Accelerated stability modeling for difficult cases:

1. When nothing happens
2. When degradants degrade

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When Nothing Happens

- In an accelerated stability (ASAP) study, we may not see any change under any conditions
- We cannot build a stability model
- Can we still assign a (minimum) shelf-life?

Step 1. Are data just noise?

- Determine average degradant/potency at each condition
- Any points differ from average by >1.645σ?
  - **Probability noise will exceed this threshold <10%**

Example Data Set

Time (days)	%Degradant	$\lvert deg - deg_{avg} \rvert$
0	0.04, 0.02, 0.03 **Average = 0.03**	0.00
7	0.01	0.02
21	0.05	0.02
	Deg_{avg} = 0.03	

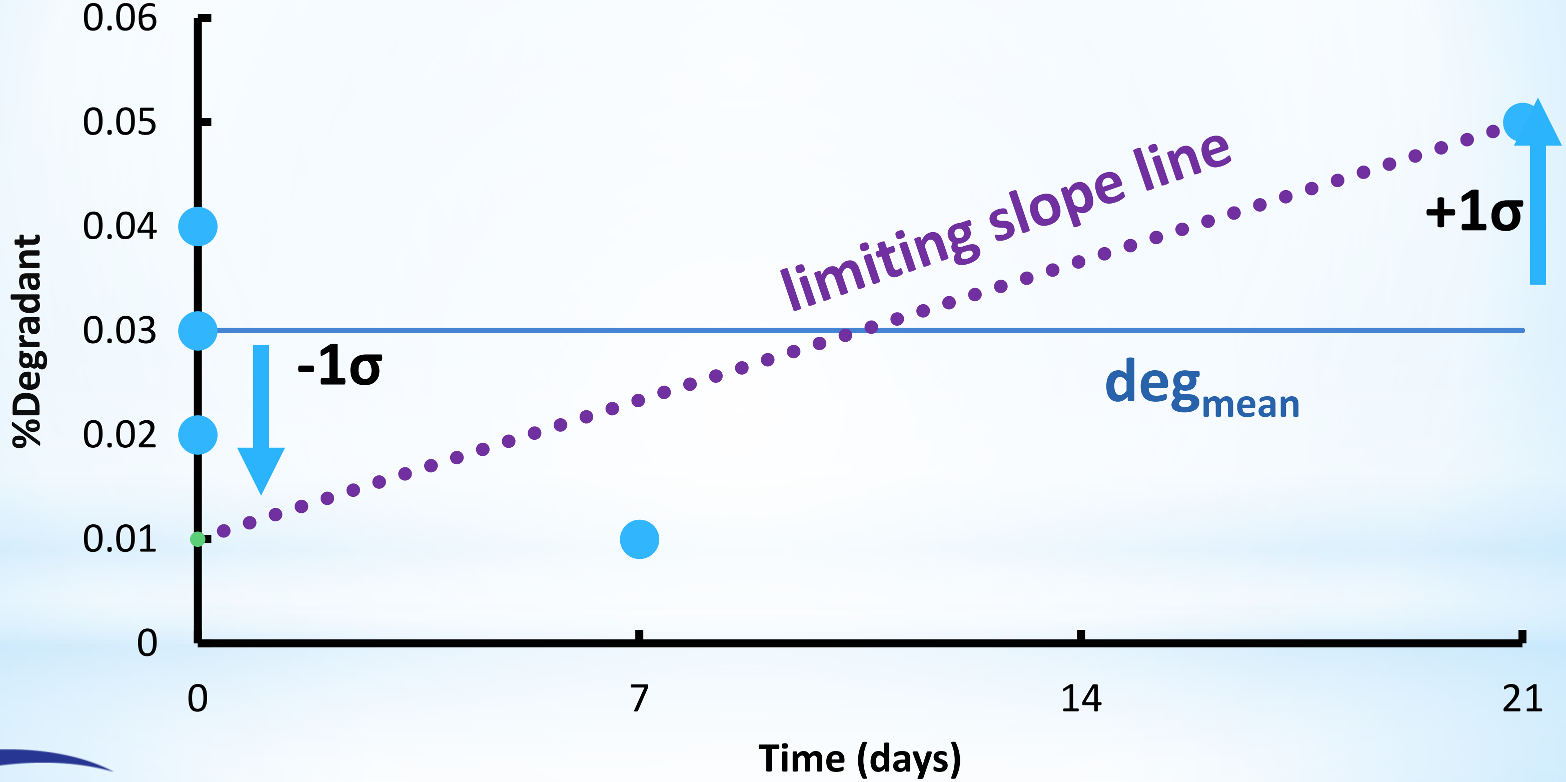
$1.645\sigma = 1.645 * LOD = 1.645 * 0.02 = 0.0329$

All conditions less than noise threshold:

