

Session 6:

Shelf Life



World Health
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Objectives

- Review the ISO/WHO shelf life and stability requirements
- Discuss problems of shelf life in the distribution chain
- Discuss how to conduct real-time stability studies
- Provide approaches to accelerated stability testing

The Problem

- Condoms deteriorate as they age
- Experience shows that condoms can deteriorate very quickly in hot climates

What is Shelf Life?

- The period during which the condom can be expected to perform satisfactorily

or

- The period during which the condom meets all the requirements of ISO 4074

ISO 4074 uses the second definition.

Current Shelf Life/Stability Requirements

- Pass inflation test after 90 days at 50°C
- Demonstrate shelf life by real-time study at 30°C, using inflation test
- Until real-time data is available, you can use accelerated tests to give provisional results

Possible New Requirements

- ISO 4074 will be amended (maybe 2010)
- Probably, it will require:
 - Real-time study (as now)
- Until real-time is complete:
 - Provisional study, using 50°C aging for about 6 months (=5 yrs) OR
 - Comparison of aging properties between new and existing products

The Most Important Tests

- **Holes:**
 - Two methods: water and electrical
 - Count number of holes
 - Limited in principle to 0.25%
- **Inflation:**
 - Measure burst volume and pressure
 - Count number below limit
 - Limited in principle to 1.5%
- **Package seal:**
 - Same as for new condoms

Previous Requirements on Shelf Life

- The standards were ambiguous about the meaning of shelf life
- Unclear whether standards were expected to apply until expiration date, for new condoms only, or for first 12 months
- Some standards explicitly stated that oven aging did not apply to products over 12 months old

Current Requirements on Shelf Life

- USFDA
 - Type test after aging at 40° to 50°C for 90 days
 - Real-time test requirement at 15° to 30°C
- ISO 4074: 2002
 - Inflation requirements until the expiration date
 - Real-time test at 30°C
- The 2003 WHO specifications
 - Refers to technical requirements of ISO 4074

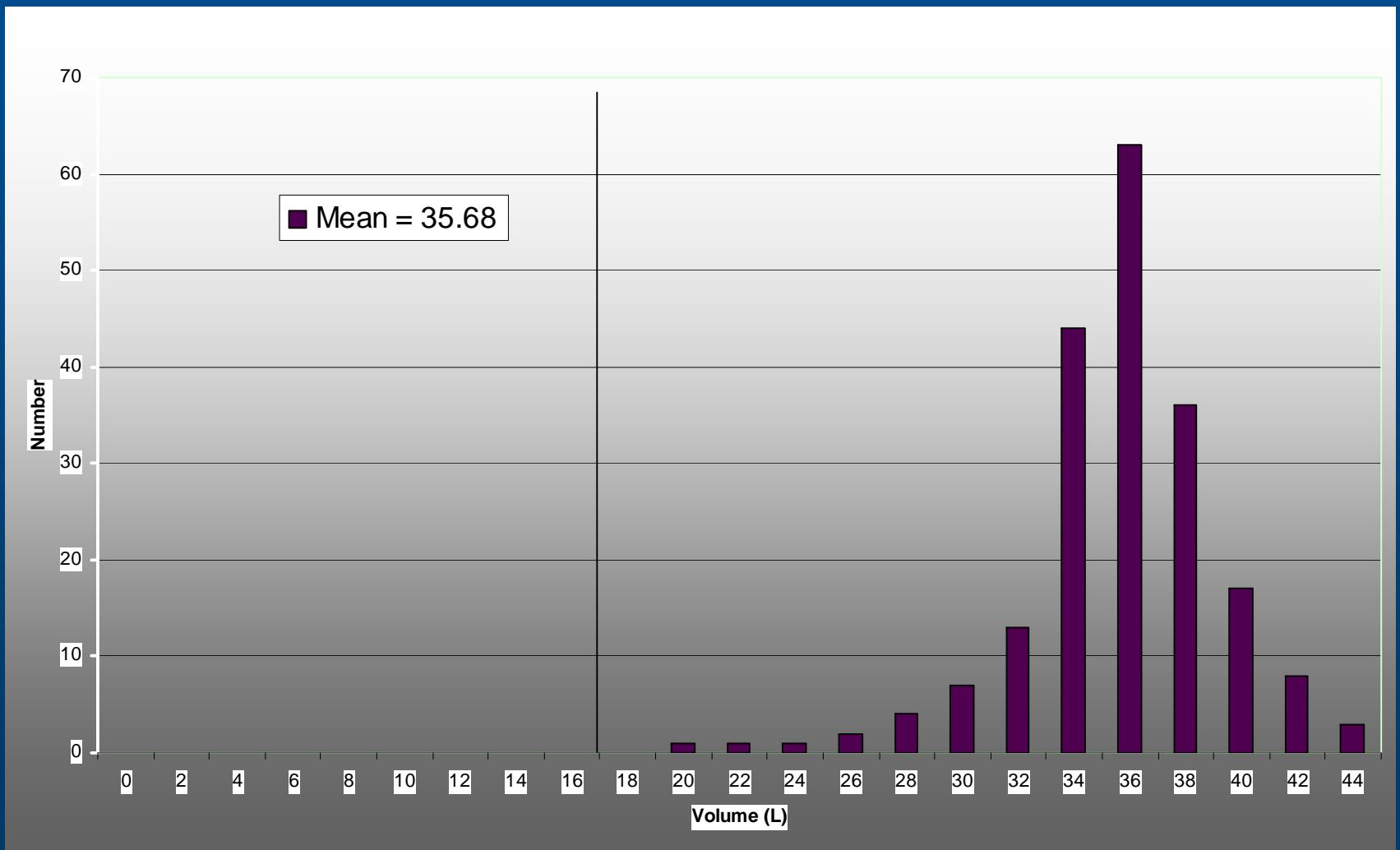
Basis of Shelf Life Model

- Physical parameters of burst volume and pressure are used as sentinel variables for deterioration
- Cause of deterioration is assumed to be a chemical reaction
- Can be monitored by burst properties

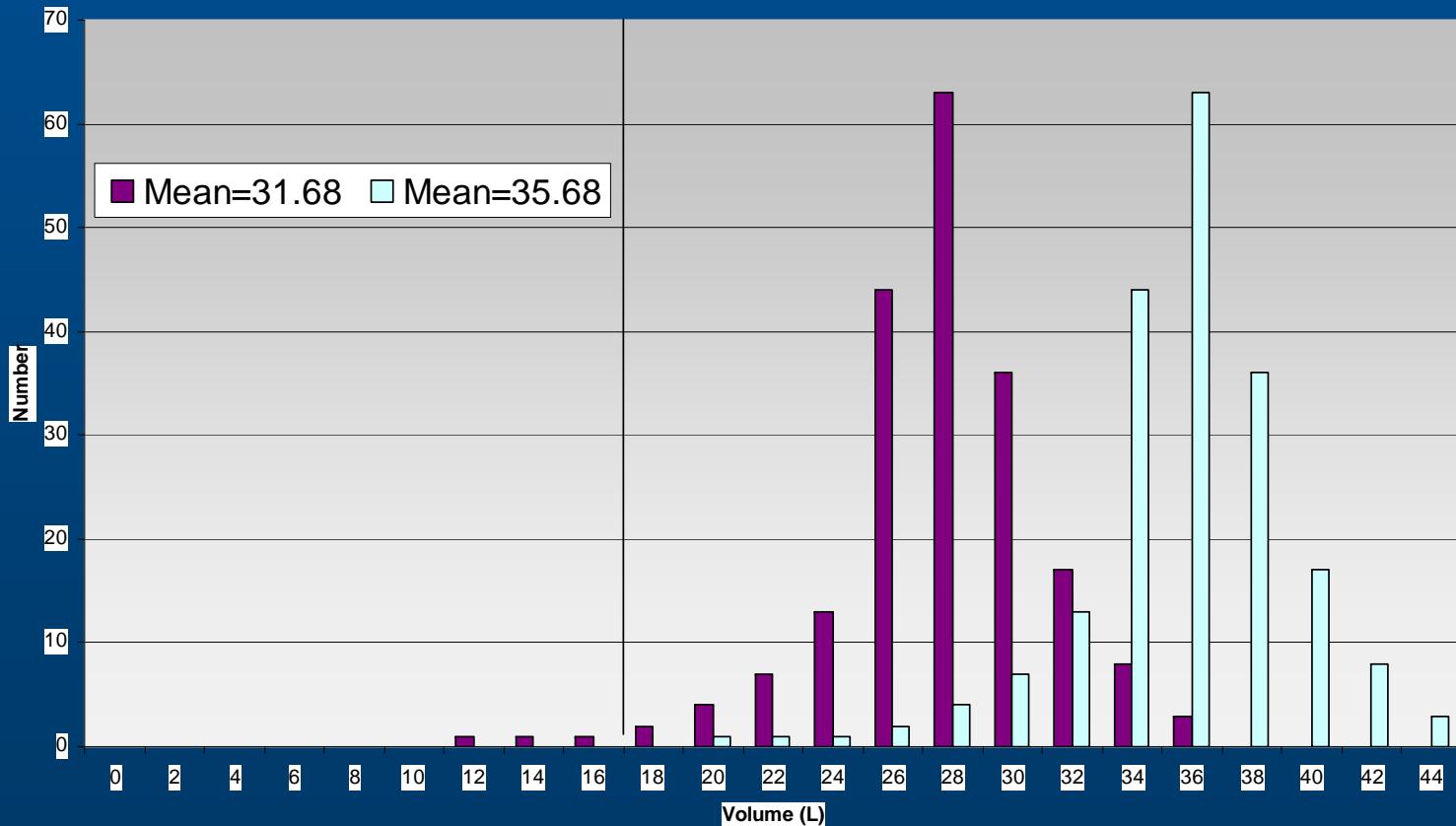
What Happens to Condoms as They Age at Room Temperature?

