report any corrosion of the commercial packaging (metal, plastic, or paper containers) in terms of visual observations (e.g., perforations, darkening, leaking, or rust at the seam). If corrosion is visually evident, a gravimetric or other evaluation of the container should be conducted.

**Reporting:**

The report must include all information relevant to the test including the following:

1) The duration of the test and the conditions under which the test was conducted.

2) Quantitative analyses for the active ingredient and impurities (if new impurities are formed) at the initiation and termination of the test.

3) Description of the physical condition of the product and container at the beginning and end of the test. Any significant variations to the weight of the container (if applicable) must be reported.

4) Details of the validated analytical method used in the test including representative chromatograms.

5) The full study and results should be submitted with the option to self-certify the data (PR Notice 98-1). The self-certified data must be assigned an MRID number.

**Additional considerations:**

1) If a product (considered suitable for the 14-day study) passes the 14-day study, then storage stability testing is complete.

2) If a product fails the 14-day study (i.e., product instability, degradation or deterioration occurs and/or new impurities are formed after 14 days, the full one-year, room-temperature study must be conducted in accordance with the OCSPP Guidelines 830.6317 and 830.6320, and 40 CFR Part 160. The purpose of the one-year study is to determine if an expiration date is needed for the product or if advisory statements resulting from the 14-day test are adequate.

3) If a product fails the one-year storage stability study after failing the 14-day study, an expiration date will be required in addition to an advisory label statement that limits exposure to increased temperatures. Examples of such a statement are "Avoid storage at high temperatures" and "Store in a cool, dry place."

4) If a product passes the one-year storage stability study after failing the 14-day study, an advisory label statement that limits exposure to increased temperatures will be required.

5) Bridging of the accelerated or the full one-year Storage Stability and Corrosion Characteristics data will be allowed for products that are identical or 100% repacks. For all other products, bridging is determined on a case-by-case basis specifically for products that EPA determines to be substantially-similar from the product chemistry point of view, i.e., the same active and inert ingredients (differing only in amounts), the same type of formulation (e.g., emulsifiable concentrate, aerosol, wettable powder, granular, etc.) and the same type of commercial packaging. Registrants must clearly identify the cited test product by the EPA registration nwnber and if more than one CSF exists for that product, the formulation actually tested must be identified with a corresponding CSF.

6) The Agency reserves the right to require submission of the one-year data for any product.

**Attachment B**

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

January 25. 201 1

MEMORANDUM:

Subject: Accelerated versus One-year Storage Stability and Corrosion Characteristics Studies

From: Maria Rivera Piansay, Chemist
Risk Management and hnplemen'tation Stanch V
Pesticide Re-evaluation Division (7508C)

To: George Herndon. Associate Director
Registration Division
Office of Pesticide Progrnms

Thru: Patnc1a Parrotl. Branch Chief
Risk Management and Implementation Branch V
Pesticide Re-evaluation Division (7508C)

The one-year Storage Stability and Corrosion Characteri stics study frequently delays product rercgislration because the timeframe for d:ita submissions is 16 months. The lack of adequa1c laboratory capacity to conduct this study also adds further delay and adds workload for registrams and the Agency in processing extension requests for these products. To improve efficiencies and facil itate reregistrati()n, PRO has developed and is allowing registrants to use an alternative protocol for producing these data using a 14-day study at an accelerated temperature. This memo provide a comparison of the data obtained using the accelerated protocol wi1h dat:i from 1he traditional one-year study. PRO believes that this analysis supports use of this protocol for both registration and product reregistration actions.

History an<l Development of a Revised Protocol for Use in the U.S.

There is precedence for the accelerated study. For example, an accelerated study is utilized by the Biocides and Pesticides Assessment Unit (BPAU) of the Health and Safety Executive (HSE) of the: UK. for regulation of non-agricuhurnl pesticides under The Control of Pesticides Regulation (COPR) of Great Brita in. According IO their guidance document, the currently preferred method for accelerated storage stability is the Collaborative lntemalional Pesticides Analytical Council (CrPAC) MT 46.3: accelerated storage procedure. This CIPAC method studies samples stored at 54°C over a period of two weeks.

ln combination with experience in the UK, PRO used parts of the OPPTS Hmmonized Test

Guidelines for Storage Stability and Corrosion Characteristics under 830.6317 and 830.6320. Additionally, Guideline 830.6313 requires technical products to be subjected to elevated temperature for 14 days.