Low Conversion appropriate

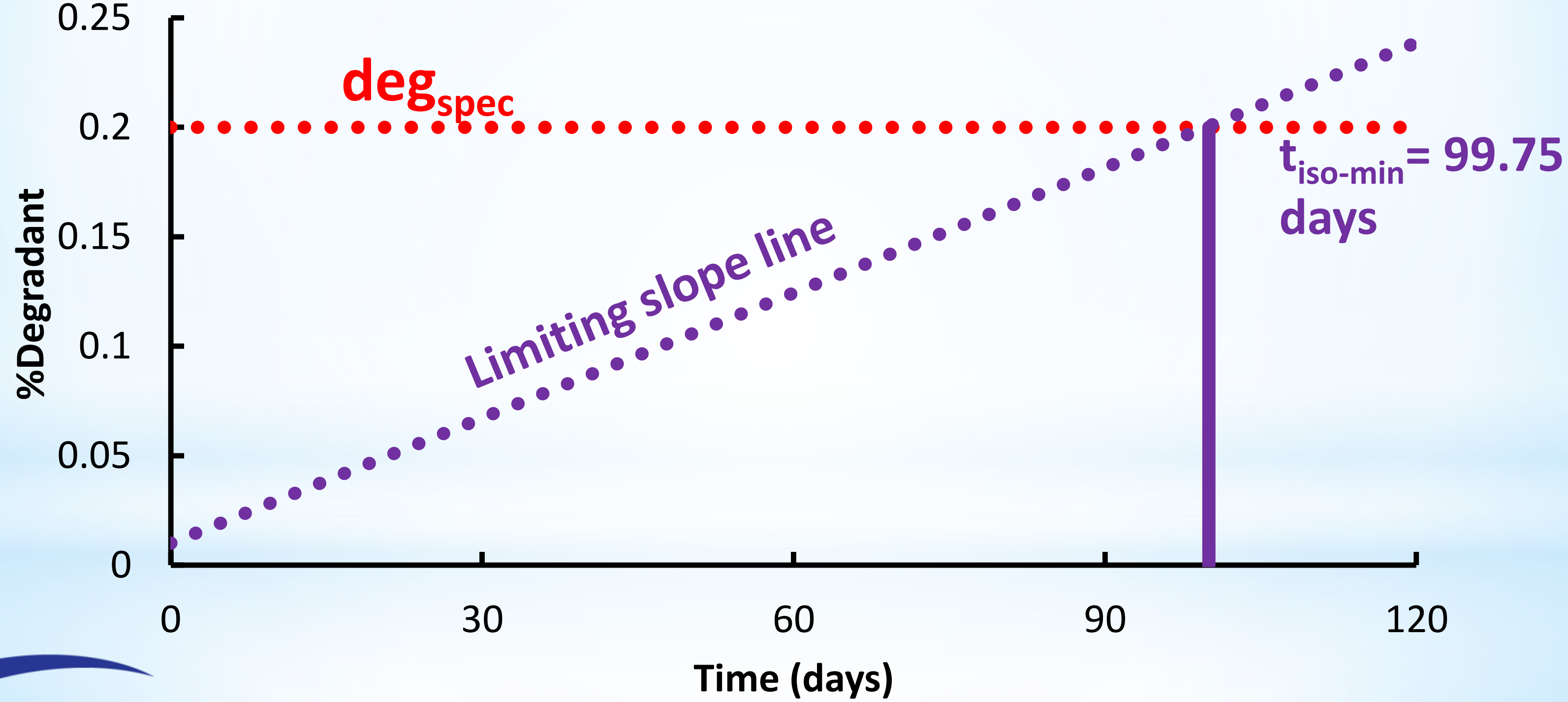
Limiting Slope Line

Step 2. Limiting slope line: data **end** points +/-1σ from mean



Minimum Isoconversion Time

Step 3. **Limiting slope line's** intercept with specification limit = $t_{iso\text{-}min}$ at each condition



Confidence Interval

Step 4. Space all points evenly and determine degradant confidence interval at $t_{iso\text{-}min}$

$$\boldsymbol{CI = \sigma\sqrt{\frac{1}{n} + \frac{(t_{iso-min} - t_{mean})^2}{\sum(t_i - t_{mean})^2}}}$$

$$\boldsymbol{= 0.02\%\sqrt{\frac{1}{3} + \frac{(99.8 - 10.5\ days)^2}{(0 - 10.5\ days)^2 + (10.5 - 10.5\ days)^2 + (21 - 10.5\ days)^2}}}$$

Spaced Points (Days)	
	0
	10.5
	21
Average	**10.5**

= 0.121%

In example:

n= 3; SD= LOD = 0.02%; $t_{iso\text{-}min}$ = 99.8 days

Adjust σ

Step 5. Adjusted σ using CI

- ≤10% of time, true $t_{iso} \le t_{iso\text{-}min}$ since only use Low Degradant mode when change was <1.645σ
- 1.282*SD corresponds to one sided 90% probability

