

This set of instructions is designed to help current users of ASAPprime® v5 transition to the newly released v6 of the software. These instructions are appropriate for users who already have a good understanding of the use of v5 and only wish to learn about the new functions. For users with no prior experience wanting to be trained on the use of ASAPprime®, or those who feel they need more extensive explanations on how to use the new features, we recommend our full day training program. To get information and a price quote for this training, please contact: Dave Lucey, Business Development Manager, [david.lucey@freethinktech.com](mailto:david.lucey@freethinktech.com).

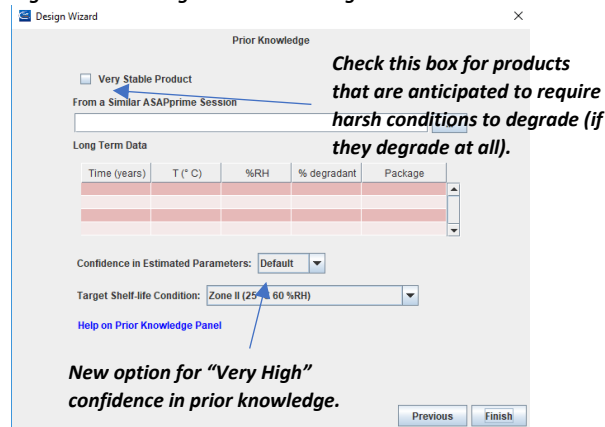
These instructions do not go into details on the algorithms and theories employed, rather they are designed to be operational. For details on these algorithms and theories, please contact FreeThink Technologies [[tech\\_support@freethinktech.com](mailto:tech_support@freethinktech.com)].

## ASAPdesign™

There are only minor changes made to ASAPdesign™ in going from v5 to v6 of ASAPprime®. The first of these changes is that when one has a very stable product (e.g., a crystalline material), there is an option to check the Very Stable Product checkbox in the Prior Knowledge window (Figure 1). This pushes the design itself to very harsh conditions (within the allowable condition space). We assume that the stable product will need these harsh conditions to get the product to hit its specification limit. In the cases where even the harshest conditions cannot induce product failure, the degree of harshness will impact the minimum shelf-life that can be established.

While v5 of ASAPdesign™ had the option of three levels of confidence in prior data, v6 has added a “very high” confidence level to the Confidence in Estimated Parameters drop-down menu (Figure 1). The higher confidence level establishes a narrower design space around the mean predicted isoconversion times at each condition.

Figure 1 ASAPdesign™ Prior Knowledge



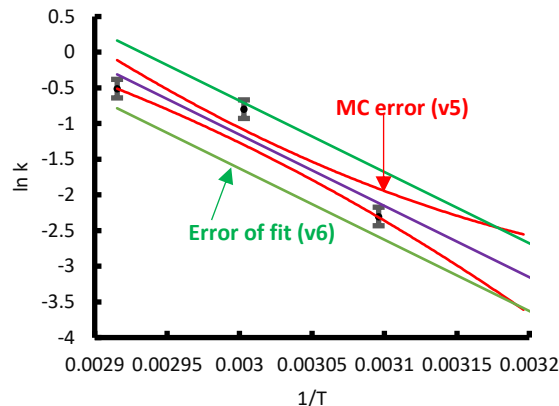
## New Data for Packaging

In the main ASAPprime® program, several new excipients have been added to the drop-down menu based on moisture sorption isotherm measurements done at FreeThink. Additional synonyms have also been included for some common excipients.

## Error Bar Calculations

A major change was made to the error bar (and corresponding probability) calculational methodology. In v5, an error bar for each isoconversion time (calculated using an extrema method) was the basis for Monte-Carlo error bar propagation using the Arrhenius or moisture-modified Arrhenius equation. In the example shown in Figure 2, the isoconversion rates (represented by the three data points) are not well-modeled; i.e., fall outside or on the outer edge of the model error (red line). This is because each point has a small error bar which results in a relatively small overall error based on the Monte-Carlo (MC) calculation. The error of the fit (illustrated by the green line) shows a wider error.