- For most condoms, the volume goes down
- For most condoms, the pressure does not change much (may go up or down)
- For some condoms, the pressure goes down
- For very few condoms, the volume remains almost constant

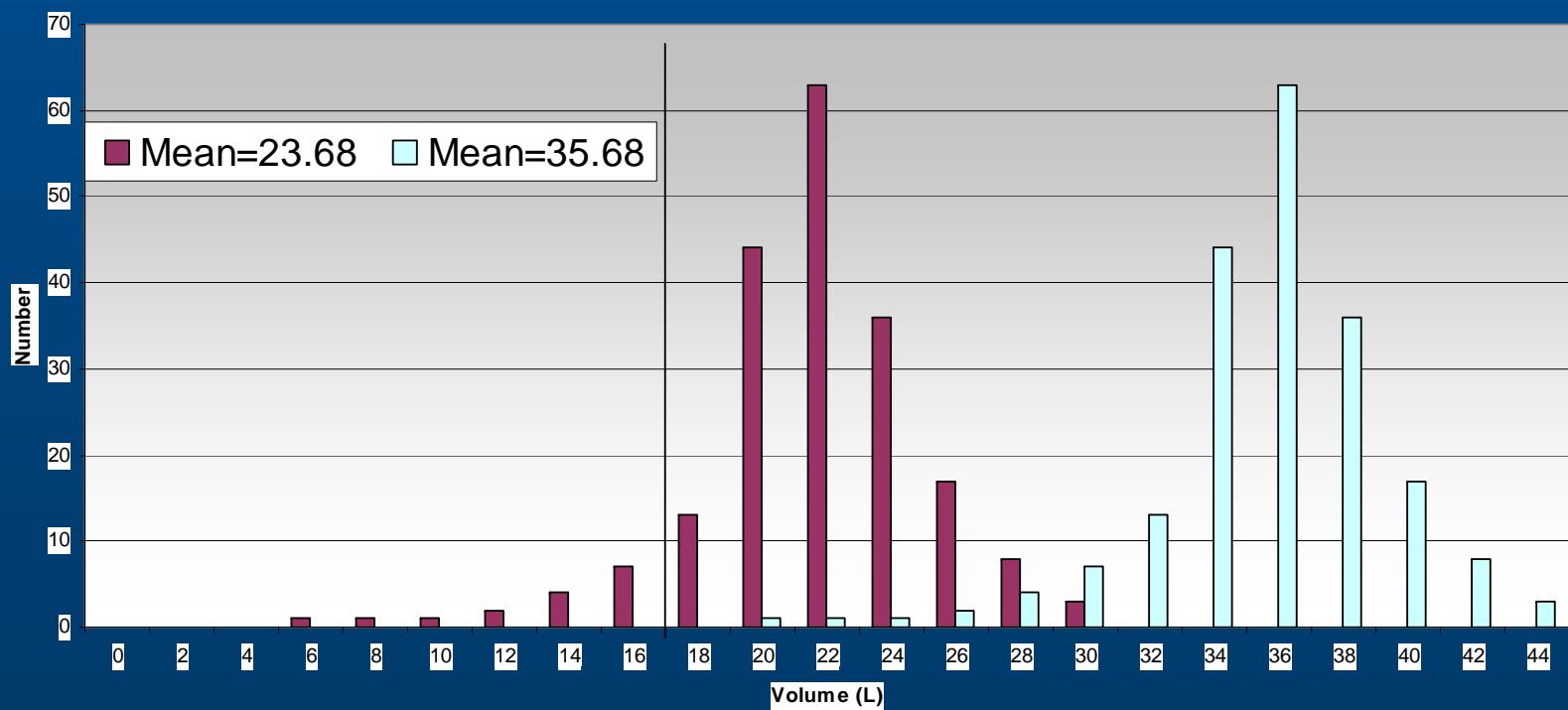
A “Good” Volume Histogram



Slight Decay...



More Decay...



Scientific Basis for Condom Aging

- Condom effectiveness depends on its physical properties
- Properties determined by molecular structure
- Decay of the physical properties must be due to chemical change
- Use tensile or inflation properties to indicate this change

Scientific Basis for Condom Aging (continued)

- Chemical reactions causing decay:
 - Oxidation
 - Chain scission
 - Breakage of sulphur links
 - Formation of additional sulphur links
 - Reorganization of sulphur links
- A significant reaction is believed to be oxidation

What We Know From the Theory

- Condoms deteriorate over time
- They deteriorate faster in hot climates than in cold ones
- Accelerated aging can provide more useful data using the Arrhenius equation if volume and pressure are analyzed separately

Questions?

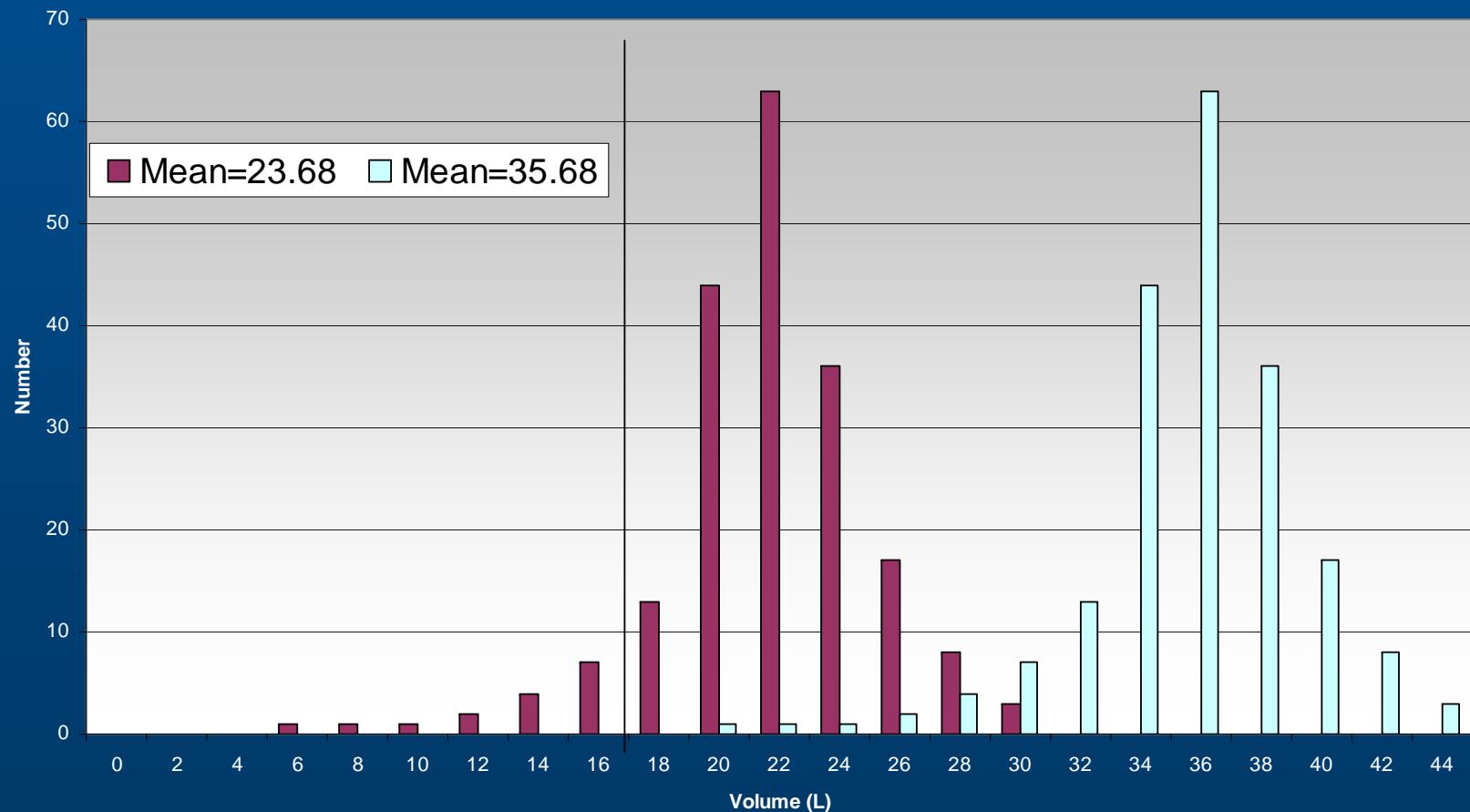
The Starting Point for All Stability Studies

- Shelf life may be measured from the date of dipping or the date of foiling
- Either way, the samples used in trials should have had **maximum storage time** between dipping and foiling

Conducting a Real-Time Study

- ISO 4074 requires a real-time study on three batches
- Should be repeated if significant change to formulation or process
- Different lubricants, pigments, flavors, packs, or shapes may change shelf life

Determining the End-point



How do Condoms Really Behave at Different Temperatures?