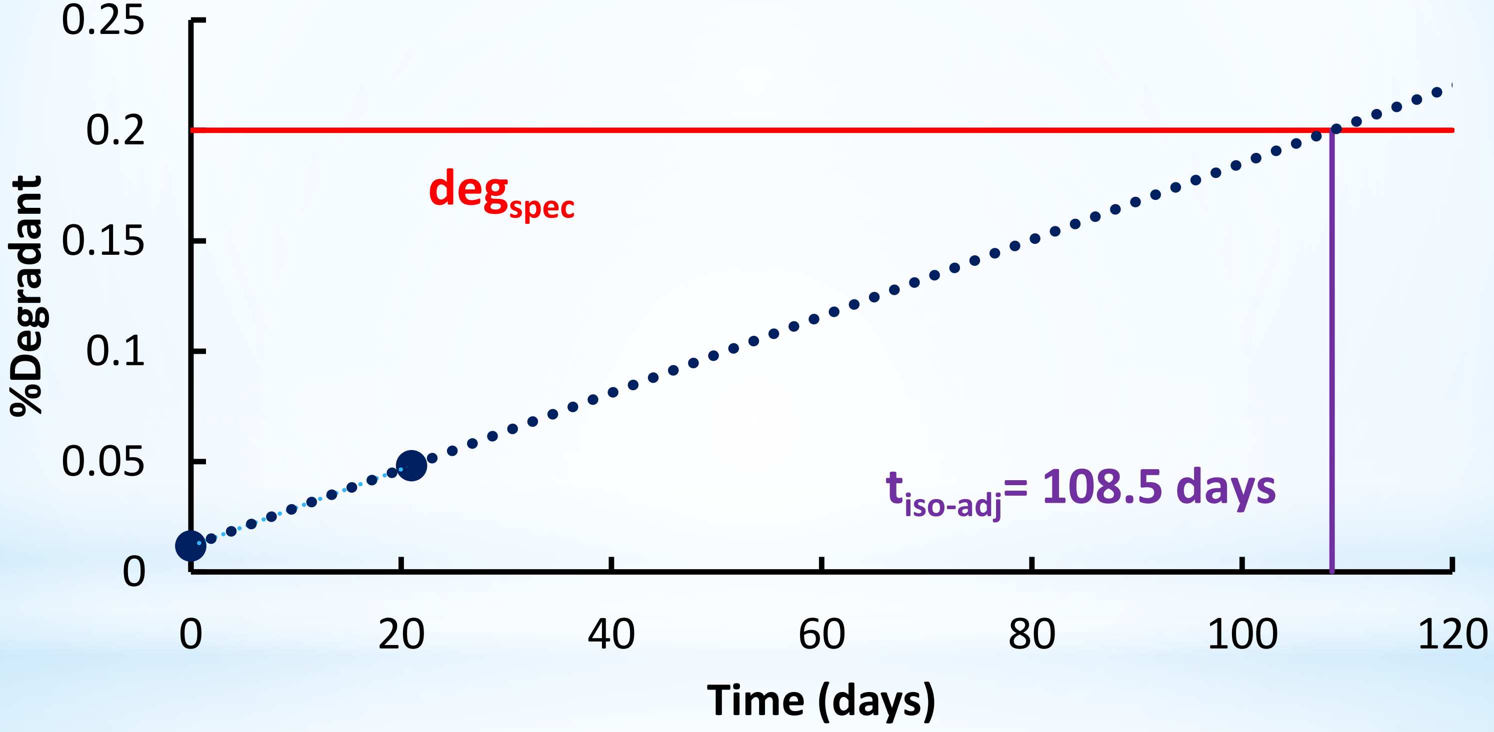
$$\sigma_{adj} = \frac{1.282CI}{\frac{2t_{iso-min}}{t_{max}} - 1}$$

$$= \frac{\mathbf{1.282 * 0.121\%}}{\frac{\mathbf{2 * 99.8\ days}}{\mathbf{21\ days}} - \mathbf{1}} =$$

$$\mathbf{0.018\%}$$

Adjust Isoconversion Time

Step 6. Adjust t_{iso} with adjusted σ



Calculate Distribution

Step 7. Calculate CI_{final} using $t_{iso\text{-}adj}$

$$CI_{final} = \sigma\sqrt{\frac{1}{n} + \frac{\left(t_{iso-adj} - t_{mean}\right)^2}{\sum_{i=1}^{n}(t_i - t_{mean})^2}}$$

$$= 0.02\%\sqrt{{}^{1}/_{3} + \frac{(108.5\ days - 10.5\ days)^2}{(-10.5\ days)^2 + (0\ days)^2 + (10.5\ days)^2}}$$

$$= 0.133\%$$

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Adjust for Conditions

Step 8: Extrapolate probability of passing to storage condition

- With nothing to model, temperature (E_a) and relative humidity (B) sensitivity unknown
- Adjust the isoconversion times at accelerated T/RH to long-term T/RH based on conservative values
  - $\uparrow E_{a\ assumed}$ $\uparrow$long-term justified
  - $\uparrow B_{assumed}$ $\uparrow$long-term justified [$RH_{long\ term} < RH_{accelerated}$]
  - $\downarrow B_{assumed}$ $\uparrow$long-term justified [$RH_{long\ term} < RH_{accelerated}$]

