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Technical Information Report

AAMI TIR17:1997

Radiation sterilization—Material qualification

AAMI
Association for the Advancement of Medical Instrumentation

AAMI TIR No. 17—1997

Radiation sterilization—Material qualification

Approved 4 August 1997

Abstract: This AAMI Technical Information Report (TIR) details steps necessary to assess compatibility of health care product and packaging materials with radiation sterilization processes. Guidance is provided on selecting appropriate materials, choosing processing protocols that optimize product performance, and material testing as part of a qualification program. An extensive review of accelerated aging techniques is also included. Companion document to ANSI/AAMI/ISO 11137:1994.

Keywords: sterilization, radiation, material qualification, accelerated aging, health care products, real time aging

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Comments on this technical information report are invited and should be sent to AAMI Standards Program, 3330 Washington Boulevard, Suite 400, Arlington, VA 22201-4598.

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FOREWORD

Guidance for device and packaging materials qualification for radiation sterilization is given in annex A of ANSI/AAMI/ISO 11137—1994, *Sterilization of health care products—Requirements for validation and routine control—Radiation Sterilization.* This AAMI Technical Information Report (TIR) was developed to provide additional guidance in order to improve the quality and reduce the costs and time required for performing material qualifications.

This TIR contains guidelines that are not intended to be absolute or to be applicable in all circumstances. Judgment should be used in applying the information in this TIR.

NOTE—This technical report is considered "informative," and use of the terms "shall," "should," etc., should be considered within the context of this technical report only. That is, if the decision is made to use a material qualification protocol contained within, then the method should be followed in adherence with the requirements ("shall") and recommendations ("should") as set forth in this technical report.

INTRODUCTION

ANSI/AAMI/ISO 11137—1994, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization*, specifies the requirements for ensuring that the activities associated with the process of radiation sterilization are performed properly. One of the activities encompassed within the standard is the evaluation of the effect of radiation on the materials that make up the product and packaging. A program to demonstrate the quality, safety, and performance of the materials throughout their shelf life or expiration date shall be performed. Testing shall include any specific properties essential to the intended function of the product. The test program should address variations in raw materials, manufacturing processes, radiation sources, radiation doses, storage conditions, and associated tolerances.

An informative annex to ANSI/AAMI/ISO 11137—1994 (annex A) provides information on design principles, lists of compatible materials to aid in the material selection process, biocompatibility testing standards, and brief guidance on aging programs. There have been numerous requests from the health care manufacturing industry to expand the information provided on materials compatibility. Therefore, this document was developed to expand the guidance.

Material qualification begins with the selection of appropriate materials (see 4). These materials should be processed in ways that optimize product performance (see 5). Note that while radiation sterilization might adversely affect the properties of some materials in some applications, these effects can be minor in comparison to adverse effects resulting from poor choice of processing parameters.

Testing materials is the next step in a qualification program (see 6). The first step toward effective material testing is to define product functional and safety requirements. Defining tests that challenge those requirements and acceptance criteria for those tests follow.

The final step in a qualification program is to ensure that the product meets the acceptance criteria throughout its shelf life. This may be accomplished via an accelerated aging program (see 7). Two accelerated aging programs are described—the fixed aging factor method and the iterative aging factor method (see 7.5).

RADIATION STERILIZATION—MATERIAL QUALIFICATION

1 Scope

The focus of this document is to provide guidance for the qualification of polymeric materials in health care products that are sterilized by radiation (gamma, electron beam, or x-ray).

Guidance provided is related to material:

a) Selection—choosing radiation compatible materials (see 4).

b) Processing—optimizing functional performance of materials selected; to avoid processing errors that can contribute to negative effects from radiation sterilization (see 5).

c) Testing—challenging critical aspects of the product for functionality and safety after sterilization and aging (see 6).

d) Accelerated aging—applying accelerated aging programs that ensure correlation with real time aging while reducing the cost and amount of time required for material qualifications (see 7).

2 Normative references

The following standards contain provisions, which, through reference in this text, constitute provisions of this TIR. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this TIR are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below.