- A study from Brazil shows that the pattern of deterioration is dependent on product and temperature
- Data from 17 lots of condoms from 6 manufacturers
- Results also show that a different use of the Arrhenius equation may give good predictions

Questions?

Session 6:

Accelerated Shelf Life Studies



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Accelerated Shelf Life Studies

- Estimate a provisional shelf life and establish a set (or sets) of ageing conditions to model real time ageing
 - Experience
 - Comparison with existing products
 - Arrhenius analysis of stability data obtained at different temperatures and time

Accelerated Shelf Life Studies (continued)

- Condition samples from 3 lots using Annex B sampling plans
- Test for
 - Airburst properties
 - Freedom from holes
 - Pack integrity
- Demonstrate compliance with ISO 4074: 2002
 - Confirm provisional shelf life

Accelerated Shelf Life Studies (continued)

- ISO Currently suggests using the Arrhenius equation
- This approach is applied only to pressure, because its behaviour usually follows the expected trends
- Risk of overestimating the shelf life
- Next edition of ISO 4074 may de-emphasise Arrhenius approach

Questions?

Arrhenius Plot Example

Analysis of Burst Pressure Data

Arrhenius Plot Example

Analysis of Burst Pressure Data

- Obtain data at different temperatures for different time periods

Temperature = 80°C

Time (Days)	Burst Pressure (% Initial)
0	100
1	88
2	84
3	84
4	79
5	74

Temperature = 70°C

Time (Days)	Burst Pressure (% Initial)
0	100
2	90
4	94
6	84
7	84
10	83

Temperature = 60°C

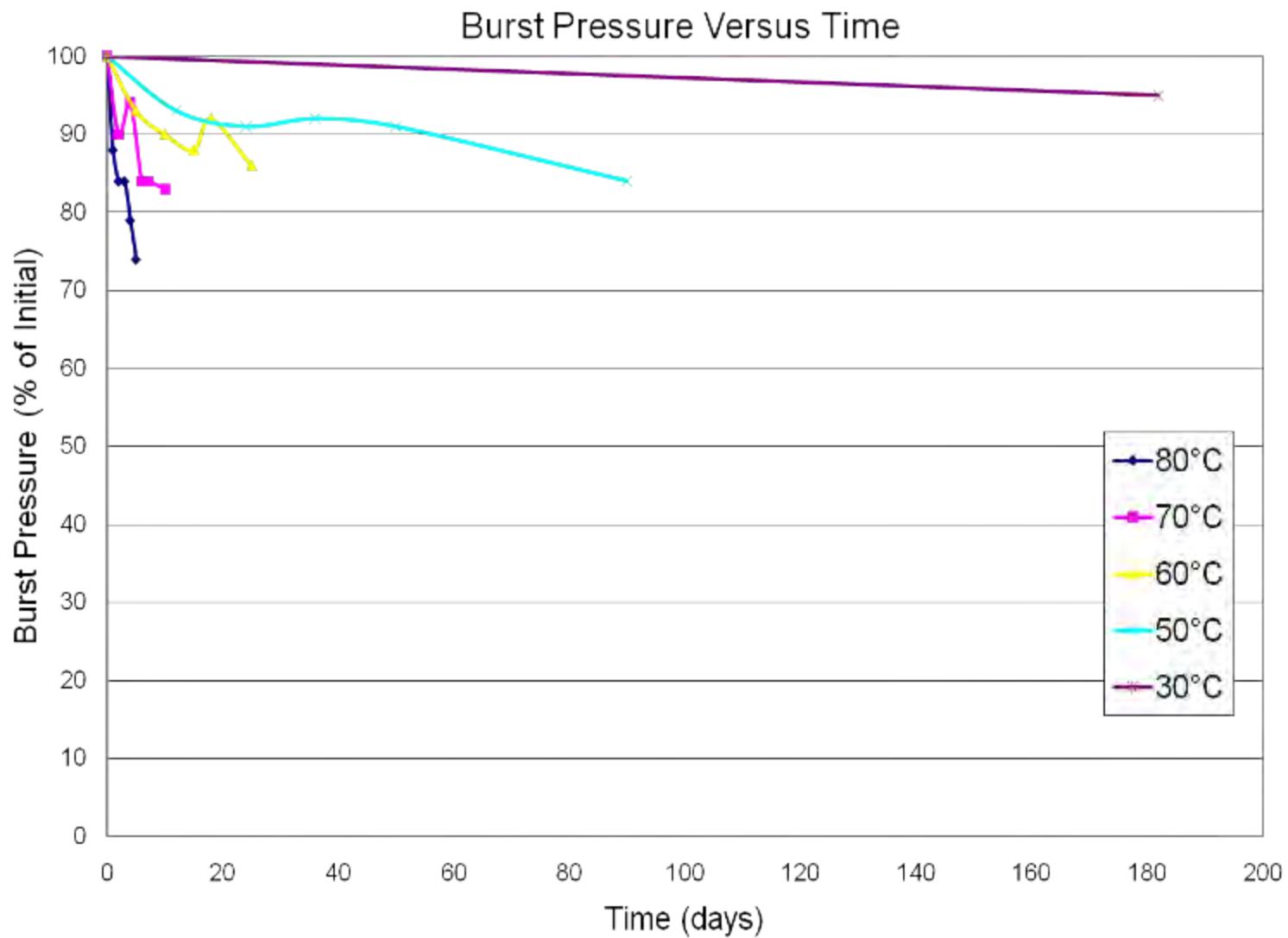
Time (Days)	Burst Pressure (% Initial)
0	100
5	93
10	90
15	88
18	92
25	86