Analysis

PRD consulted with the Technical Review Branch (TRB) of the Registration Division (RD) to discuss the use of this revised protocol for reregistration of conventional products. After a meeting on April 13, 201 1, between PRD and RD (attended by Patricia Moe. Maria Piansay. Shyam Mathur. and Dan Kenny) and additional input from RD. the document was finalized. The protocol was entitled "Combined Accelerated Storage Stability and Corrosion Characteristics Study"' (Attachment A). Storing the products for 14 days at elevated temperatures, 40 to 54°C. and obtaining infonnation regarding deterioration or degradation of the active ingredient and physical changes to lhc test product and the packaging are required data. The study guideline also specifies that the Agency reserves the right to require submbsion of the one-year data if results of the accelerated study are unacceptable or for individual product formulations that do not qualify as test materials for this type of study: for example. volatile or highly flammable substances would not be suitable for lhis protocol.

PRD prented the document to the Office of General Counsel (OGC) and on Apri I 13, 20 I I. OGC determined that the FIFRA regulations allow EPA lhe flexibility to use this accelerated study to fulfill the one-year Storage Stability and Corrosion Characteristics requirements for reregistration of conventional and antimicrobial chemicals.

A meeting between tl1c Product Science Branch of the Antimicrobials Division (AO) and PRD was held to discuss the possibility of als.o using the accelerated study for antimicrobial products. On April 18, 2011, AD detennined that the accelerated study is acceptable for use in reregistration of AD products.

As you suggested at our September 8. 201 1 meeting, PRO collected reviews of accelerated and one-year Storage Stability and Corrosion Characteristics studies for your reference. Attached is a summary of reviews reccnLly conducted by PRD. The tables show comparisons between the accelerated. elevated-temperature studies and the one-year studies at ambient temperature. The products for this analysis contain the active ingredients PBO. Pyrethrins. Permethrin, MGK 264, Pynamin forte, Imazapyr. Sumithrin and Malathion, which were undergoing product reregistration at lhe time of this analysis. For this analysis, 23 accelerated studies of EUPs. MUPs, and TGAls were assembled and compared to the onc-yea1 sn1dy of the same or similar formulation. The CSFs of the respective products were reviewed to ensure lhe products being compared were substantially similar.

Not all accelerated studies in this snmpl ing arc 14-day studies; rather some arc conducted for o varying number of dayi; from one month to one year. These deviations in protocol were reviewed and in all instances were found to be acceptable, as the protocol is guidance only. All studies were conducted at temperatures from 40 to 54°C. with the exception of the Malathion study,

which was conducted at 55°C (Table I). Products are compared based on their active ingredient concentnltions and registration numbers for each product and MRID numbers for each study have hecn included.

An estimated 50 studies have been submiued using this protocol since PRD informed registrams of this modified study option. Each submitted study has been found acceptable and each methodology has been thoroughly described. All sll.ldies were conducted in accordance with the data requirements, including compliance with the criteria for physical changes such as clumping or any other changes that would interfere with the usefulness or safe handling of the product when used according lo label instmctions. A few registrants have cited older accelerated tudies conducted at the same elevated temperature range but longer storage times, i.e. 1 1o 12 months.

Conclusion

In all amples tested, no increased degradation of the active ingredient was observed in the accelerated storage time; in fact. all accelerated data arc comparable to results obtained in studies conducted for an extended storage time. In all the accelerated studies presented in Table I, the data have shown that throughout the study periods, the products were stable when stored at elevated temperatures (40 to 54°C, including 55°C). None of the resuJting active ingredient concentrations fell outside their respective standard certified limits range. No significant difference in concentrations of the active ingredients was observed between the accelerated and the one-year studies. The variations in active ingredient concentrations (increase or decrease), whether in an accelerated or a full study. showed close compliance with 40 CFR 158.350(b)(2). In addition, corrosion of the containers was not observed in these studies.

Most of these data arc from insecticides and data are not yet available for other classes of chemicals. However, these preliminary data indicate that for many chemical:;, the stability of a pesticide formulation can be characterized through accelerated. elevated temperature studies. In the interest of expedience and workload reduction for both the Agency and the registrants, OPP should adopt the 14-day. elevated temperature study as an alternative to the one year study for appropriate fommlations undergoing registration actions.