Figure 2 New Model Fit Error Bar Calculation Method



In v6, a new algorithm takes the square root of the sum of the squares of the errors from the Monte-Carlo propagation (the only error bar used in v5) and of the fit itself:

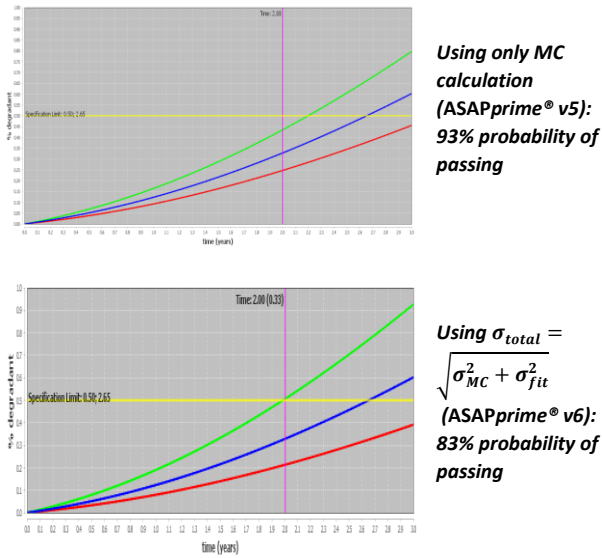
$$\sigma_{total} = \sqrt{\sigma_{MC}^2 + \sigma_{fit}^2}$$

In some cases, this new calculation algorithm will result in significantly larger error bars which in turn will impact the probability of passing. However, when the fit is poor, the confidence interval will be increased such that there is more likelihood that the true value lies within the error bars.

Because of this improvement in the calculation of the confidence interval, while the mean shelf-life values remain the same, there can be differences between the probability of passing calculations in v5 as compared to v6 (see Figure 3). If a client needs results from an older version of ASAPprime® (for example, for a regulatory filing purpose), FreeThink maintains an archive of all prior versions and will provide appropriate support. If the calculations are not being used for regulatory filings, we would advise using the most up to date release.



Figure 3



## Confidence Interval Display

In ASAPprime® v5, the displayed confidence interval on the degradant vs. time plot was always set to one standard deviation (i.e., 68.2% of the time the true value is predicted to lie within the interval shown). That meant that where the green line hit the specification limit, there was an 84% probability of passing and where the red line hit there was a 16% probability of passing (interval is 84 - 16 or 68%). With v6, additional interval choices are available for the display. This option can be accessed from the main menu bar under the “Options” drop-down (**Options → Isoconversion → SD Method**). There is an additional option that contains new available intervals: one SD (84-16% probability), 80% (90-10% probability), 90% (95-5% probability), 95% (97.5-2.5% probability) and 99% (99.5-0.5% probability).

## Results Comparison

The graph in the new Results Comparison dialog box (reached from the main menu bar under **Tools → Results Comparison**) has changes the graph to consider the isoconversion fitting model (**Figures 4, 5**). Since the data are still fit using isoconversion, this will only approximate the behavior far from the specification limit; however, when the fitting model is non-linear (e.g., Avromi-Erofeyev or Diffusion), the comparison should provide a better fit to the long-term data. It is recommended to use the fitting model that was used in the main program, but the displayed graph has the option to use different fitting models for the long-term comparison than used in the isoconversion fitting itself. The program also now provides a way of quantifying the quality of the fit of the long-term data to the model. The **Mean Absolute Percentage Deviation** value represents the absolute value of the average difference between the predicted and long-term values as a percentage of the values.

Figure 4 ASAPprime® v5 Results Comparison:

In this example, the isoconversion model was built using Avromi-Erofeyev, but the long-term data are fit to linear. Note that the intercept with the specification limit is accurate but not the other points.

