A → B → C Reactions: Secondary Degradation in ASAP Studies

Kristina Flavier

FreeThink Technologies, Inc.

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What Is Secondary Degradation?

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

- Secondary degradation may be observed as **leveling off** (steady state reached) or **turnover** (decrease at longer timepoints) of B (a primary degradant).
  - C (a secondary degradant) may not be observed in the analysis, and its presence is only inferred by the behavior of B.
- The level of B at a given timepoint is determined by the ratio of k_1 to k_2, which can vary with temperature and RH.
  - If this is below the specification limit, it may not impact shelf life.

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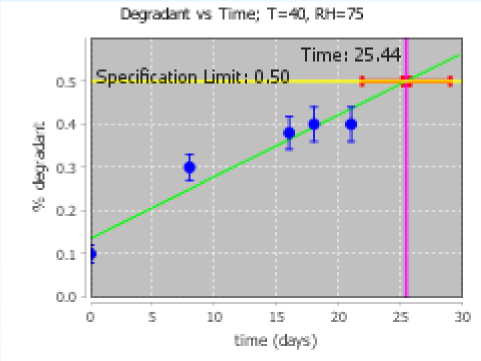
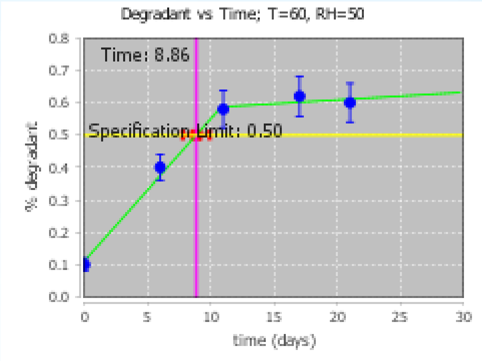
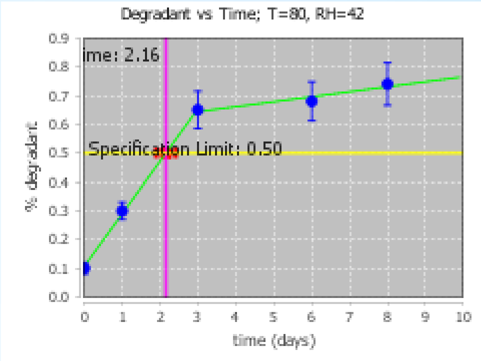
Secondary Degradation Examples

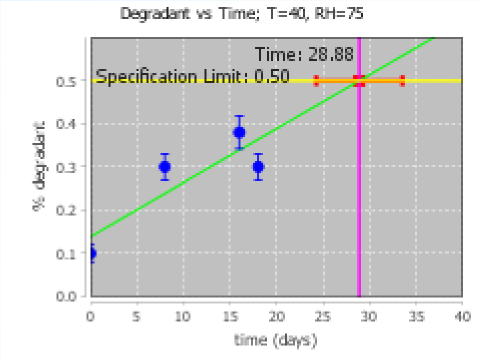
- Steady state

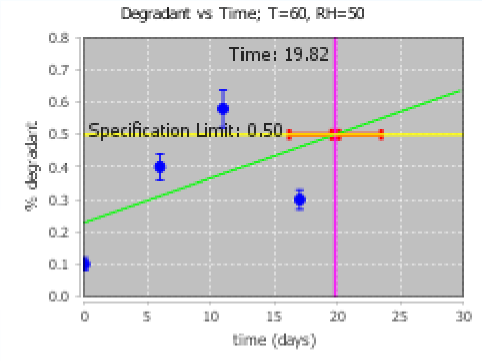


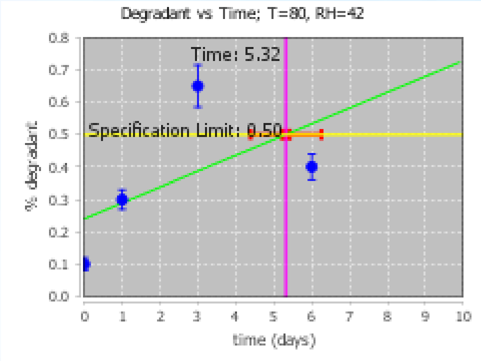




- Turnover







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Secondary Degradation and Non-Linear Kinetics

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

- Traditional accelerated stability may not accurately predict behavior of B.
  - Assuming linear growth results in overprediction.
  - Steady state or peak level may depend on storage conditions and packaging.
- Using ASAP, we can model secondary degradation processes.