Attachments {2)

cc: Loi Rossi
Richard Keigwin

Table I. Accelerated vs. One-year Storage Stability Test. The two data secs from similar fonnularions comparing he accelerated and I-year study are grouped sequent ially in the table. below. All accelerated studies arc 14-day.except where noted.

| Active lngredie nr | Study type: 1- | Reg. No. | MRID | Label claim (% ai) | Label Claim UCL I} | Label Claim LCL % | Standard certified lunits(±%) | Results lnitial (%) | Results Final (%) | Change (% increase or decrease) | Acceptable (YIN) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PBO | [redacted] | | | | | | 10 | 0.4383 | 0.481 | 0.41 / | У |
| | l-yr | | | | | | 10 | 0.243 | 0253 | 4.1 | У |
| PBO | | | | | | | 5 | 4.32 | 4.13 | 4.9! | У |
| | l-yr | | | | | | 5 | 4.23 | 4.31 | 1.89i | У |
| PBO | | | | | | | 5 | 4.993 | 5.1 16 | 2.46 | У |
| | | | | | | | 5 | 5.19 | 5.15 | 0.771 | У |
| PBO | | | | | | | 5 | 6.65 | 6.66 | 0.15 | У |
| | | | | | | | 5 | 9.376 | 9.649 | 2.9lj | У |
| PBO | | | | | | | 5 | 9.673 | 9.668 | 0.05 | У |
| | | | | | | | 5 | 9.386 | 9.409 | 0.24t | У |
| PBO | | | | | | | 3 | 60.446 | 60.505 | 0.101 | У |
| | | | | | | | 3 | 58.4 | 58.5 | 0.17} | У |
| Penncthrin | * | | | | | | 10 | 0.195 | 0.203 | 4.1t | У |
| | l-yr | | | | | | 10 | 0.207 | 0.218 | 5.3 | y |
| Permechrin | | | | | | | 10 | 9.76 | 10.18 | 4.3 | У |
| | | | | | | | 10 | 9.82 | 10.13 | 3.2j | У |
| Pennethrin | * | | | | | | 3 | 39.37 | 39.90 | 1.3j | y |
| | l-, | | | | | | 3 | 37.73 | 37.50 | 0.61i | |

| Active Ingredient | Study type: 1-yr or 14-day | Reg No. | MRID | Label claim ('} ai) | c., | Srandard tenified lim i1s(±%) | Results lni11al (%) | Results Final ('7<.) | Change (Ck mcrea:.c or dec rease) | Accepratile (Y/N) |
|---|---|---|---|---|---|---|---|---|---|---|
| MGK 264 | | | | | | 5 | 1.189 | 1.221 | 2.Jr | y |
| | | | | | | 5 | 1.98 | 2.01 | | y |
| MGK 264 | | | | | | 5 | 2.807 | 2.794 | | y |
| | | | | | | 5 | 2.99 | 2.98 | | y |
| MGK 264 | | | | | | 5 | 14.83 | 14.92 | | y |
| | | | | | | 5 | 16.9 | 16.8 | | y |
| Pyrcthrins | | | | | | 10 | 0.496 | 0.495 | | y |
| | | | | | | 10 | 0.445 | 0412 | | y |
| Pyrcthrinl' | | | | | | 10 | 0.959 | 0954 | | y |
| | | | | | | 10 | 0.0952 | 00922 | | y |
| Pyrcthrin | | | | | | 10 | 1.009 | *1004* | | y |
| | | | | | | 10 | 0.99 | 1.08 | | y |
| Pyrethrin | | | | | | .5 | 6.01 | 6.05 | 0.61T | y |
| | | | | | | 5 | 610 | 6.02 | 2.9. | y |
| Pyrcthrin | | | | | | 3 | 49.4 | 50.4 | 2.0 | y |
| | | | | | | 3 | 29.7 | 29.9 | 0.77 | y |
| Pynamin Fone | | | | | | 3 | 94.4 | 94.I | 0.32! | y |
| | | | | | | 3 | 94.4 | 94.0 | *OAI!* | y |
| Pynam in Forte | | | | | | 3 | 92.0 | 92.0 | 0 | y |
| | | | | | | 3 | 94.4 | 94.0 | 0.42! | y |
| Jmazapyr | | | | | | 1 | 97.0 | 96.0 | 1.03! | y |
| | | | | | | 3 | 97.0 | 98.1 | 1.12· | y |
| Surnithrin | | | | | | 3 | 93.7 | 93.I | 0.641 | y |
| | | | | | | 3 | 93.9 | 93.9 | 0 | y |

| Active Ingredient | Study cype: 1-yr or 14-day | Reg. No. | MRID | Label claim (% ai) | Label Claim UCL % | Label Claim LCL % | Standard certified limits(±%) | Results Initial (',') | Results Final ('X) | Change ('if incrase or decrease) | Acceptable (YIN) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Malathion | 14-day | [redacted] | | | | | 3 | 96.6 | 95.9 | D.68! | y |
| | 1-yr | | | | | | 3 | 96.2 | 95.6 | 0.62 | y |
| Malathion | 14-day | | | | | | 3 | 96.9 | 96.2 | 0.72 | y |
| | 1-yr | | | | | | 3 | 96.7 | 97.3 | 0.62 | y |

*I-month study
**I-year ;,tudy at SO C
***6-month study