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Activation Energy

- Based on FreeThink database (n = 138) for solids:
  - E_a = 27.3 ± 9.6 kcal/mol (114 ± 40 kJ/mol)

- Assuming a normal distribution, 95% of products have $E_a \geq$ **11.5 kcal/mol (48 kJ/mol)** ***[default]***

- Liquid/solid drug products similar

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B-Term

- Based on FreeThink database:
  - $B = 0.037 \pm 0.026$
  - Assuming a normal distribution, >95% of products will have $0.09 \geq B \geq 0.01$
  - To be conservative [***default***]:
    - If RH long term $<$ accelerated: $B = 0.0$
    - If RH long term $>$ accelerated: $B = 0.1$

Use Activation Energy + B Term

$$shelflife_{Ts,RHs} = t_{iso-adj\,Ta,RHa} e^{\left(\left(\frac{E_a}{R}\right)\left(\frac{1}{T_s}-\frac{1}{T_a}\right)-B(RH_s-RH_a)\right)}$$

s = storage condition

a = accelerated condition

Example:

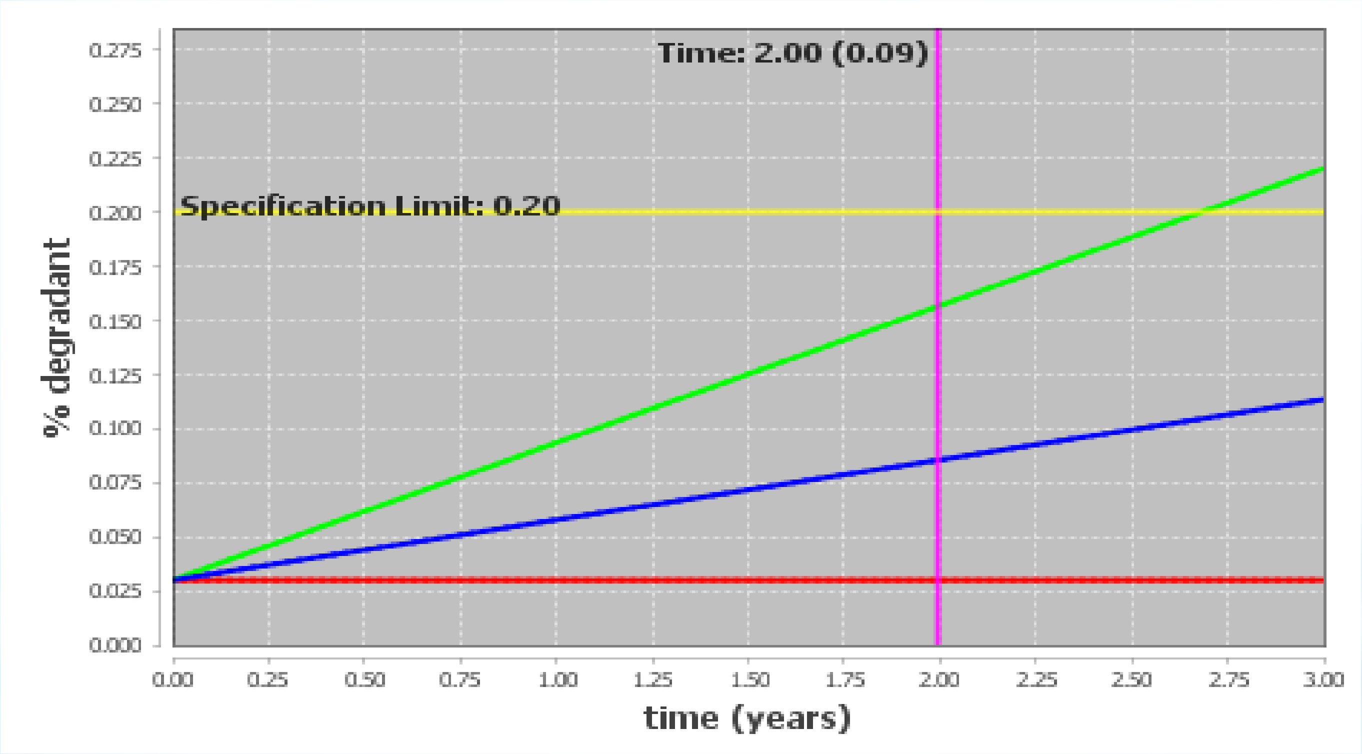
- Shelflife 25°C/60%RH = 108.5 d(80°C/60%RH) =

$$108.5\ d * e^{\left[\frac{11500cal}{mol} \Big/ \frac{1.986cal}{mol*K}\left(\frac{1}{298K}-\frac{1}{353K}\right)-0(60-60)\right]}$$

= 2240 days (**<u>6.1 years</u>**)