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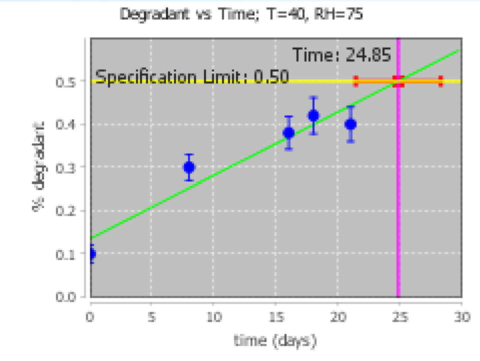
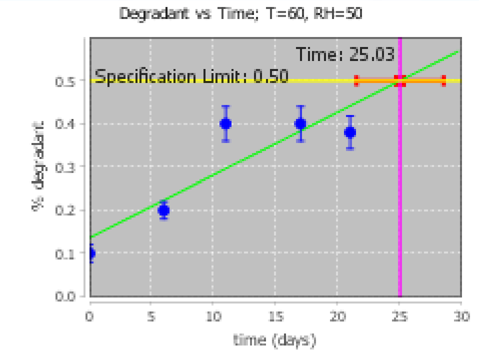
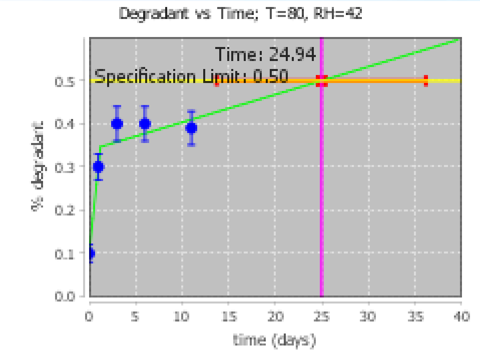
Plateau Behavior

- B may reach steady-state levels at ASAP conditions.
- Does steady state % degradant vary with temperature and RH?
  - If steady-state level remains consistent between stress conditions: k_1 and k_2 have similar Arrhenius parameters, and their ratio does not vary much with temperature and RH.
  - Plateau can vary with temperature and RH, and the specification limit may not be reached at long-term storage conditions.







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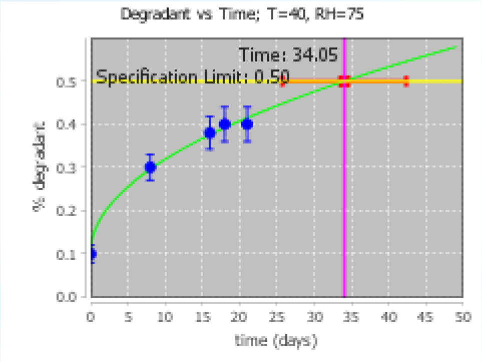
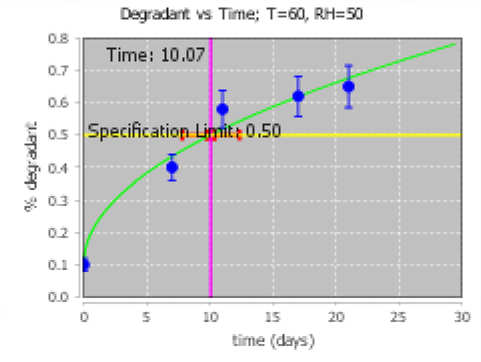
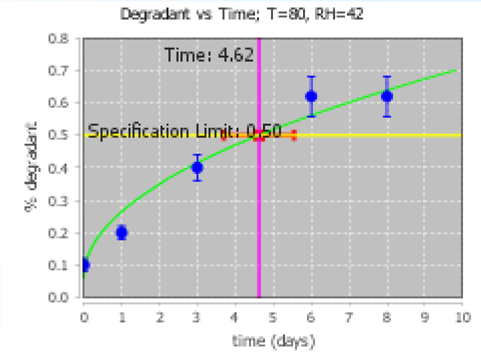
Modeling Secondary Degradation: Initial Approach

- Model growth of B in ASAP*prime*®, ignoring secondary degradation.
  - If growth of B shows similar curve shape independent of T/RH, the standard ASAP approach can be used.
  - Secondary degradation observed as slowdown in degradant growth: <u>diffusion fit</u> often useful.