Temperature = 50°C

Time (Days)	Burst Pressure (% Initial)
0	100
12	93
24	91
36	92
50	91
90	84

Temperature = 30°C

Time (Days)	Burst Pressure (% Initial)
0	100
182	95

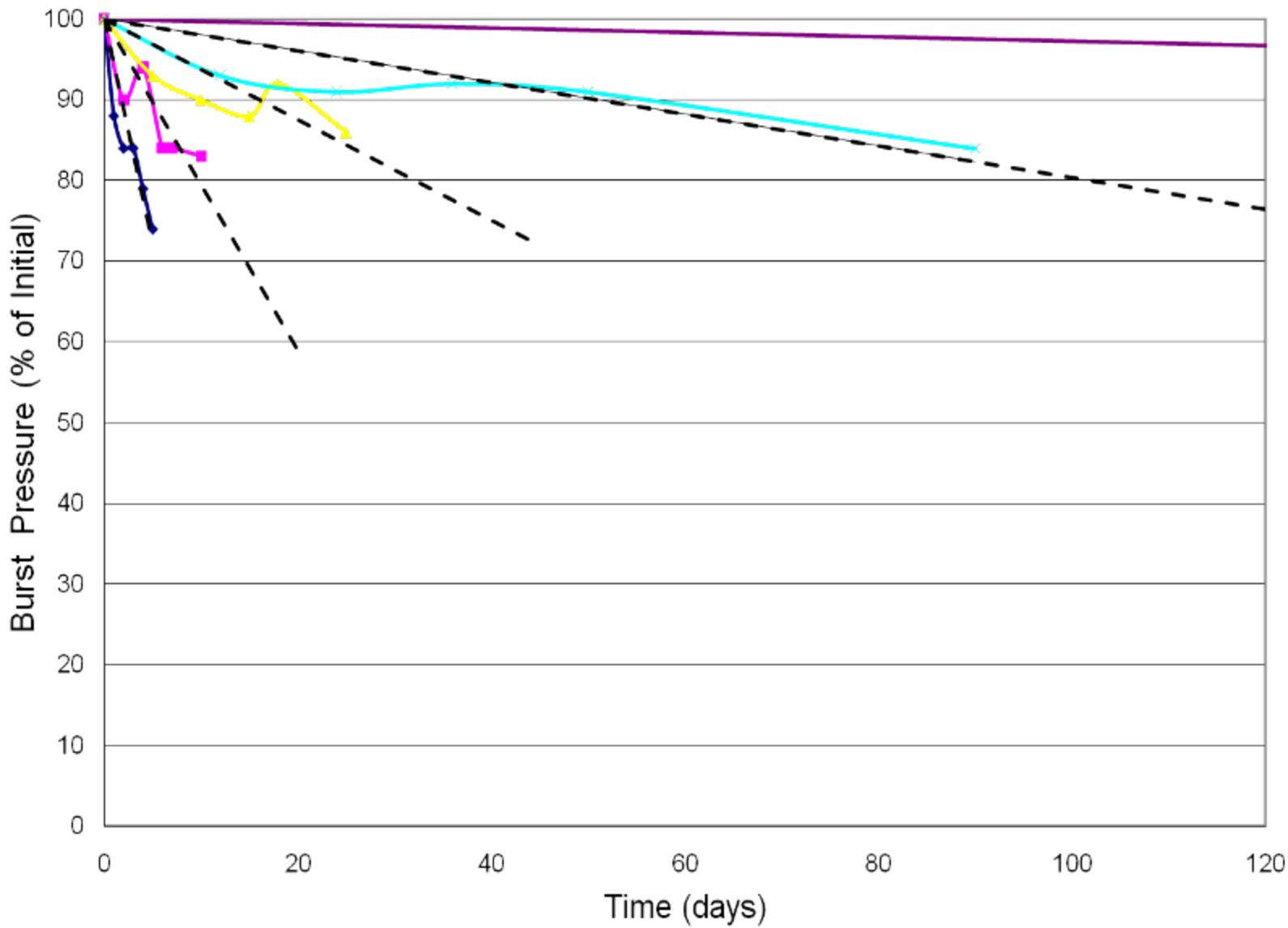


Arrhenius Plot Example

Analysis of Burst Pressure Data

- Choose a threshold value
 - Limit for compliance with ISO 4074
 - Sufficiently large to be statistically meaningful
 - Appropriate for the time scale of the study
- Example
 - 20% fall in burst pressure
- Determine time at each temperature to reach the chosen threshold

Burst Pressure Versus Time



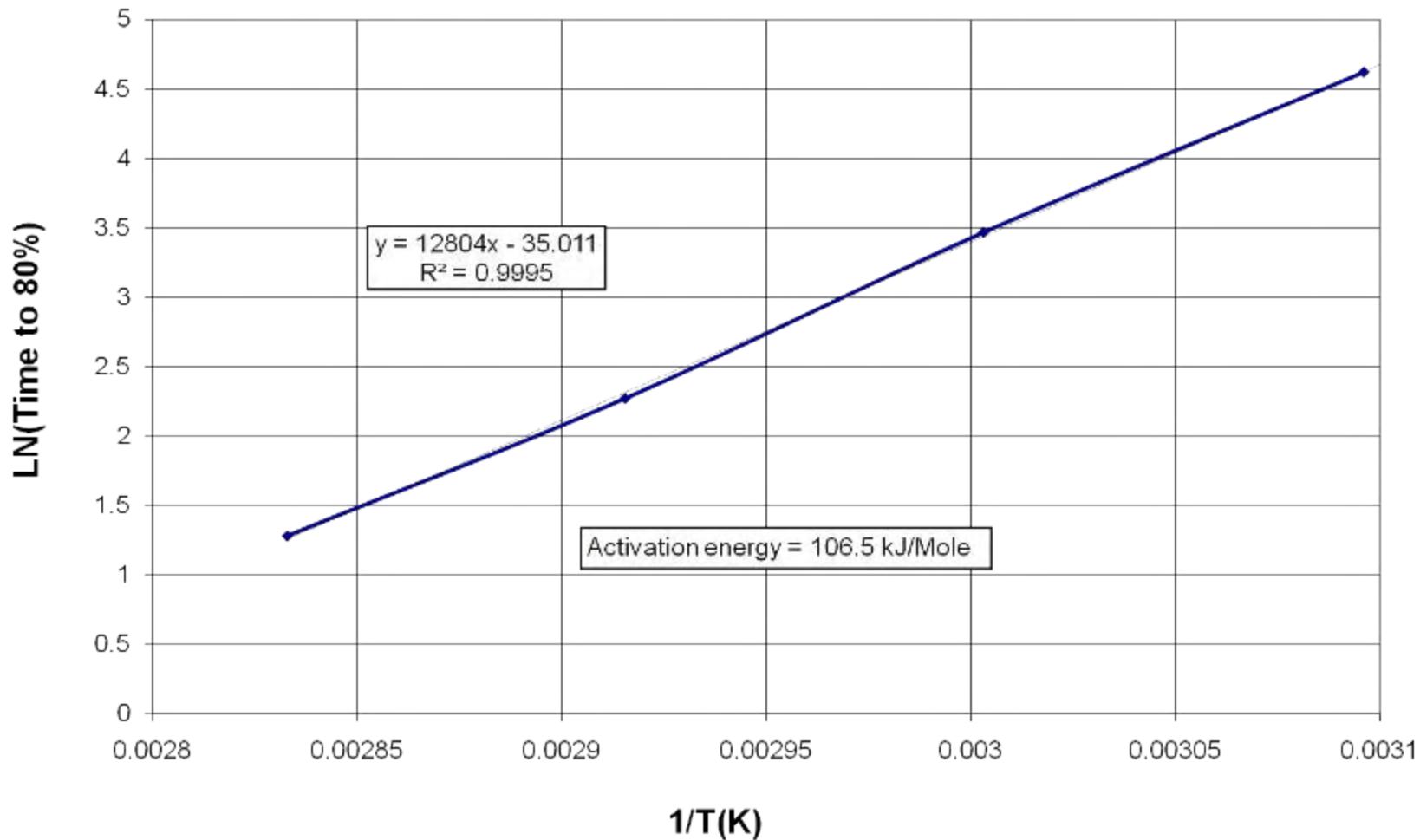
Time for Burst Pressure to Drop to 80% of Initial

Temperature (°C)	Time (days)
80	3.6
70	9.7
60	32.1
50	101.9

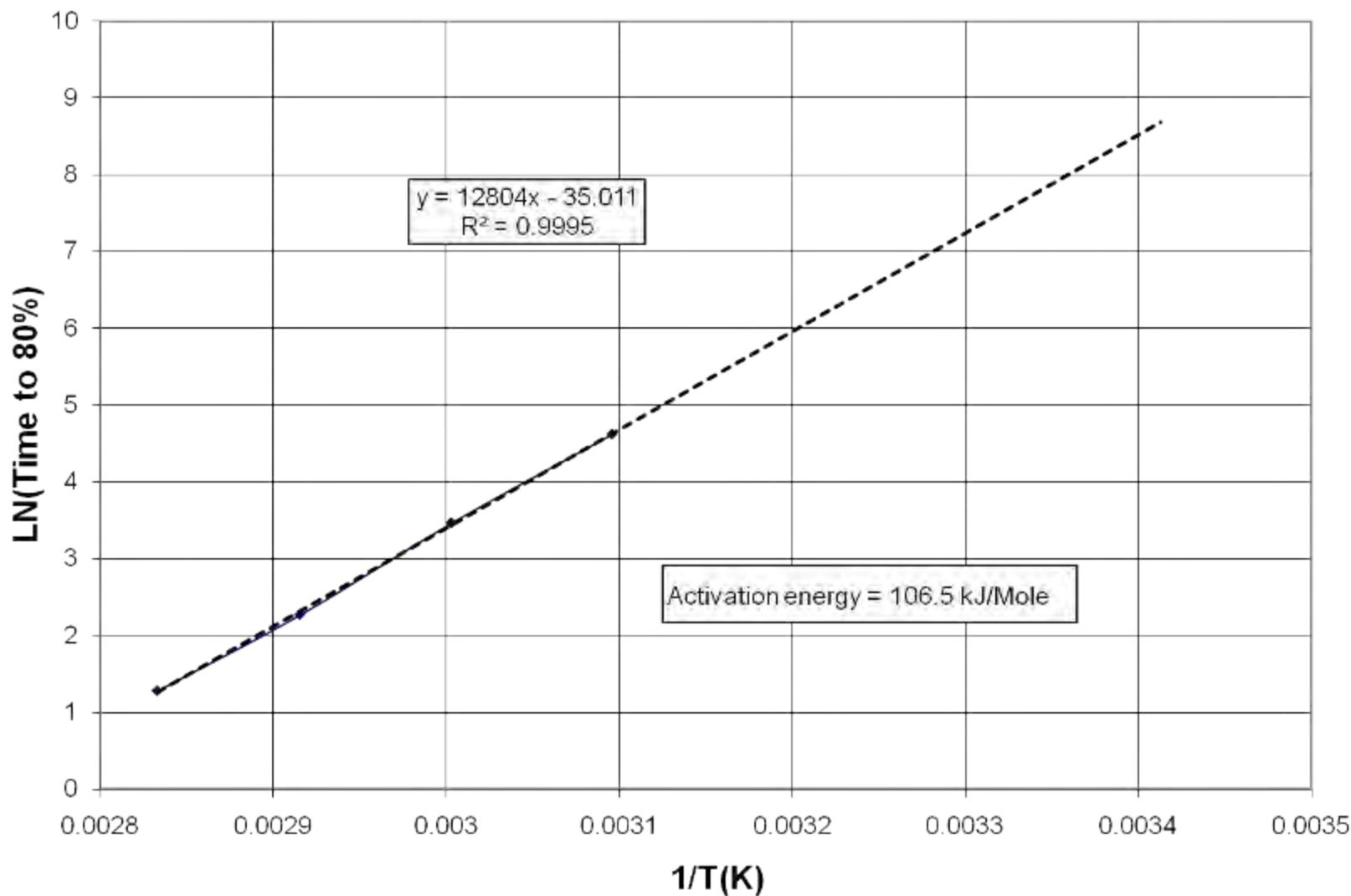
Construct Arrhenius Plot

- Plot $\ln(\text{Time to } 80\%)$ against $1/\text{Temperature}$
 \ln is the natural logarithm
 - Temperature is in degrees Kelvin
- If Arrhenius relationship is followed the graph will be a straight line
- Slope will be equal to E_a/R
 - E_a is the activation energy
 - R is the gas constant