Determine Probabilities

Step 9. Use CI_{final} to determine probabilities at time



Probability of passing = 99.6% at 2 yrs

Use All Conditions

Step 10. Use maximum shelf-life of all conditions tested

- Designs use different times at different T/RH conditions, may give different shelf-life values for each condition

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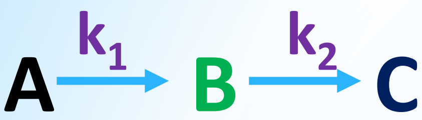
Low Conversion Notes

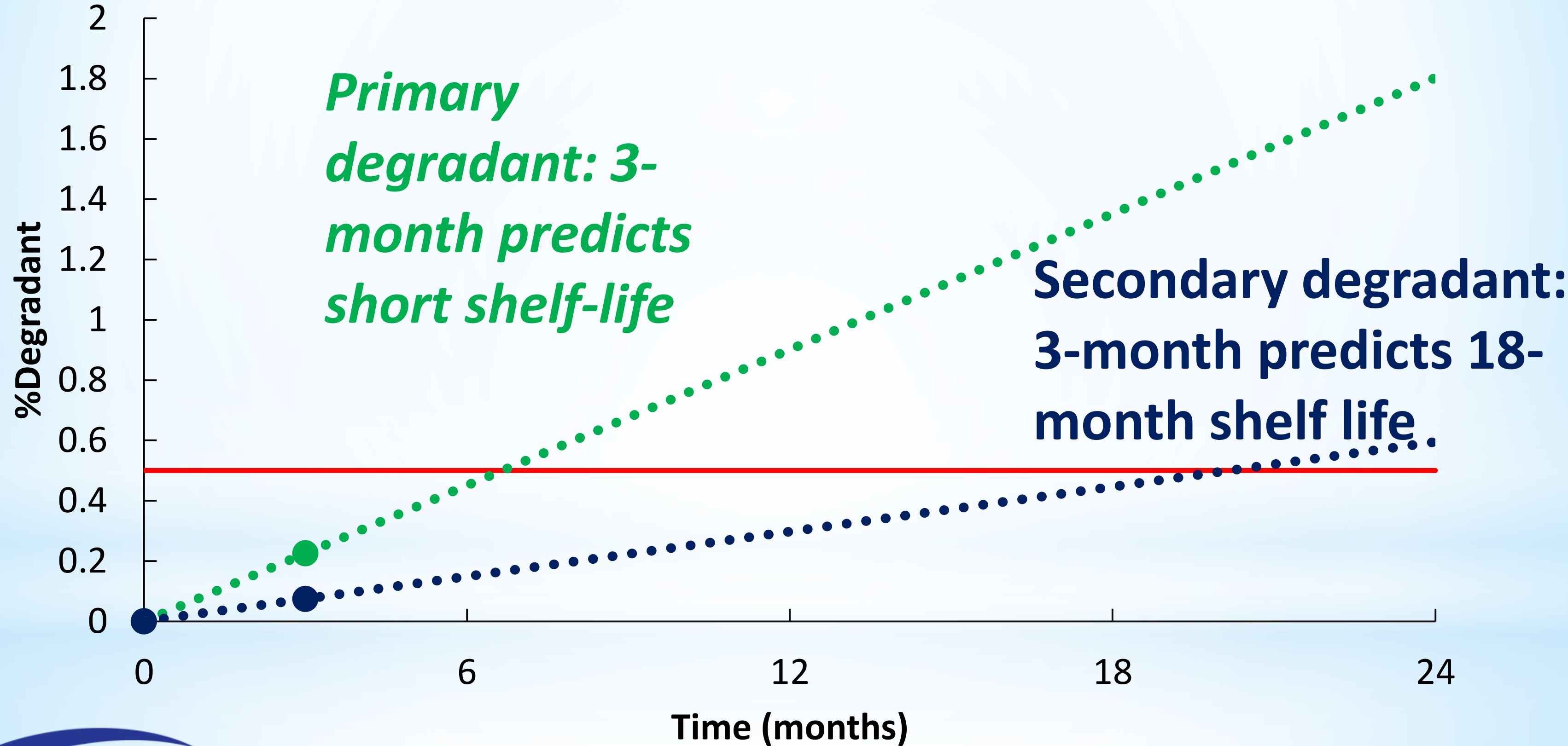
- If see some change at only highest temperatures:
  - Drop highest T's and use low conversion model (most conservative)
  - Include highest T and check consistency with not seeing anything at lower T (discontinuous or continuous)
  - E_a will be higher and give longer shelf-life if including high T

When Degradants Degrade

- Secondary degradation complicates stability determinations for both real time + accelerated