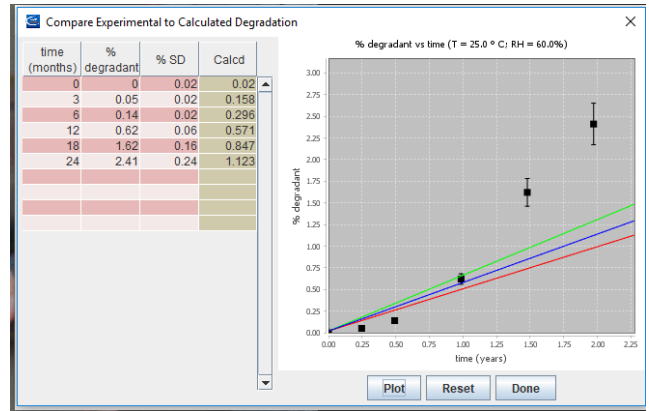
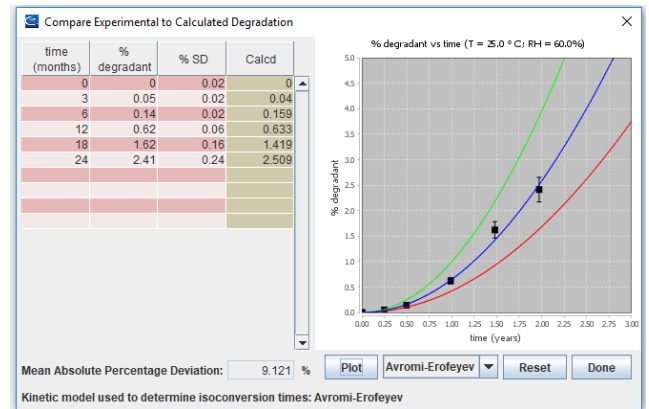


Figure 5 ASAPprime® v6 New Results Comparison:

These same data are again fit to Avromi-Erofeyev, but the long-term data are also fit to the same function.

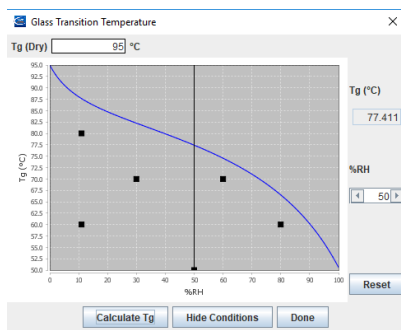


## Glass Transition Temperature

A new tool under “Properties” (from the main menu bar: **Tools → Properties → Glass Transition Temperature**) provides a calculation of the glass transition temperature ( $T_g$ ) as a function of RH (**Figure 6**). This calculation is appropriate for amorphous materials (typically an API or a dispersion). The calculation is based on the moisture sorption isotherm for the amorphous material under consideration in the Dosage panel. That

means that using moisture sorption isotherms for the entire formulation will not be appropriate. This calculation assumes that moisture plasticizes the material (lowers the  $T_g$ ) as a function of the water content. The option exists to have the conditions (T/RH) used in the study be displayed on the graph. This shows whether some of the conditions are potentially a problem for going from glassy to rubbery state and presumably could have discontinuous behavior (often more stable than expected because of crystallization).

**Figure 6 Glass Transition Temperature ( $T_g$ ) Calculation Tool**

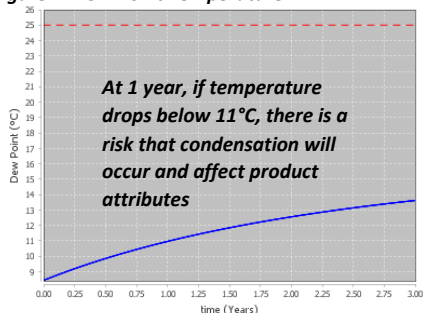


*Uses isotherm to calculate. Note that this will not be accurate for the API if isotherm for product is loaded rather than for the amorphous API material.*

## Dew Point Temperature

Another new tool under “Properties” (from the main menu bar: **Tools → Properties → Dew Point Temperature**) is useful when a packaged solid undergoes a sudden temperature drop (Figure 7). In this situation, the RH inside the packaging will spontaneously increase. If the temperature goes below the dew point, the RH will be above 100% and result in moisture condensation. This condensation may lead to issues with the product including sticking, disintegration failures and chemical instability. The dew point temperature tool allows users to establish a safe low temperature excursion condition with respect to condensation: if the temperature does not drop below the dew point, there is little to no risk for these stability concerns. Since the RH inside a packaging will not, in general, be constant, the dew point will change with time. It should be mentioned that even if condensation occurs, there still may not be a stability issue.