Arrhenius Plot Based on a 20% Decline in Burst Pressure



Arrhenius Plot Based on a 20% Decline in Burst Pressure



Calculate Shift Factors

$$T_{(Ref)} = T_{(Age)} \times Shift\ Factor$$

$$Shift\ Factor = Exp\left\{E_a\left(\frac{1}{T_{(Ref)}} - \frac{1}{T_{(Age)}}\right)/R\right\}$$

Arrhenius Shift Factors Relative to 30°C

Activation energy = 106.5
kJ/mole

Temperature (°C)	Shift Factor
80	397.6
70	138.1
60	45.0
50	13.7

Equivalent times at 50°C

Activation energy = 106.5
kJ/mole

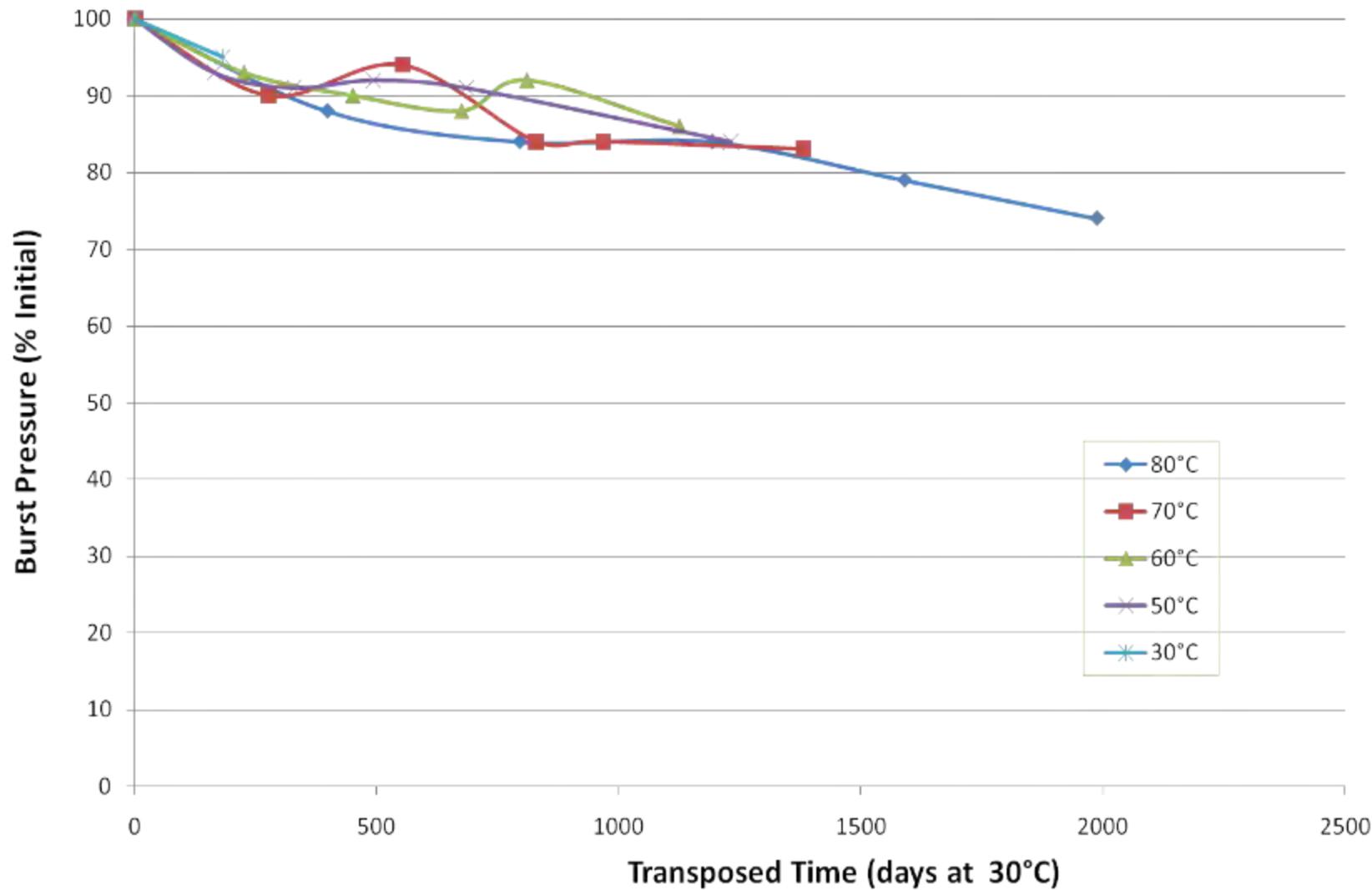
Time at 30°C (Years)	Time at 50°C (Days)
1	27
2	53
3	80
4	107
5	133

Construction of Time-Temperature Superposition Plot

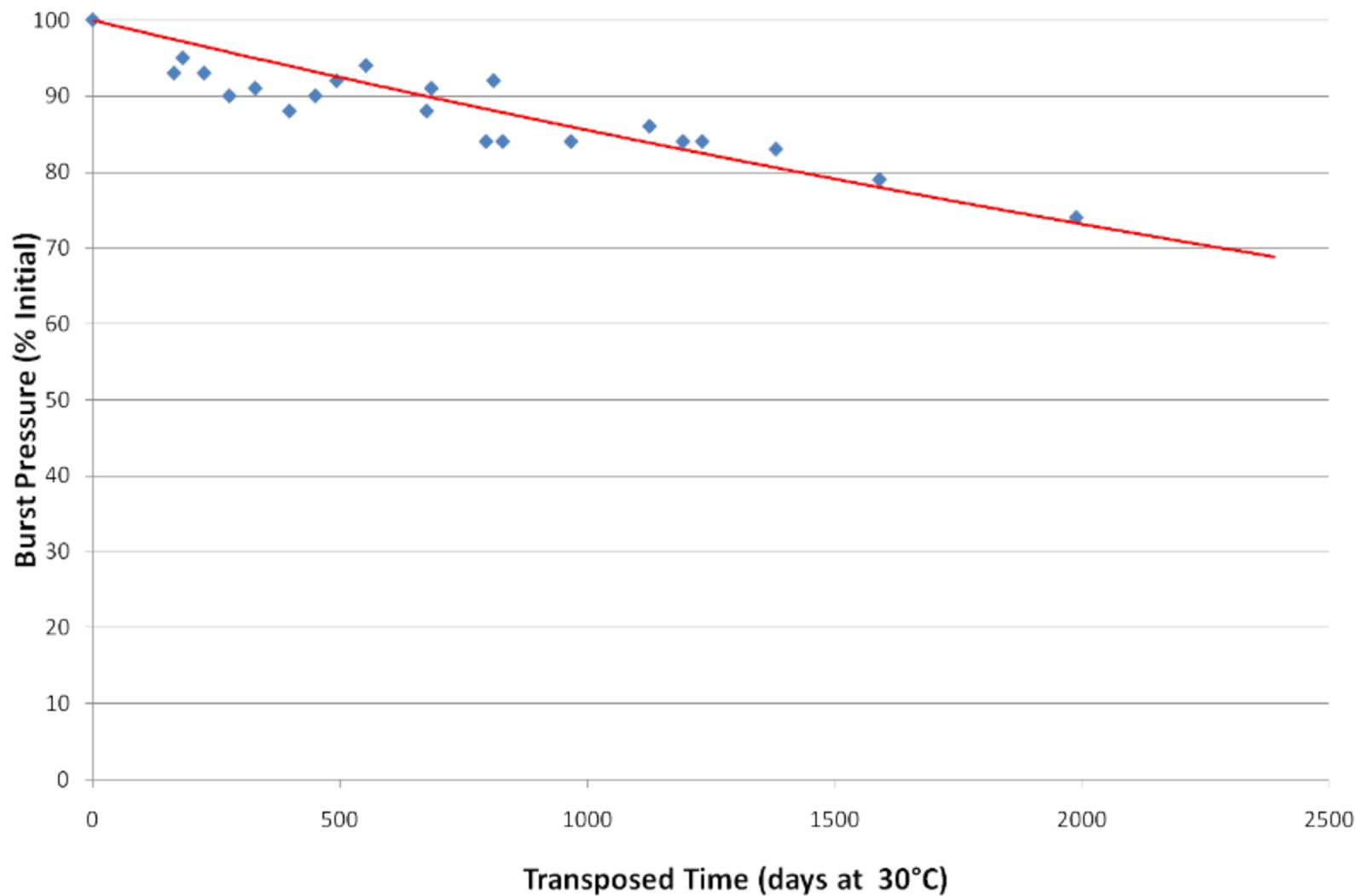
Temperature = 80°C, Shift Factor = 398

Time (Days)	Time x Shift Factor(days)	Burst Pressure (% Initial)
0	0	100
1	398	88
2	785	84
3	1193	84
4	1590	79
5	1988	74