Secondary Degradation



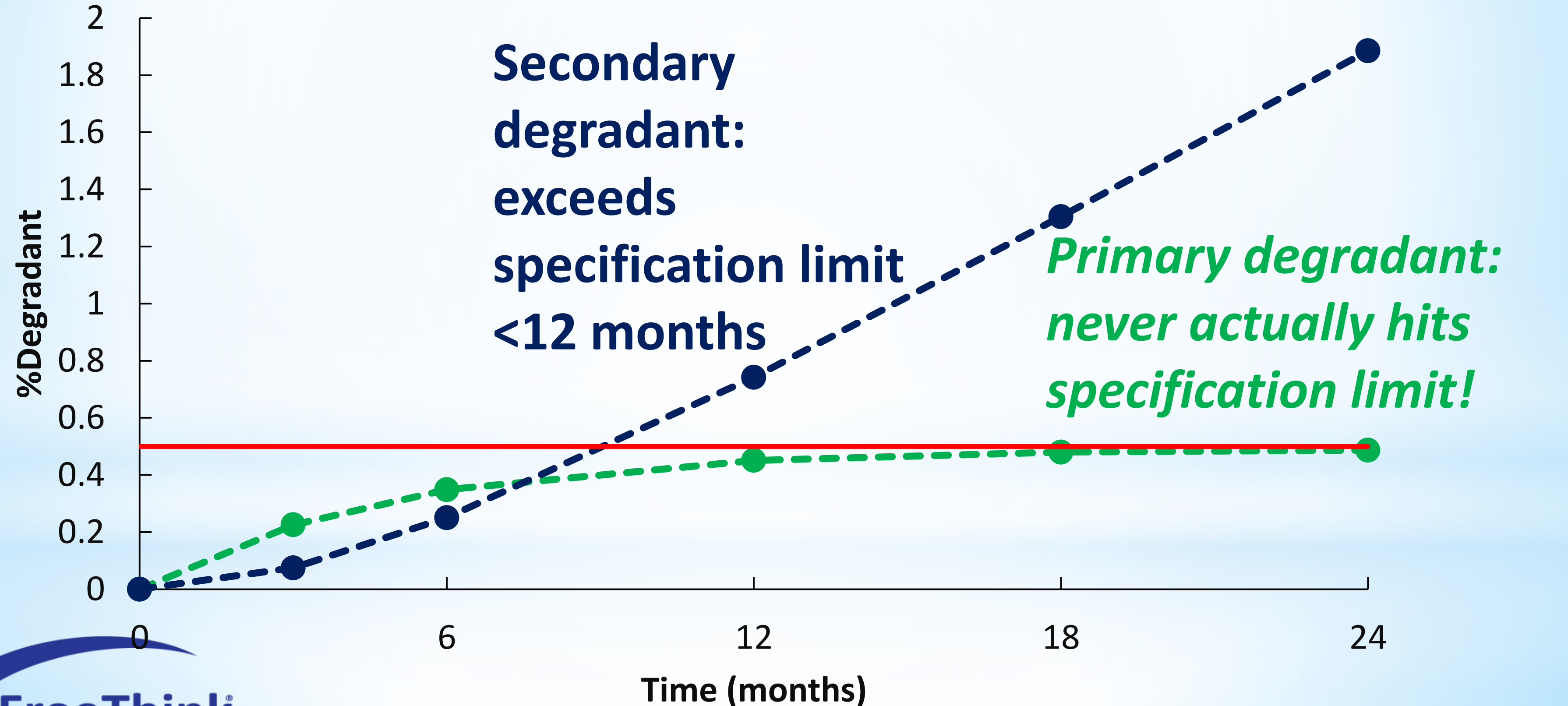


Secondary Degradation

$$\%B = \frac{k_1}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) \quad k_1 \neq k_2$$