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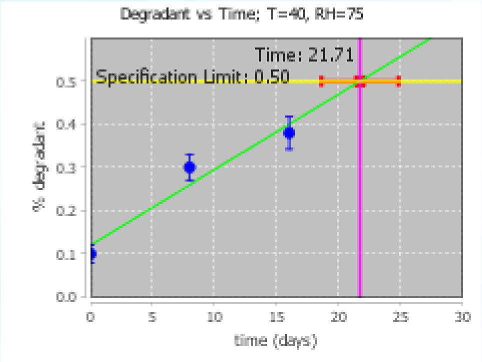
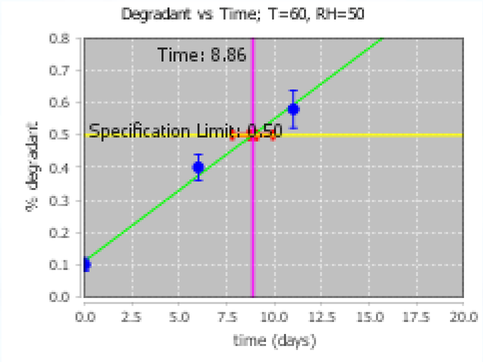
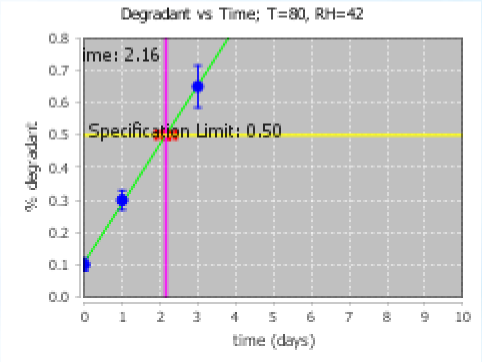
Conservative Approach

- When diffusion fit is poor, limit fitting to the initial growth of B.
  - Assume growth of B occurs without a secondary process reducing B: the initial rate is the maximum reaction rate.
  - If the product is predicted to be stable using this approach, more complex calculations are not necessary.







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Modeling Secondary Degradation

With sufficient timepoints, k_1 and k_2 can be determined at each ASAP stress condition.

$$A \overset{k_1}{\rightarrow} B \overset{k_2}{\rightarrow} C$$

- **Assumptions**
  - k_1 and k_2 are first-order reactions
  - Both processes are irreversible

$$B_t = A_0 \frac{k_1}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) + B_0 e^{-k_2 t}$$

- **Parameters**
  - Need to solve for k_1 and k_2 at each condition: minimum of 3 time points, generally ≥ 5 time points per condition

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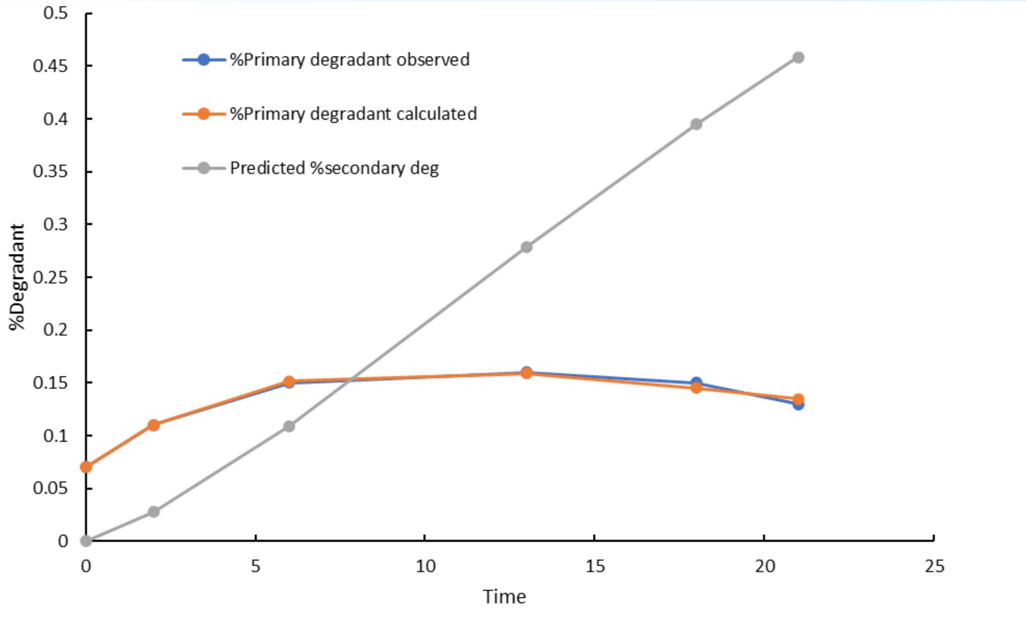
Calculation of k_1 and k_2