ANSI/AAMI/ISO 11137—1994, *Sterilization of health care products—Requirements for validation and routine control—Radiation sterilization.*

ANSI/AAMI/ISO 11607—1997, *Packaging for terminally sterilized products.*

ANSI/AAMI 10993-1—1994, *Biological evaluation of medical devices—Part 1: Evaluation and testing.*

ISO/DIS 14538, *Method for the establishment of allowable limits for residues in medical devices using health based risk assessment.* (in development)

ISO/TR 8550:1994, *Guide for the selection of an acceptance sampling system, scheme or plan for inspection of discrete items in lots.*

3 Definitions, symbols, and abbreviations

For the purposes of this TIR, the following definitions and abbreviations related to aging apply.

3.1 Aging definitions

3.1.1 real time aging (RT): Storage of health care products at ambient conditions in order to evaluate functional properties over time.

3.1.2 accelerated aging (AA): Storage of health care products at elevated temperatures and/or at other intensified environmental conditions in order to simulate real time aging in a shorter amount of time.

3.1.3 T: Symbolizes temperature, measured in degrees Celsius, utilized in aging studies.

NOTE T_{RT} and T_{AA} symbolize real time and accelerated aging temperatures, respectively.

3,1,4 t: Symbolizes time, over which aging studies are conducted.

NOTE t_{RT} and t_{AA} symbolize the storage time over which real time and accelerated aging studies have been conducted.

3.1.5 real time equivalent (RTE): Amount of real time to which given accelerated aging conditions are estimated to be equivalent.

NOTE For example, if AA samples are held at an elevated temperature for 6 months and the aging factor (AF_0) for the system has been estimated to be 2, then the RTE is 1 year:

RTE $= t_{AA} \times AF_0$
$= 6 \text{ months} \times 2$
$= 1 \text{ year}$.

3.1.6 time zero (t_0): Starting time of any timed investigation, experiment, or study.

NOTE In this TIR, t_0 is the time of commencement of an aging study.

3.1.7 aging factor (AF): Ratio of time between T_{RT} and T_{AA} that is estimated or calculated to achieve the same level of functional degradation of the health care product in real time as that observed under accelerated aging.

3.1.7.1 AF_0: Initial estimate of AF.

NOTE For example, $AF_0 = 2^3 = 8$ is commonly used when a temperature 30° C higher than ambient is used for the accelerated aging study (based on a $Q_{10} = 2$[see Q_{10} definition]).

3.1.7.2 AF_1: First iteration of AF_0 based on initial real time data.

3.1.7.3 AF_2, AF_3, etc.: Subsequent iterations of AF_0 based on additional real time data.

3.1.8 Q_{10}: Symbol used to express the expected or observed change in the rate of a reaction occasioned by a 10° C change in reaction thermal environment.

NOTE $Q_{10} = 2$ is a common and conservative estimate for most polymer systems.

3.1.9 S: Symbolizes the slope of the plot of the aging curve for chosen parameters under study. Thus S(RT), S(AA), and S(RTE) are the slopes of real time, accelerated aging, and real time equivalent (i.e., accelerated aging data modified by the aging factor) curves, respectively.

3.1.10 shelf life: Length of time that a product can remain at the typical storage conditions prior to use without having an unacceptable effect on its functionality and biocompatibility or the length of time chosen for its expiration.

3.2 Statistical definitions

3.2.1 variable data: Data that have a numerical value (not attribute data).

3.2.2 attribute data: Pass/fail data; go/no go data

NOTE No numerical value is associated with the data.

3.3 Miscellaneous definitions

3.3.1 materials qualification dose (D_{QUAL}): Maximum radiation dose at which the functional integrity of the health care product or its components has been demonstrated.

3.3.2 T_m, T_g: Melt temperature and glass temperature, respectively; two common thermal transitions of polymeric materials.

3.3.3 absorbed dose: Quantity of radiation energy imparted per unit mass of matter.

NOTE The unit of absorbed dose is the gray (Gy) where 1 gray is equivalent to absorption of 1 joule per kilogram.

3.3.4 dose: See absorbed dose.