**Figure 7 Dew Point Temperature**

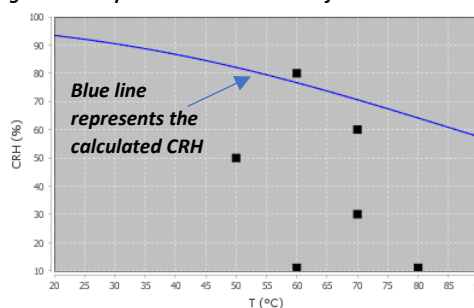


## Deliquescence

A final new tool under “Properties” (from the main menu bar: **Tools → Properties → Deliquescence**) calculates critical relative humidity (CRH), i.e., the RH above which a sample will condense moisture from the air to

form a solution (Figure 8). Any material in a formulation that is highly soluble can be responsible for deliquescence when exposed to high RH conditions. As this represents a phase transition, it is likely that above the CRH there will be discontinuous behavior. Since the solubility of a material is most often temperature dependent, the calculated CRH as a function of temperature can be used to identify stress or storage conditions that may be problematic (use “Show Conditions” to display the conditions for which the degradant/potency data (T,RH) are entered in the main program).

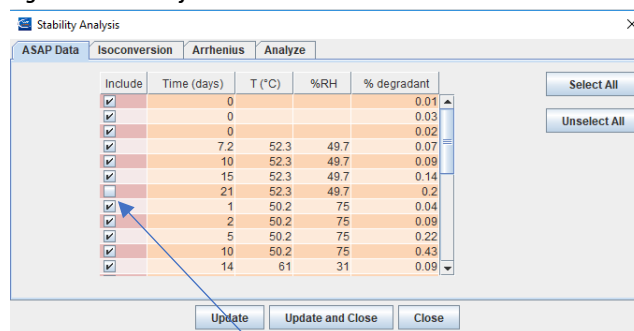
**Figure 8 Deliquescence: Calculation of Critical Relative Humidity (CRH)**



## Stability Analysis—Checkboxes

Sometimes it can be useful to remove a specific data point(s) (Time/Temperature/RH) in the primary dataset from the ASAP analysis (degradation or potency) without permanently deleting the data. For example, a point may be an outlier, due to a sample analysis issue. The new checkbox option (Figure 9) allows the user to do this. This can be accessed from the Degradation table (by right clicking, selecting “Stability Analysis”, then using the tabs at the top to select “ASAP Data”). The actual removal of the points from the analysis does not occur until the user selects “Update and Close”, where the user is returned to the main interface. Note that if “Close” is selected, no update is performed before returning to the main dialog. The ASAPprime® report (from the main menu bar) can include the full original dataset and indicate which points were omitted from the modelling.

**Figure 9 Checkbox for Individual Data Points**

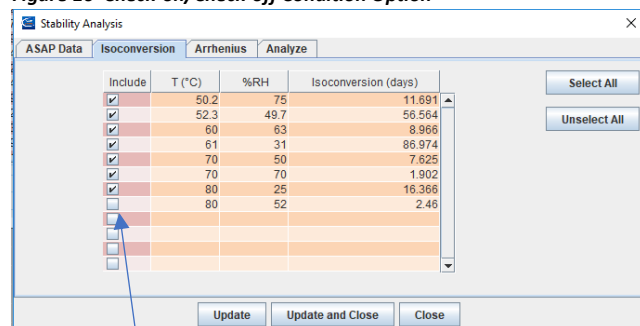


*Data from 21d/52.3°C/49.7%RH will not be used in the modelling*



Similarly, it can be useful to remove an entire condition (T/RH) in the primary dataset from the ASAP analysis without permanently deleting the data. For example, one might consider that a particular condition is above a phase boundary. This is handled using the Isoconversion tab from the Stability Analysis (**Figure 10**).