- Using the first-order rate equations for sequential reactions, calculate k_1 and k_2 at each stress condition.

Time (days)	Measured % B	Predicted % B	Predicted % C
0	0.070	0.070	0.000
2	0.110	0.110	0.028
6	0.150	0.151	0.109
13	0.160	0.159	0.279
18	0.150	0.145	0.395
21	0.130	0.135	0.459



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Modeling Secondary Degradation

$$A \xrightarrow{k_1} B \xrightarrow{k_2} C$$

- k_1 and k_2 follow the modified Arrhenius equation with temperature and RH:

$$\ln(k) = \ln(A) - \frac{E_A}{RT} + B(RH)$$

- A minimum of 3 stress conditions (generally ≥ 5) with both k_1 and k_2 solved are needed to fit to the Arrhenius equation.
- 6 conditions x 6 time points per condition + 3 controls = **39 samples**

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Converting to Long Term Conditions

- Calculate the Arrhenius parameters for both the primary and secondary degradation reactions: $\ln A_1$, $\ln A_2$, E_{a1}, E_{a2}, B_1, B_2.
- By determining k_1 and k_2, behavior at different temperature and RH conditions (incorporating packaging) can then be modeled explicitly.
- Because of the number of parameters, error bars become larger, and more data may be needed to get adequate precision.

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When Secondary Degradation Is Expected…

- Additional timepoints should be included in the ASAP study to better define the behavior of the primary degradant.
  - Include early timepoints to determine behavior of B before turnover or steady state is reached.
- If the secondary degradant is observed, the data can be used to help model behavior of primary degradant.
  - Growth of secondary degradant usually models cleanly with the ASAP approach (may or may not exhibit a lag phase).

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Summary

- Modeling of secondary degradation can involve complex kinetics.
- Using initial rise of the primary degradant gives the most conservative shelf life prediction.
- If steady state is reached, take into account where the plateau occurs at each ASAP condition: if this is relatively constant with temperature and RH, more complex calculations may not be necessary.
- Kinetic-rate equations and the modified Arrhenius equation can be used in combination to explicitly determine the rate constants k_1 and k_2 at the target storage condition.

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Questions?

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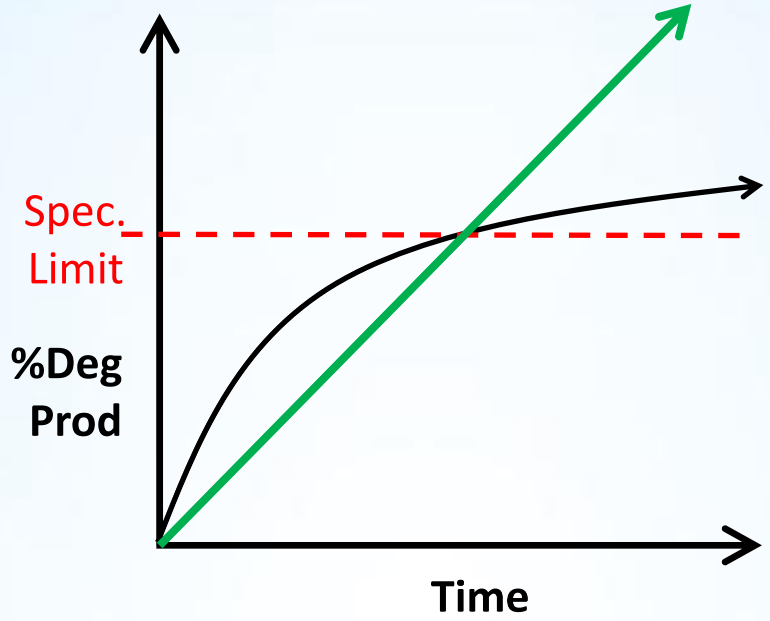
Isoconversion Approach

- Stress conditions and timepoints used for ASAP studies are targeted towards reaching the specification limit.