3.3.5 material biocompatibility: Lack of an adverse health effect from exposure to materials from which a device is made or in which a device is packaged.

3.3.6 functionality: Performance of a product from the perspective of its physical properties, rather than the perspective of biocompatibility.

3.3.7 health care product: Term encompassing medical devices, medicinal products (pharmaceuticals and biologics) and *in vitro* diagnostics.

NOTE In this document, the term health care product, or product, refers to the finished medical device and/or additional components with the final package.

4 Material selection

NOTE Knowledge about radiation-induced effects can help in the appropriate selection of polymers, which can in turn lead to successful and cost-effective validation programs. Background fundamentals about polymers and associated radiation effects can be found in annex A.

4.1 Functional compatibility

4.1.1 General

The loss of functional properties is often the most important characteristic effect of polymer irradiation. Properties affected may include tensile strength, impact strength, shear strength, and elongation, among others. The influence of radiation on these properties and the general performance of a polymer (including physical properties, odor, and color) differs depending on whether a polymer scissions (causing reduced toughness and elongation) or cross-links (causing increased strength and stiffness). All materials break down at very high radiation doses; however, below the destructive level of exposure, radiation treatment can enhance properties and impart benefits of commercial value. The dose range in which a given plastic maintains its valuable properties depends greatly on the chemical structure of the polymer. Thus, the dose necessary to produce similar significant physical property changes in two different polymers could vary from as low as a few kilograys to as high as hundreds or thousands of kilograys (see below).

Database and literature sources, in combination with experience, can be employed to identify potential radiation-induced problems with materials that are less radiation resistant than required for the particular product design and function. The majority of polymers are radiation stable at the doses typically used in the radiation sterilization of health care products. However, radiation stability of any polymer may vary significantly depending on:

a) residual or functional stress (processing, part design and function);

b) product cross-section thickness (films, coatings, and fibers);

c) molecular weight;

d) morphology (e.g., percent crystallinity);

e) environment during irradiation, storage, and use (e.g., oxygen, temperature, and moisture);

f) dose rate (i.e., gamma, x-ray, or electron beam);

g) radiation dose absorbed.

Therefore, all polymer selections should be thoroughly challenge-tested in the specific application and processing conditions under consideration.

Table 1 (polymer families) and table 2 (individual polymers) summarize a great deal of the information available from government, industrial, and scientific studies and publications concerning radiation effects on polymer properties after exposure to various doses. These tables graphically display the dose at which a number of common thermoplastics and thermosets experience a 25% loss in elongation. Loss of elongation is a commonly used measure of the effect of irradiation. These tables provide a visual means of making an

initial estimate of a polymer's ability to withstand a particular radiation sterilization process. A more qualitative summary of the radiation stability of selected polymeric materials is given in Table 3—General guide to radiation stability of materials.

NOTE Metals and ceramics are excluded from these tables due to their inherent stability at sterilization doses.

4.1.2 General functional guidelines

Selection of materials should start with the following basic radiation application guidelines:

a) Most polymers are durable at the radiation doses typically employed for sterilization of health care products. Exceptions may be products that are under significant functional stress or are constructed from those few polymers (e.g., polyacetal, unstabilized polypropylene, and polytetrafluoroethylene; see tables 1, 2, and 3) that are significantly degraded at these doses. Like all materials, these should be carefully evaluated over the product's shelf life.

b) All polymers both scission and crosslink; those that crosslink more than they scission generally do better in the radiation environment.

c) Aromatic materials are more radiation resistant than aliphatic materials. The benzene ring structure present in aromatic polymers acts as a stabilizer, rearranging itself to accept or donate an electron as needed. Examples of aromatic polymers are styrene, polyester, polycarbonate, and polysulfone.

d) Antioxidants and UV stabilizers improve radiation resistance; the impact of these additives on biocompatibility should be considered.

e) The highest molecular weight material possible for the application (with the most narrow molecular weight distribution) should be used.

f) Amorphous materials provide better radiation enhancement when compared to semicrystalline materials. Likewise, for semicrystalline materials, higher amorphous content provides better radiation enhancement. (NOTE—The exception to this guideline is highly crystalline [> 95% crystallinity] materials which generally have high radiation resistance due to the dominance of their strong, nested, compact, and mutually reinforced polymer chains.)