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

$$\%C = 1 + \frac{e^{-k_1 t} - e^{-k_2 t}}{k_2 - k_1} \quad k_1 \neq k_2$$



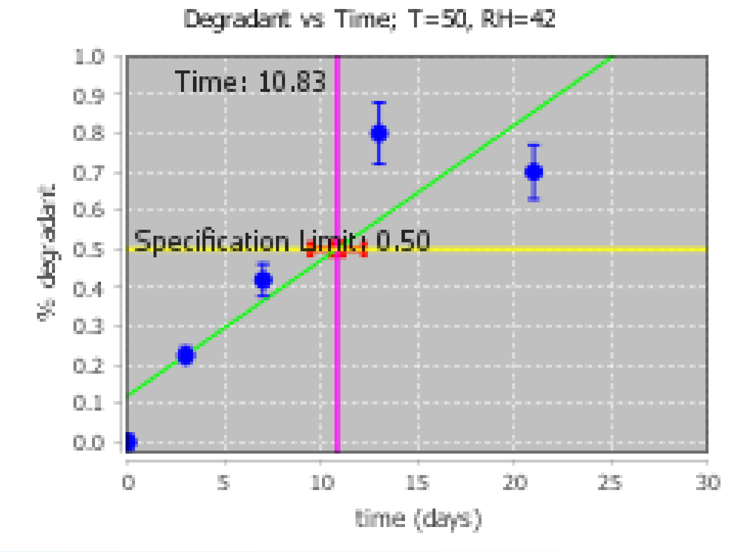
Secondary Degradation and ASAP

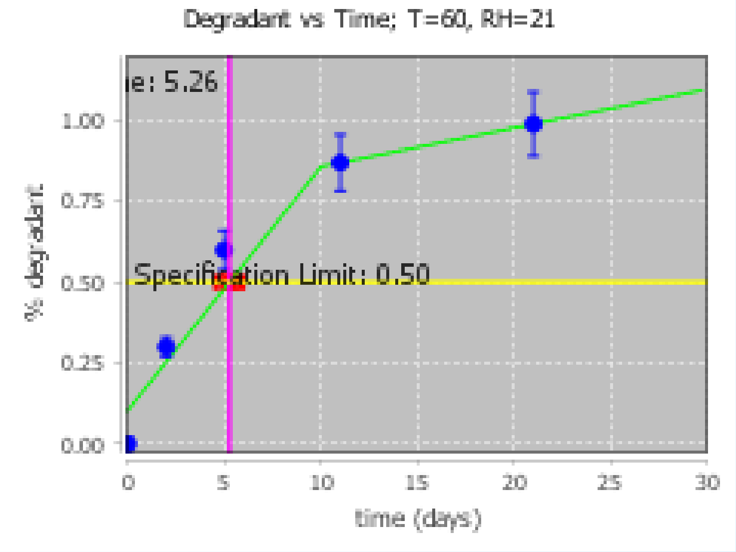
- Extrapolation with traditional stability can be way off
- With ASAP, isoconversion (time to fail), should be fine
- Unless…
  - E_a and/or B very different for $k_1 + k_2$: curve shape will vary across accelerated conditions

Accelerated Modeling with Secondary Kinetics

- Determine k_1, k_2 at each condition
  - Need ≥3 time points per condition
  - Can add secondary degradant values
- Determine ln A_1, ln A_2, E_{a1}, E_{a2}, B_1, B_2 using all conditions (≥6 with RH; ≥4 without RH) adding estimated error bars
- Model behavior at storage condition and determine probabilities based on error bars

Example for Primary Degradant Formation



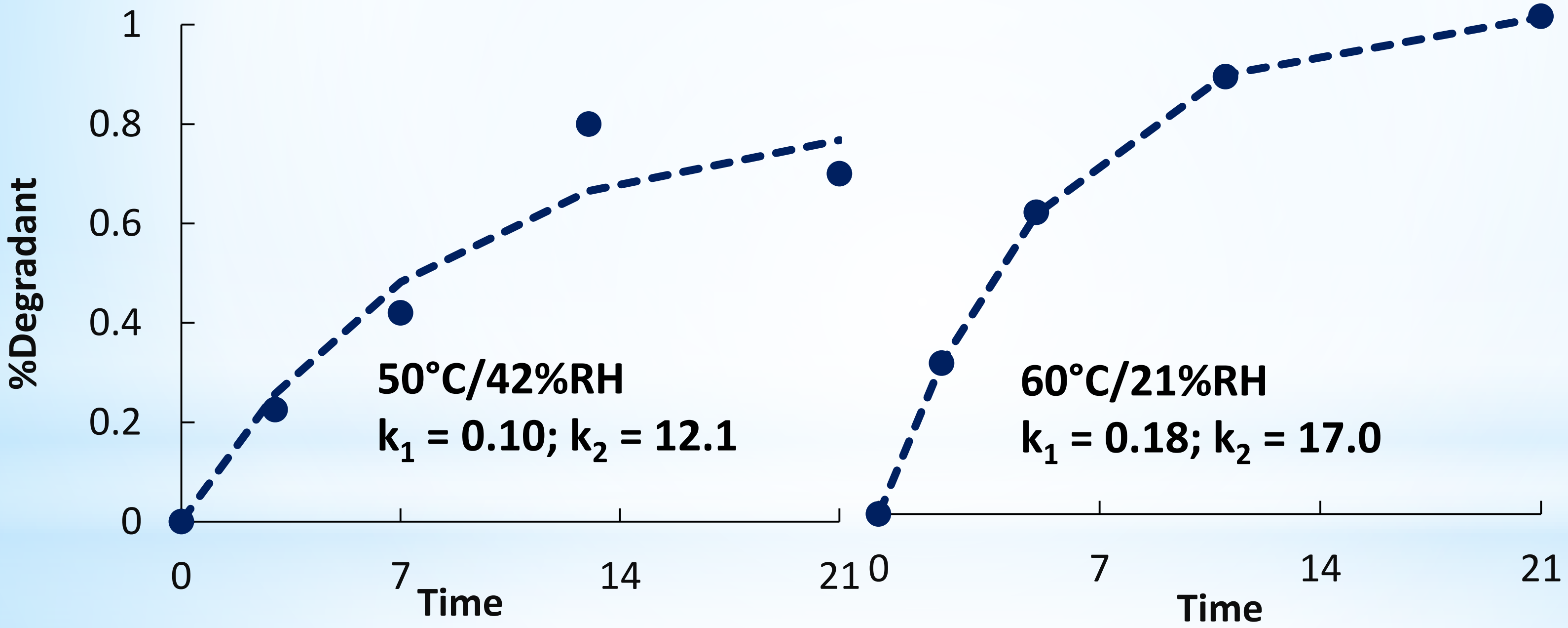


50°C/42%RH

60°C/21%RH

Example Data Fit for k_1 and k_2

$$\%primary\ deg = \frac{k_1}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right)$$