Time-Temperature Superposition Plot



Time-Temperature Superposition Mater Curve



Conclusion

- Arrhenius plots and time-temperature superposition plots allow:
 - Provision shelf life to be estimated
 - Selection of aging temperature and time to verify provisional shelf life estimate

Shelf Life History

Previous Requirements

- Initially, condoms were assumed to behave much like other rubber articles.
- It was believed that oven conditioning at 70°C was like real life, accelerated.
- Seven days at 70°C was assumed to be similar to five years at room temperature. In fact, the EN standard of 1996 used two days at 70°C to imply a five-year shelf life (for Europe).
- The standards were ambiguous about the meaning of shelf life.
- Even when a manufacturer was required to indicate expiration date on the pack, the meaning was not defined.
- It was not made clear whether standards were expected to apply until the expiration date, only when the condoms were new, or for the first 12 months.
- Some standards explicitly stated that oven aging did not apply to products over 12 months old.
- In the 1980s, PATH demonstrated that condoms with very low burst volumes were likely to break in use.
- Up to the mid-1990s, ASTM and WHO required only the manufacturing date (shelf life was assumed by WHO to be site-dependent).
- Oven conditioning for as little as two days at 70°C was assumed to be an assurance that the condoms would last five years.
- Some standards required an expiration date, but did not define it.
- In the 1980s, in response to obvious problems with product quality, PATH introduced the CDI, then the CQI, to measure the quality of condoms in the distribution chain.
- Inflation and leaks requirements on new condoms were gradually tightened.
- WHO required Al foil packs and a package seal test.
- In the 1990s, PATH undertook a major study of condom deterioration.
- At the same time, ISO and WHO began requiring expiration dates on packs.
- FHI conducted a breakage trial of condoms of different age and burst volume, finding that condoms with lower burst volume broke more often.

Current Requirements

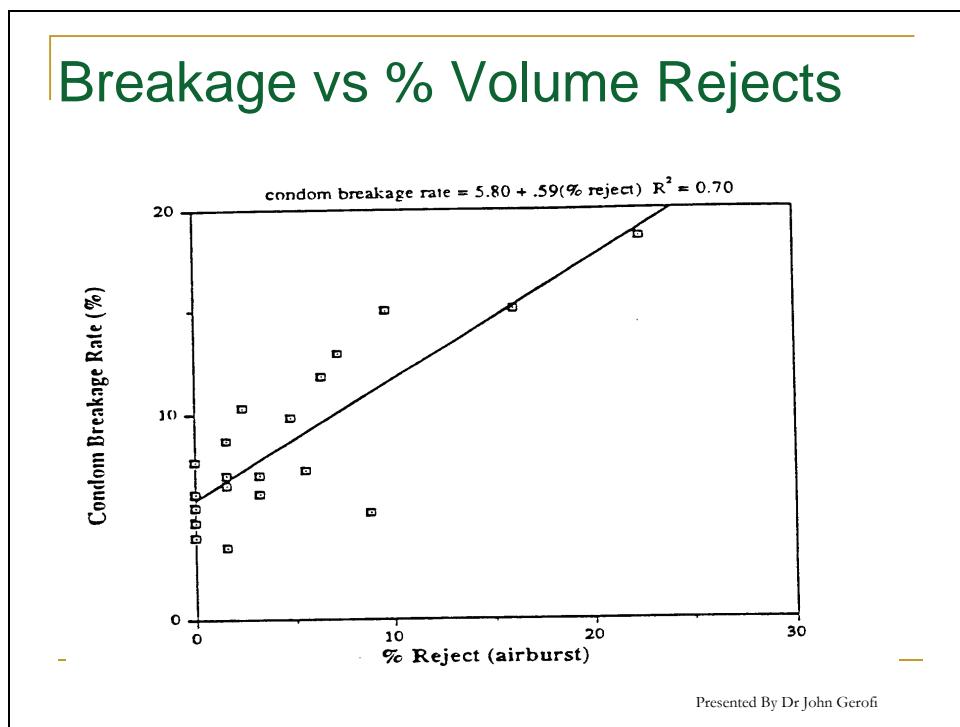
- In 1997, the USFDA introduced requirements for a type test after aging at 40° to 50°C for 90 days, and a real-time test requirement at 15° to 30°C.
- ISO 4074:2002 explicitly states that the condoms must meet the inflation requirements until the expiration date, and requires a real time test at 30°C.
- The 2003 WHO Specifications call up the technical requirements of ISO 4074.
- Thus products purchased to these documents must meet the inflation requirements (but not leaks—yet) until they expire.

Basis of Shelf Life Model

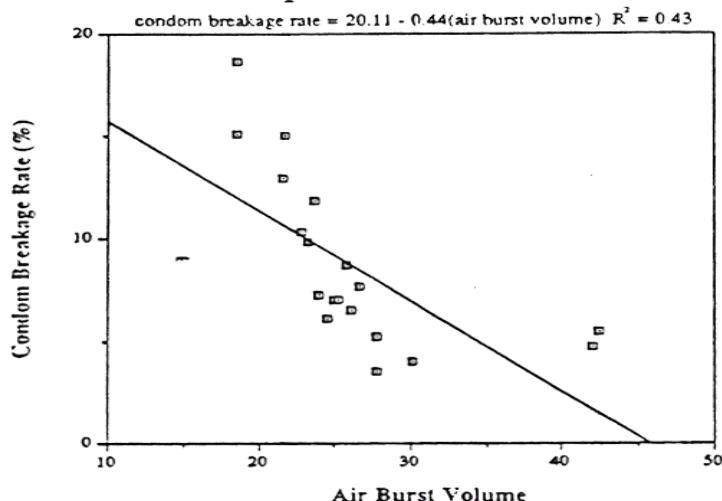
- Physical parameters (currently burst volume and pressure) are used as the sentinel variables for deterioration.
- The cause of deterioration is assumed to be a chemical reaction, which can be monitored by the burst properties.

Clinical Basis for Using Volume

- In 1980 to 1986, PATH did trials in Indonesia that showed condoms with (very) low burst volumes tended to break in use—also that UV exposure causes burst volumes to fall.
- In 1991, Family Health International measured breakage rates as a function of inflation and tensile properties.
- Also, old condoms broke more often than new ones (but older condoms had lower burst volumes).



Breakage vs Mean Volume



Conducting a Real-Time Shelf Life Study

Background

- ISO 4074 requires a real-time study on three batches.
- The study should be repeated if there is a significant change to the formulation or process.
- Different lubricants, pigments, flavors, and packs (or even shapes) may change the shelf life.

Study requirements

- A room held at 30°C (28°C to 35°C) for the entire study.
- Define the date of manufacture.
 - Dipping or foiling
- Decide maximum desired shelf life:
 - WHO requires three years minimum, five years maximum.

Conducting the study

- Test a relatively small number of condoms (30 to 50) at selected intervals to determine the trend of burst properties over time.
- When it looks as if the product may be reaching its limit, do an inflation and full holes test per ISO 4074 to verify that it still passes.
- You should have enough samples to do the full test at least twice, in case you want to extend by one time interval.

Determining the end point

- Good-quality condoms have a near-normal pressure/volume distribution.
- ISO 4074 has a maximum shelf life of five years.
- Toward the end of the shelf life, test every six months.
- Calculate the expected number of noncompliers from the mean and standard deviation.
- 1.5% of the distribution can be below the limit.
- Assume a normal distribution.
- You can use the normal distribution and the value of the standard deviation to calculate what the expected number of noncompliers will be.
- Build in a safety margin—do not push the shelf life to the limit where the product would really fail.

Conducting an Accelerated Shelf Life Study

Background

- ISO suggests using the Arrhenius equation.
- Generally, this approach is applied only to the pressure, because its behavior usually follows the expected trends.
 - Pressure decreases with increasing temperature and time.
- If you follow this approach, you risk overestimating the shelf life.