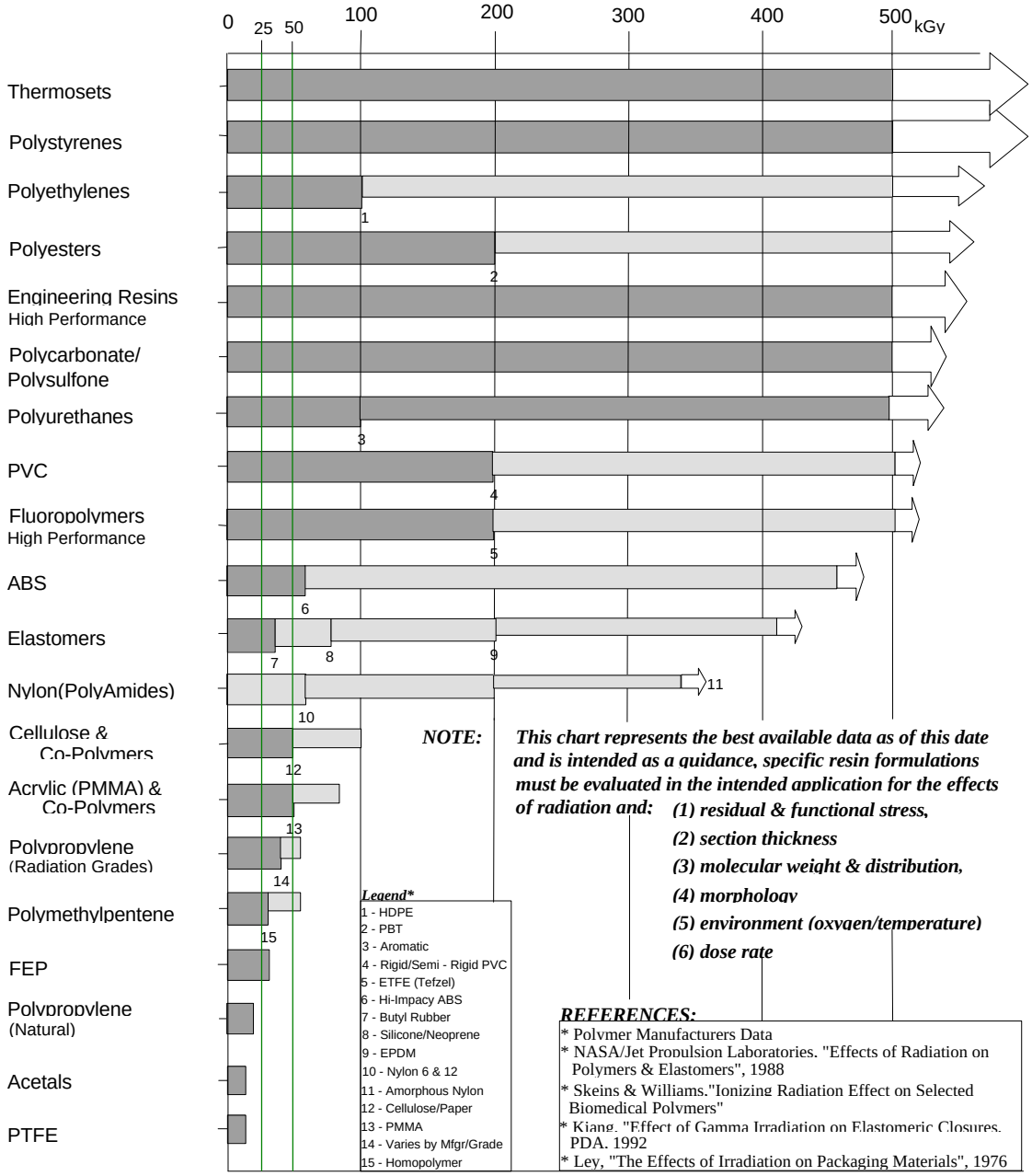
g) Materials with low O_2 permeability are more radiation resistant.

h) Materials utilized in thin films and fibers should be selected with caution due to the enhanced effect of oxidation resulting from the large surface-to-mass relationship.

i) Effects of radiation on polymers are generally cumulative with each subsequent exposure of a product.