**Figure 10 Check-on/Check-off Condition Option**

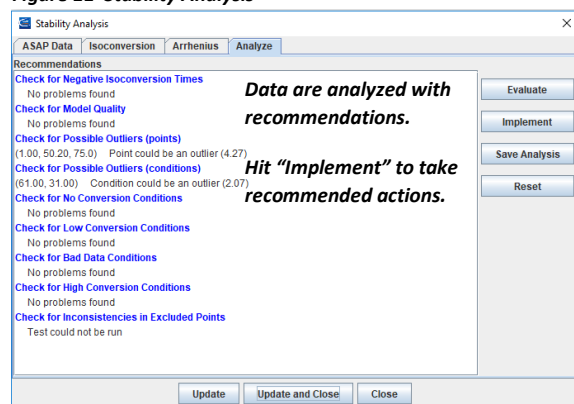


*Data from 80°C/52%RH will not be used in the modelling*

## Data Evaluation

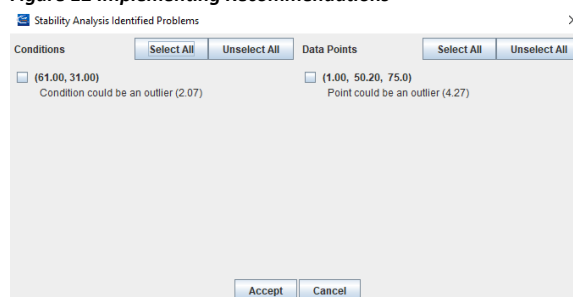
ASAPprime® v6 now contains two options for evaluating primary data. The first option (Option 1) allows the program to directly take actions (such as removing points or conditions) without the user's input. Because the actions are taken without user input, the program is very conservative about removing points or conditions. This option is especially useful when data analysis is carried out as part of a cGMP process. In other words, the program can remove points/conditions under its set algorithm rather than based on what might appear arbitrary if conducted at the user's discretion. To access this option, the user enters the "Tools" dropdown menu from the main menu bar. From this pull down, the user selects "Evaluate Model" and "Original Data". ASAPprime® v6 removes points and conditions based on its algorithm. The evaluation results are accessed from the "Stability Analysis" by right-clicking on the Degradation Table.

**Figure 11 Stability Analysis**



In the second option (Option 2), the program provides advice, but the user can elect to use or ignore each suggestion (**Figure 11**). This option is accessed by right clicking in the Degradation table, selecting "Stability Analysis", then going to the "Analyze" tab. After clicking on "Evaluate", the program returns analysis results which can be printed or saved (note that this table is also populated when running Option 1). The recommendations and rationales should be carefully examined, and decisions made on which suggestions to apply. In order to put into effect recommendations, the user clicks on "Implement". This opens a window with the suggested data points or conditions to be removed (**Figure 12**). Checking the boxes and then clicking "Accept" will execute the changes to the modeling data set.

**Figure 12 Implementing Recommendations**



## Low Conversion

When data for all conditions cannot be distinguished from noise, ASAPprime® v6 provides a conservative calculation to determine a minimum shelf-life. The low conversion calculation window can be reached either through the "Evaluate Model" or **Tools → Low Conversion**. In each case, the user is prompted to either use data as if all points were checked on ("Original Data"), or to use the current set of checkbox-indicated data ("Current Data").

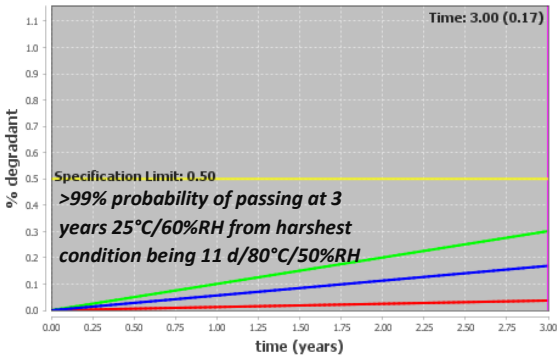
The Low Conversion algorithm will be invoked if all the data points at every condition are within 1.645 times the SD of the mean of the points at the condition. The SD used is that of the control point. In other words, the program will go into this calculation space when all conditions show data that is hard to distinguish from noise.