Conducting the study

- The traditional method of applying the Arrhenius equation is to use ISO 11346.
- Choose a percentage drop in pressure (e.g., 20%).
- Determine the time (t) taken to reach 20% drop for each of several temperatures (T).
- Plot a graph of $\ln t$ vs $1/T$ (T in Kelvin).
- Extrapolate back to $T=30^\circ\text{C}$ (303K).
- This gives time taken for mean to drop by 20% at 30°C .
- Must now translate to a pass/fail decision, based on pressure distribution.

Alternative approaches

- ISO 4074/16038 suggests an alternative approach using a known activation energy of 83 kJ/mole.
- With this assumption, it is possible to calculate a time multiplier for each elevated temperature.
- One week at 70°C is like 50 weeks at 30°C .
- Gives a multiplier of 50.
- Pressure decay at all temperatures can thus be plotted on one graph using these time multipliers, with the X axis showing time at 30°C .
- If you want to make a relatively small change to an existing formulation for which you know the shelf life, you can compare the elevated temperature results for the old and new formulations.
- Use at least two temperatures, including the lowest temperature that can be completed in a reasonable time (e.g., 50°C).
- If the result is at least as good for the new formulation at both temperatures, you can assume it will be OK at 30°C .

First approximation using elevated temperatures

- Use results obtained at 50°C , and extrapolate back to 30°C .
- The time-temperature correspondence depends on the product, but typically about 120 days at 50°C is about three years at 30°C .
- This approach is simpler and sounder than full application of several elevated temperatures as described in ISO 4074/16038.

More accurate accelerated aging

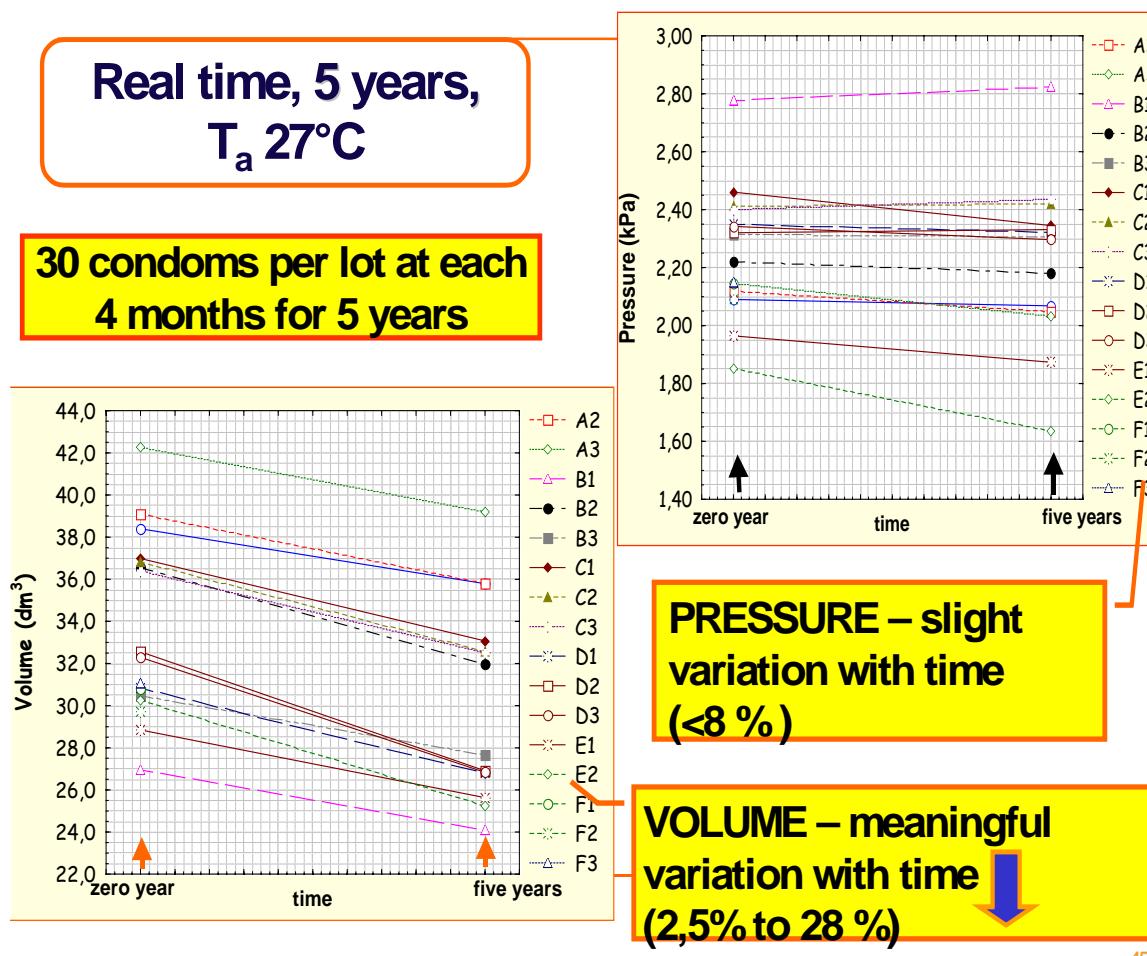
- Must analyze decay of volume and pressure separately.
- Can use the Arrhenius equation.
- Best to use statistical correlation to determine activation energy (E).
- For some products, high temperature data must be excluded, because it varies in the opposite direction from the real-time data.

Problems with using elevated temperatures

- At 60°C and 70°C, the burst volume may remain relatively unchanged, while at room temperature, it almost always decreases.
- Thus, the direct use of pressure alone in the Arrhenius equation does not describe the behaviour of the volume well.
- However, it is usually the drop in volume that determines the shelf life.

Data from Brazil Study – by Dr M C Bó

The graphs below summarise a shelf life study done in Brazil over the period 2000-2006.



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The curves above show the behaviour of 16 different lots of condoms, from 6 manufacturers (A to F) over 5 years at approximately 27C.

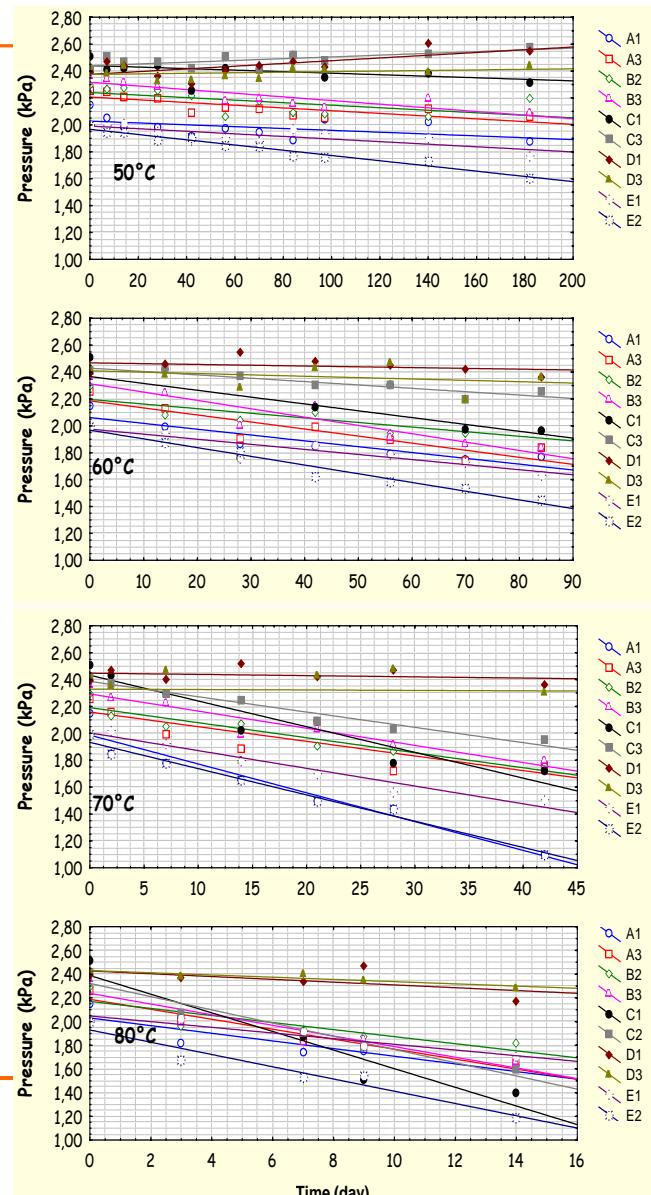
For the pressure, most lots showed very little variation in pressure over the time. Some increase very slightly, some decrease very slightly, and one (E2) dropped by 8% over 5 years.

For the volume, all means decreased over the 5 years. The extent of the change varied depending on the products and lots.