Table 1 - Relative Radiation Stability of Medical Polymer "Families"

Dose (Kilogray) in Ambient Air at which Elongation Decreases by 25%

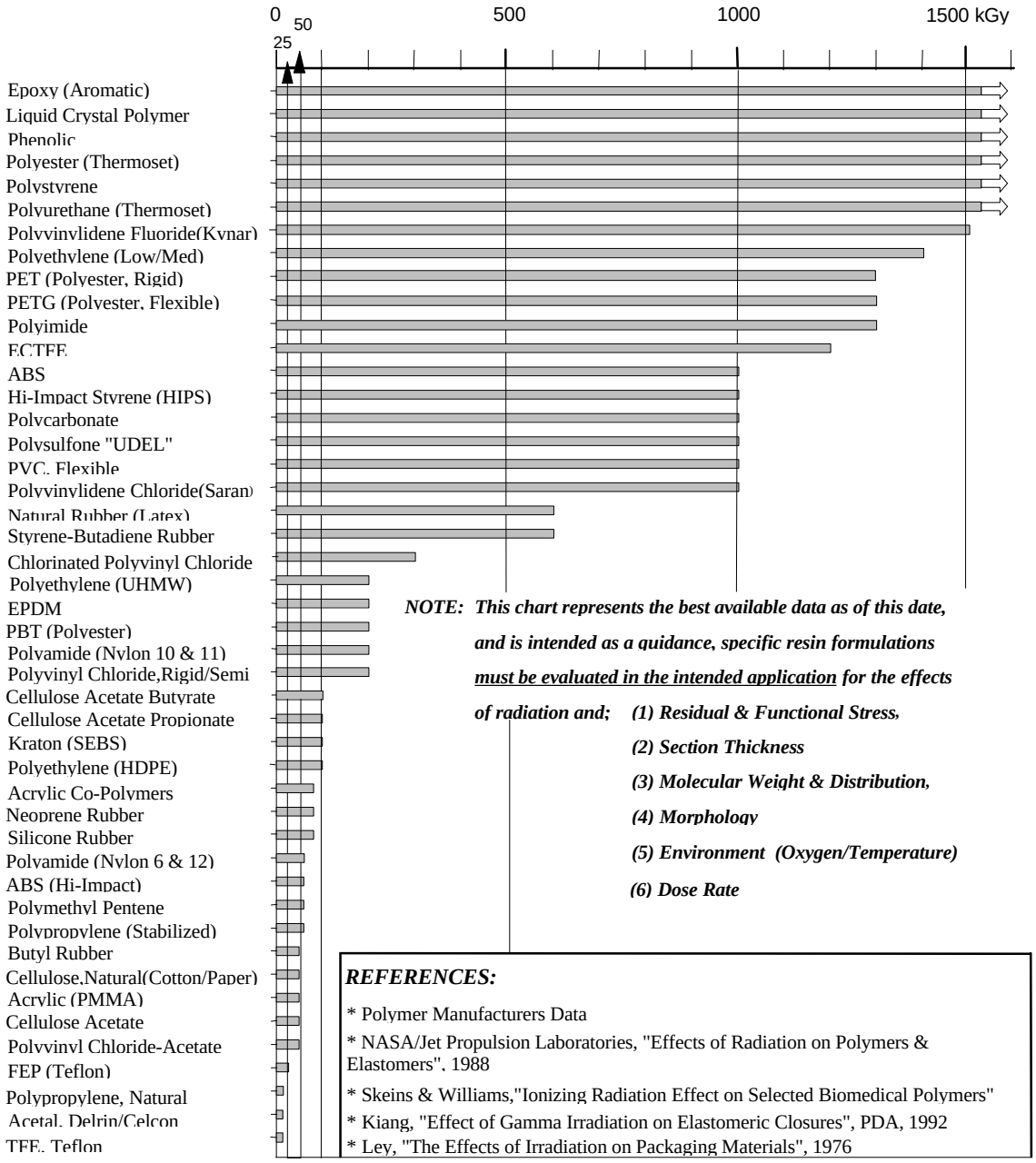


* - Within each family is a range of radiation stabilities, the "steps" are intended to show significant family members