While the data cannot be distinguished from noise, there remains a possibility that in fact there is low degradation occurring, just not enough to detect. This information plus conservative estimations of  $E_a$  (and B) are used to set the conservative probabilities. Reducing the LOD (or SD) may result in the program concluding that the data are no longer noise or extending the shelf-life. Users can adjust the assumed  $E_a$  and B values (**Options → Isoconversion → Low Conversion**). The default assumes an  $E_a$  (11.5 kcal/mol; 48.1 kJ/mol) representing a lower  $E_a$  than 95% of products in FreeThink's database have a greater value. With B, the program assumes the more conservative limit depending on whether the accelerated conditions used for the calculations are above or below the RH of the long-term storage conditions (B = 0.00 if long term RH below



accelerated; 0.10 if above), again based on a 95% limit from FreeThink's database.

**Figure 13 Shelf life when nothing happens: Low Degradant Calculation**

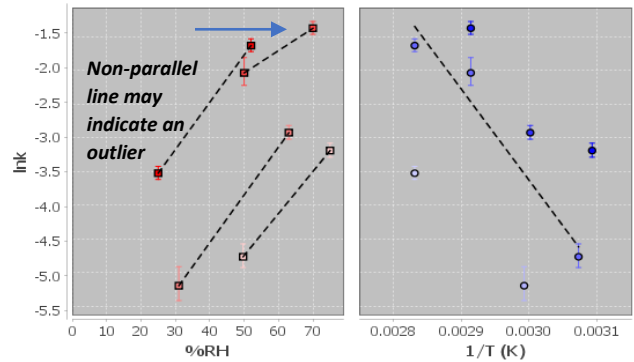


While the graphs in the Low Conversion Mode (**Figure 13**) look similar to what one would obtain from an ASAP<sup>prime</sup>® model, they do not really represent a model. Instead, these reflect conservative estimations to allow minimum shelf-life assignments.

## Arrhenius Analysis

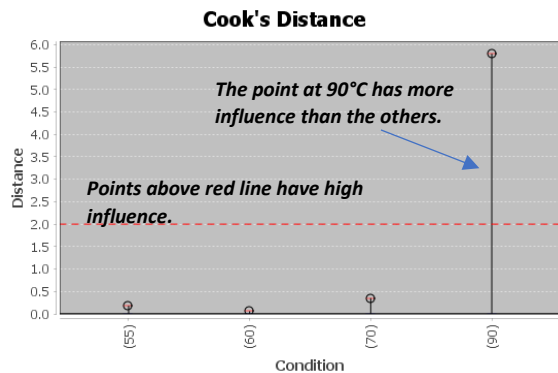
By right clicking from the Arrhenius tab, the user can now select a new option: "Arrhenius Analysis". The "Arrhenius Analysis" window provides additional model diagnostics (**Figure 14**). The first tab, the residual graph, is the same as with v5. The second tab provides Time/Humidity graph(s). There will be two graphs when RH is used and only one when the study is temperature only. In the left-hand graph, the logarithm of isoconversion rates at each condition is plotted against RH. When multiple conditions have similar RH values, they are grouped in lines. These lines represent Arrhenius lines and in a perfect model should be parallel to each other. In the right-hand graph, the logarithm of isoconversion rates at each condition is plotted against 1/T (where T is in Kelvin). When multiple conditions have similar temperature values, they are grouped in lines. These lines represent RH dependence lines and in a perfect model should be parallel to each other. Conditions which show non-parallel lines may indicate outliers or issues with the modeling.