- Products that exhibit complex kinetics, such as secondary degradation and sequential reactions, may present difficulties in modeling.

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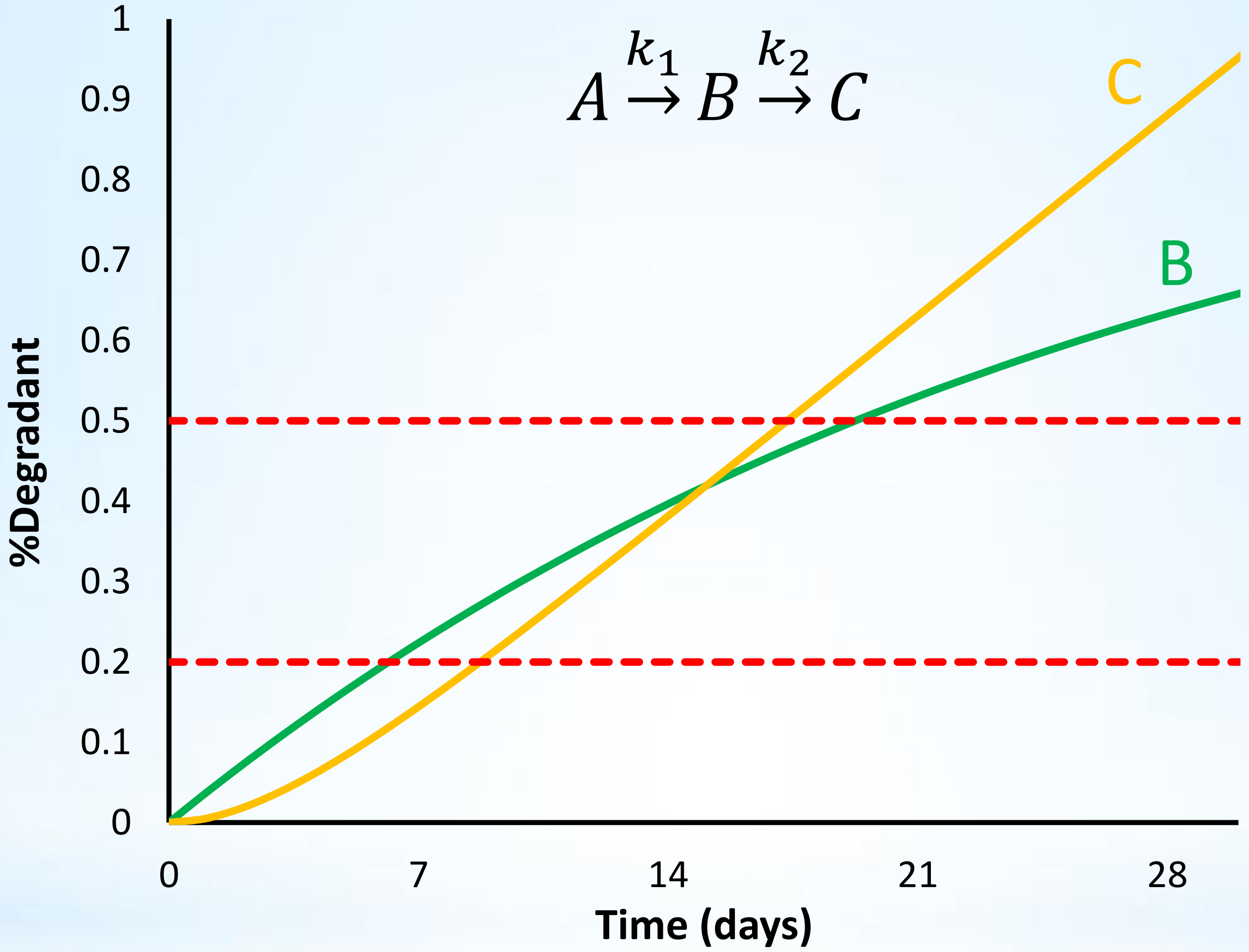

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