Courtesy of Karl J. Hemmerich, Ageless ProcessingTechnologies

Table 2 - Relative Radiation Stability of Medical Polymers

Dose (KiloGray) in Ambient Air at Which Elongation Decreases by 25%



Courtesy of Karl J. Hemmerich, Ageless ProcessingTechnologies

Table 3—General guide to radiation stability of materials

MATERIALS	RADIATION STABILITY	COMMENTS
Thermoplastics		
ABS	Good	High impact grades are not as radiation resistant as standard impact grades.
Acrylics (PMMA)	Fair–Good	
Cellulosics Esters Cellulose acetate propionate Cellulose acetate butyrate Cellulose, paper, cardboard	 Fair Fair Good–Fair Fair–Good	Esters degrade less than does cellulose.
Fluoropolymers Polytetrafluoroethylene (PTFE) Perfluoro Alkoxy (PFA) Polychlorotrifluoroethylene (PCTFE) Polyinyl fluoride (PVF) Polyvinylidene fluoride (PVDF) Ethylene-Tetrafluoroethylene (ETFE) Fluorinated ethylene propylene (FEP)	 Poor Poor Good–Excellent Good–Excellent Good–Excellent Good Fair	When irradiated, PTFE and PFA are significantly damaged. The others show better stability. Some are excellent.
Liquid Crystal Polymer (LCP)	Excellent	Commercial LCPs; Natural LCPs not stable.
Polyacetals	Poor	Irradiation causes embrittlement. Color changes have been noted (yellow to green).
Polyamides (Nylon)	Good	Nylon 10,11,12,6-6, more stable than 6. Nylon film and fiber are less resistant.
Polycarbonate	Good–Excellent	Yellows—mechanical properties not greatly affected; color-corrected radiation formulations are available.
Polyesters	Good–Excellent	PBT not as radiation stable as PET resins.
Polyethylene, various density	Good–Excellent	HD not as stable as MD and LD.
Polyimides	Excellent	
Polyphenylene sulfide	Excellent	
Polypropylene, natural Polypropylene, stabilized	Poor–Fair	Physical properties greatly reduced when irradiated. Radiation stabilized grades, utilizing high Mw and co-polymerized and alloyed with polyethylene, should be used in most radiation applications; High dose rate electron beam may reduce oxidative degradation.
Polystyrene	Excellent	
Polysulfone	Excellent	Natural material is yellow.
Polyurethane	Excellent–Good	Aromatic discolors; polyesters more stable than esters. Retains physical properties.
Polyvinylchloride (PVC)	Good	Yellows—antioxidants and stabilizers prevent yellowing. High molecular weight organotin stabilizers improve radiation stability: color-corrected radiation formulations available.
Polyvinylchloride-Polyvinylacetate	Good	Less resistant than PVC.
Polyvinylidene dichloride (Saran)	Good	Less resistant than PVC.
Styrene/Acrylonitrile (SAN)	Good–Excellent	

Table 3—General guide to radiation stability of materials (continued)

MATERIALS	RADIATION STABILITY	COMMENTS
Elastomers		
Butyl	Poor	Friable, sheds particulate.
Chlorosulfonated polyethylene	Poor	
EPDM	Excellent	
Natural rubber	Good–Excellent	
Nitrile	Good–Excellent	Discolors.
Polyacrylic	Poor	
Polychloroprene (neoprene)	Good	Discolors; the addition of aromatic plasticizers renders the material more stable to irradiation.
Silicone	Good	Phenyl-methyl silicones are more stable than are methyl silicones. Platinum cured silicones are superior to peroxide cured silicones. Full cure during manufacture can eliminate most post-irradiation effects.
Styrene-butadiene	Good	
Urethane	Excellent	
Thermosets		
Allyl diglycol carbonate (Polyester)	Excellent	Maintains its excellent optical properties after irradiation.
Epoxies	Excellent	All curing systems.
Phenolics	Excellent	Includes the addition of mineral fillers.
Polyesters	Excellent	Includes the addition of mineral or glass fibers.
Polyurethanes Aliphatic Aromatic	 Excellent Good–Excellent	 Darkening can occur. Possible breakdown products could be derived.