**Figure 14 Arrhenius and RH Graphs using  $\ln(1/\text{isoconversion times})$  [ln k]: Ideally all lines should be parallel**



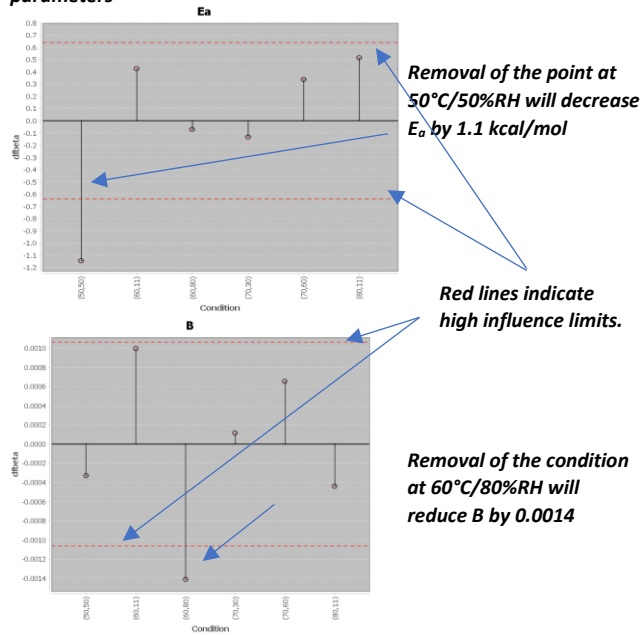
The third tab from the Arrhenius Analysis option, "Model Influence" is the Cook's distance. This diagnostic illustrates which conditions impact the results most significantly (**Figure 15**). The impact will depend both on how much leverage a point (isoconversion rate for that condition) has and how far off it is from where the ASAP model predicts it should be (its residual).

**Figure 15 Cook's distance is based on both leverage and residuals for each condition**



The next "Arrhenius Analysis" option (fourth tab) is entitled "Parameter Influence". This dfbeta calculation indicates how much an Arrhenius parameter ( $\ln A$ ,  $E_a$ ,  $B$ ) would shift if a condition was removed (**Figure 16**). The units are the same units as the value uses. As with the Cook's distance, points with high influence (above or below the lines) are not necessarily outliers but are more influential on the final result and warrant special scrutiny.

**Figure 16** Dfbeta indicates influence of each point on the parameters

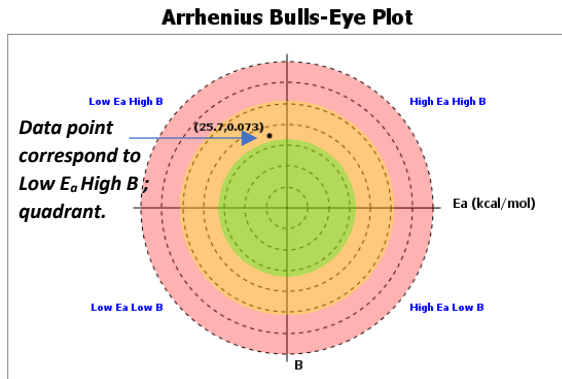


The final “Arrhenius Analysis” tab (fifth tab) represents “Relative Values”. The fitted  $E_a$  (and B) values are shown (black data point) in comparison to the distribution of products studied in FreeThink’s database (Figure 17). A product that exactly matches the average from the database will be in the center of the bull’s eye plot. With just temperature, the image indicates whether a product is greater or less than the average product with respect to  $E_a$  (temperature sensitivity). When RH is also used, the point represents the position in both axes. Points fall into different quadrants depending on their relative temperature ( $E_a$ ) and RH (B) sensitivity. The color coding is as follows:

- Green: 90% of products studied
- Orange: 9% of products studied; 99% are within the orange circle

Each line represents one half of one standard deviation.

**Figure 17** Comparison of data to average product



## Arrhenius Table

Another right-click option from the “Arrhenius” tab is the “Analysis Table” (Figure 18). This includes both a tabular (already in v5) and a new graphical view of the experimental isoconversion times at all the conditions vs. the model fitted isoconversion times at the same conditions, each with their corresponding error bars. The points can be color coded for temperature or humidity. Ideally, all the points are on the unity line; i.e., the model fitting matches the values used to build the model. This graph provides a visual to check if the points fit the ASAP model within the estimated error bars (either from the isoconversion SD or the model fit SD).

**Figure 18** Arrhenius Table: Graphical View