Fit Modified Arrhenius Equation for k_1 and k_2

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

T (°C)	%RH	k_1	k_2
50	42	0.103	12.14
50	81	0.266	129.2
60	21	0.188	17.0
60	29	0.129	123.5
60	53	0.282	100.45
70	28	0.736	117.9
70	0	0.103	4.87
80	0	0.343	22.4
80	51	1.507	514.1

	lnA	E_a (kcal/mol)	B
k_1	37.04	25.90	0.025
k_2	52.67	33.49	0.056

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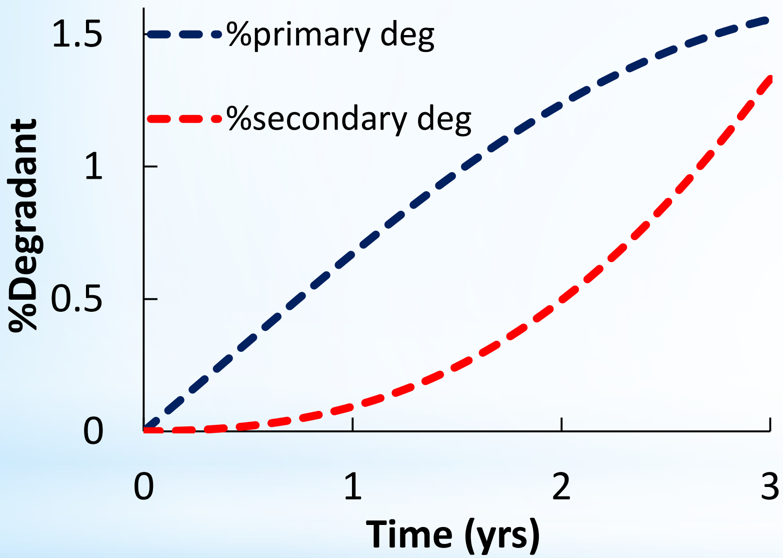
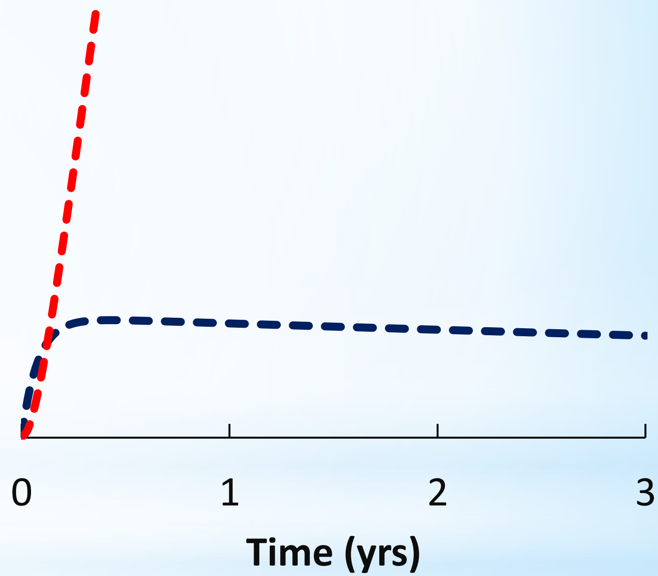
Project to Storage Condition for Primary and Secondary Degradant

$$\%primary = \frac{k_1}{k_2 - k_1}\left(e^{-k_1 t} - e^{-k_2 t}\right) \quad \%secondary = 1 + \frac{e^{-k_1 t} - e^{-k_2 t}}{k_2 - k_1}$$

25°C/60%RH on bottle + desiccant



30°C/75%RH open



Notes on Secondary Degradation

- Primary degradant usually overestimated by ASAP when assuming no secondary degradation occurs
- Secondary degradant usually accurate by ASAP even ignoring that it is a secondary degradant
- Determining full behavior requires more analyses
- Can see very unusual behavior as a function of T/RH
  - Negative temperature dependence (E_a)
  - Negative humidity dependence (B)

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Conclusions

- Two challenging situations for accelerated aging examined
- Assigning a minimum shelf-life when nothing happens was developed using mostly a statistical argument
  - Now incorporated into ASAP*prime*®
- Handling secondary degradation complex but possible with accelerated aging
  - Only critical to deconvolute two rate constants when activation parameters (E_a, B) differ significantly
  - With enough data, can accurately model behavior across storage conditions