Accelerated aging (50°C, 60°C, 70°C, 80°C)

**Analysis of trends
assuming linear
behavior with time**

**INCREASE of
TEMPERATURE
INCREASES the
variation in PRESSURE**



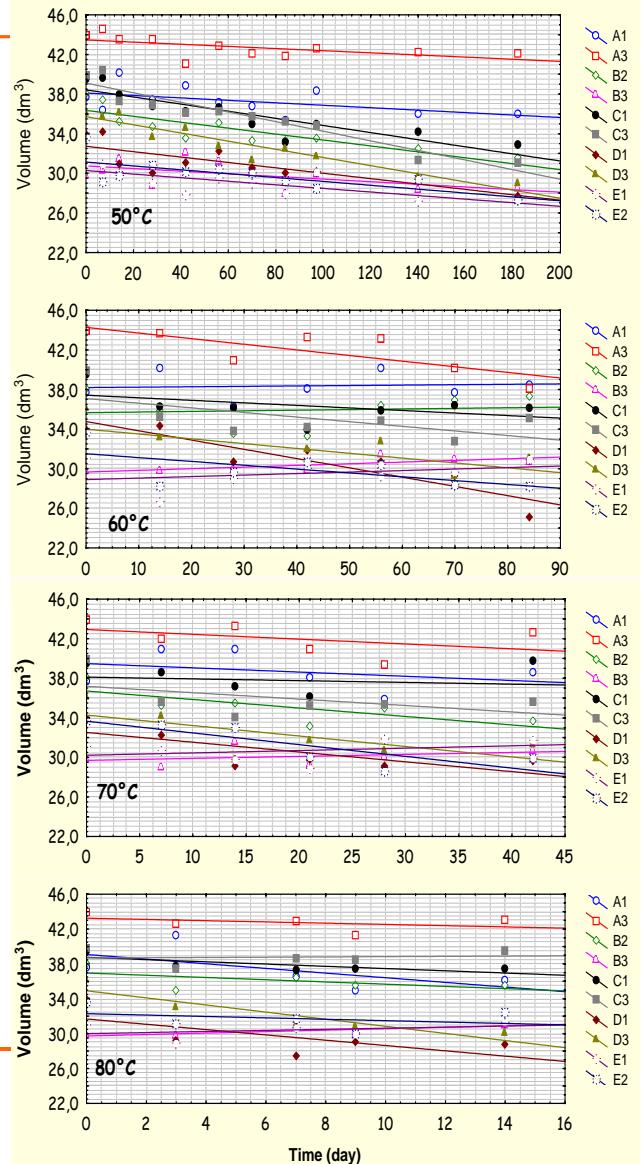
These graphs show how pressure varies with time at elevated temperatures (50, 60, 70 and 80C).

The higher the temperature, the more the decline of pressure with time. At 50C, some products show an increase of pressure with time (like the 27C curves). By 60C, all brands show declining pressure with time. The rate of decline increases with increasing temperature.

Accelerated aging (50°C, 60°C, 70°C, 80°C)

**Analysis of trends
assuming linear
behavior with time**

**INCREASE of
TEMPERATURE
REDUCES the
variation in VOLUME**



These graphs show the variation of volume with time at elevated temperatures (50, 60, 70 and 80C)

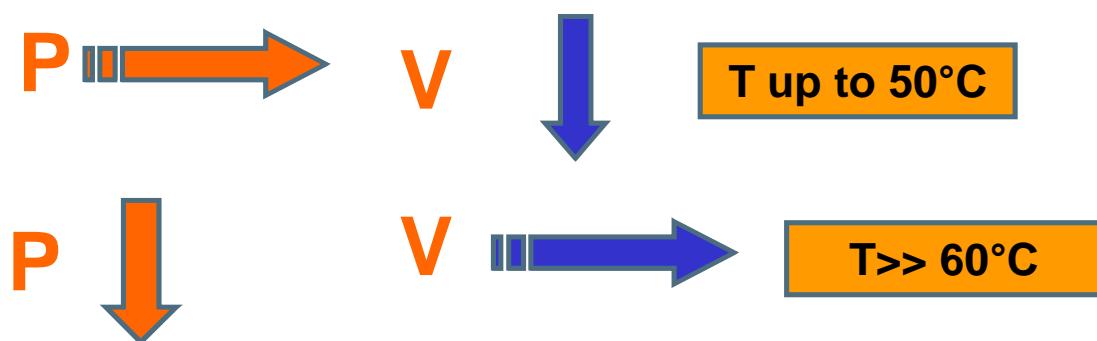
The time scales used are the same as for the pressure case.

The volume changes decline with increasing temperature, compared with what happens to pressure.

In the 80C case, the volumes of many of the products remained unchanged over 2 weeks, while the pressures all declined significantly over the same period.

Compare this with the real time graphs, where the volumes all decline with time, and some of the pressures increase (over 5 years).

At 50°C, the behaviour of P and V tends to follow the same trends as at ambient temperature = 27°C



The results suggest that the behaviour of P and V are different, and that the degradation of these properties needs to be treated separately.

Presented By Dr John Gerofi

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It appears that a simple equivalence could be possible between an aging time at 50C and aging time at room temperature, because the trends in P and V are the same at both temperatures.

Thus in principle, a prediction of shelf life may be possible by looking at the behaviour of the product at 50C, for some fraction of the intended shelf life.

Higher temperatures show the volume and pressure trending in the opposite direction from the way they change at room temperature in several cases, so a simple scaling factor relating life at room temperature and at, say, 70C is difficult to define.

On the other hand, more accurate predictions can be made by treating the volume and pressure variations completely separately, and calculating separate reaction parameters for each. This method uses separate Arrhenius models for volume and pressure, and uses all the high temperature data, except where it is overtly varying in a different direction from the room temperature variation.

Estimated parameters - PRESSURE – Individual lots					
Lot	P_0 experimental (kPa)				
		P_{0c} (kPa)	E (kJmol ⁻¹)	A	R
A1	2,15	2,05	122	-6,2	0,86
B2	2,29	2,21	121	-6,2	0,86
C1	2,51	2,43	139	-5,8	0,90
E2	1,99	1,96	94	-4,2	0,95

Combined model (N=320)		
E (kJmol ⁻¹)	A	R
112	-5,57	0,83

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E is the activation energy in Arrhenius eqn, A is the constant in the Arrhenius eqn

R is the correlation coefficient when all possible data points at all temperatures are included.

Results for Arrhenius model for Volume using all possible data.

The examples below are for 4 of the 16 lots.

The combined model is a composite model combining the data from all four lots

Estimated parameters for VOLUME – Individual lots					
Lot	V_0 experimental (dm ³)	V_{0c} (dm ³)	E (kJmol ⁻¹)	A	R
A3	43,8	43,8	72	-3,3	0,65
B2	38,1	35,6	68	-4,3	0,30
C3	39,9	37,8	64	-3,3	0,65
E2	33,6	31,6	58	-3,5	0,75

Combined model (N=278)		
E (kJmol ⁻¹)	A	R
73	-2,8	0,77

Prediction of shelf life (typical values)

Relationship of time and temperature for predicting shelf life (based on Arrhenius eqn)

$$\frac{t_2}{t_1} = e^{\frac{E}{R} \left[\frac{1}{T_2} - \frac{1}{T_1} \right]}$$

Times needed for volume are longer than those for pressure.

PRESSURE (E= 112 kJmol ⁻¹)					VOLUME (E= 74 kJmol ⁻¹)				
T ₂ =	80°C	70°C	60°C	50°C	T ₂ =	80°C	70°C	60°C	50°C
T ₁ = 27°C	t ₂ in days				T ₁ = 27°C	t ₂ in days			
t ₁ = 3 yrs	1	4	13	45	t ₁ = 3 yrs	13	27	59	134
t ₁ = 5 yrs	2	7	22	75	t ₁ = 5 yrs	22	45	98	224

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The tables above assume a shelf life of 5 years at 27°C, and show how the shelf lives determined by the separate Arrhenius models would vary as the temperature is changed.

Influence of Temperature on degradation rate

PRESSURE DEGRADATION				
Shelf life, years				
lot	27°C	32°C	37°C	42°C
A1	31	15	7	3
B1	44	21	10	5
C3	33	16	7	3
D2	30	14	7	3
E1	28	13	6	3
F3	29	14	7	3

VOLUME DEGRADATION				
Shelf life, years				
lot	27°C	32°C	37°C	42°C
A1	9	5	3	2
B1	1	0	0	0
C3	5	3	2	1
D2	5	3	2	1
E1	4	5	2	1
F3	7	4	2	1

Requirements of standard:

$$P > 1 \text{ kPa} \quad \& \quad V > 18 \text{ dm}^3$$

$$P_f = 1 + 2,33\sigma \quad V_f = 18 + 2,33 \sigma$$

$\sigma = \text{SD of } P_0 \text{ or } V_0$ (assuming a normal distribution)

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The table above shows the shelf life determined for 6 of the 16 lots at 27C and at 32, 37 and 42C, using the separate Arrhenius models for volume and pressure.

The life as determined by declining volumes is clearly shorter than that determined from the pressure in all cases, but the effect of temperature on the shelf life is greater on the pressure than on the volume.