Primary source: INTERNATIONAL ATOMIC ENERGY AGENCY. *Guidelines for industrial radiation sterilization of disposable medical products, Co 60 gamma irradiation.* TEC DOC-539. Vienna: IAEA, 1990.

4.2 Biocompatibility

A health care product should be adequately designed to assure biocompatibility for its intended end use after radiation sterilization and throughout its shelf life. In most situations, it is sufficient to demonstrate that the material(s) or product provides no significantly measurable or predictable biological hazard to the patient or user.

It has been observed that extracts from radiation-sterilized polymers may show increased turbidity and oxidizable substances, greater conductivity, and lower pH after compendial extraction studies when compared with other sterilization processes. However, the overall effects of radiation sterilization are assumed to be small, and failures in typically performed toxicity screening assays (e.g., those identified in ANSI/AAMI/ISO 10993-1) are not believed to be related to the radiation sterilization process alone. It is good practice, however, to screen materials for biocompatibility (see 6.2.2) early in the design process to identify potential biosafety issues that could lead to unnecessary redesign expense later in the process.

Material characterization is important to determine what substances are present and evaluate their potential to become bioavailable. Extractables from various plastics and rubbers are of primary concern. Most polymeric materials contain, in addition to relatively inert high molecular weight polymers, other

constituents such as solvents, binders, catalysts, additives, antioxidants and fillers. They are added at varying concentrations depending upon the material properties and processability desired; some additives may be included specifically to counter deleterious effects from the radiation sterilization process. In addition, the radiation sterilization process itself may generate low molecular weight byproducts from the polymer. All of these may migrate from the product into the human body and should be considered when assessing the safety of the product for human clinical use; biocompatibility testing (see 6.2.2) may play a role in this process.

Radiation sterilization of PVC is illustrative of potential biocompatibility issues related to the radiation sterilization of polymeric materials. With respect to low molecular weight byproducts, HCl is evolved in low concentrations from irradiation of PVC (Lappo, et al. [1991]; Landfield [1983]). Related to the leachability of additives, an increased rate of additive and plasticizer migration to the surface of thin-walled health care products has been observed after radiation sterilization (Yianni [1995]; Hong [1995]). The latter may result from the radiation-induced modification of the polymer matrix through cross-linking and scission reactions or from the breakdown of additives into smaller components that migrate more readily. For information regarding biocompatibility guidelines, see the normative reference ANSI/AAMI 10993-1 and the informative references listed in the bibliography.

5 Material processing

An essential point of guidance relative to many polymeric materials is that their functional performance is affected substantially more by other processing variables than by radiation. Therefore, a review of processing issues relative to health care product materials will help avoid problems and increase the probability of designing and implementing radiation-compatible health care products.

5.1 Polymer processing overview

Processes as injection molding, tubing extrusion, film calendering, subassembly, and product assembly can profoundly affect the subsequent physical performance of a polymer. These effects are even more noteworthy in conjunction with radiation processing because molecules that are already stressed (from sources such as residual molding stress, shrinkage stress, rapid crystallization, solvent attack, sonic welding, designed-in-loading, etc.) have greatly enhanced susceptibility to radiation degradation. Tables 1 and 2 show typical medical polymer radiation resistances of stress-free parts measured at the point where 25% of the polymer's elongation is lost due to radiation. This may well be "best case": if the part being considered has a significant degree of residual stress as a result of manufacture, the dose at which the 25% loss of elongation occurs may be considerably lower. Annex B provides additional guidance relative to optimum temperatures for processing as well as other process variables such as antioxidant burnout, heat history, excessive residence time, use of regrind, etc.

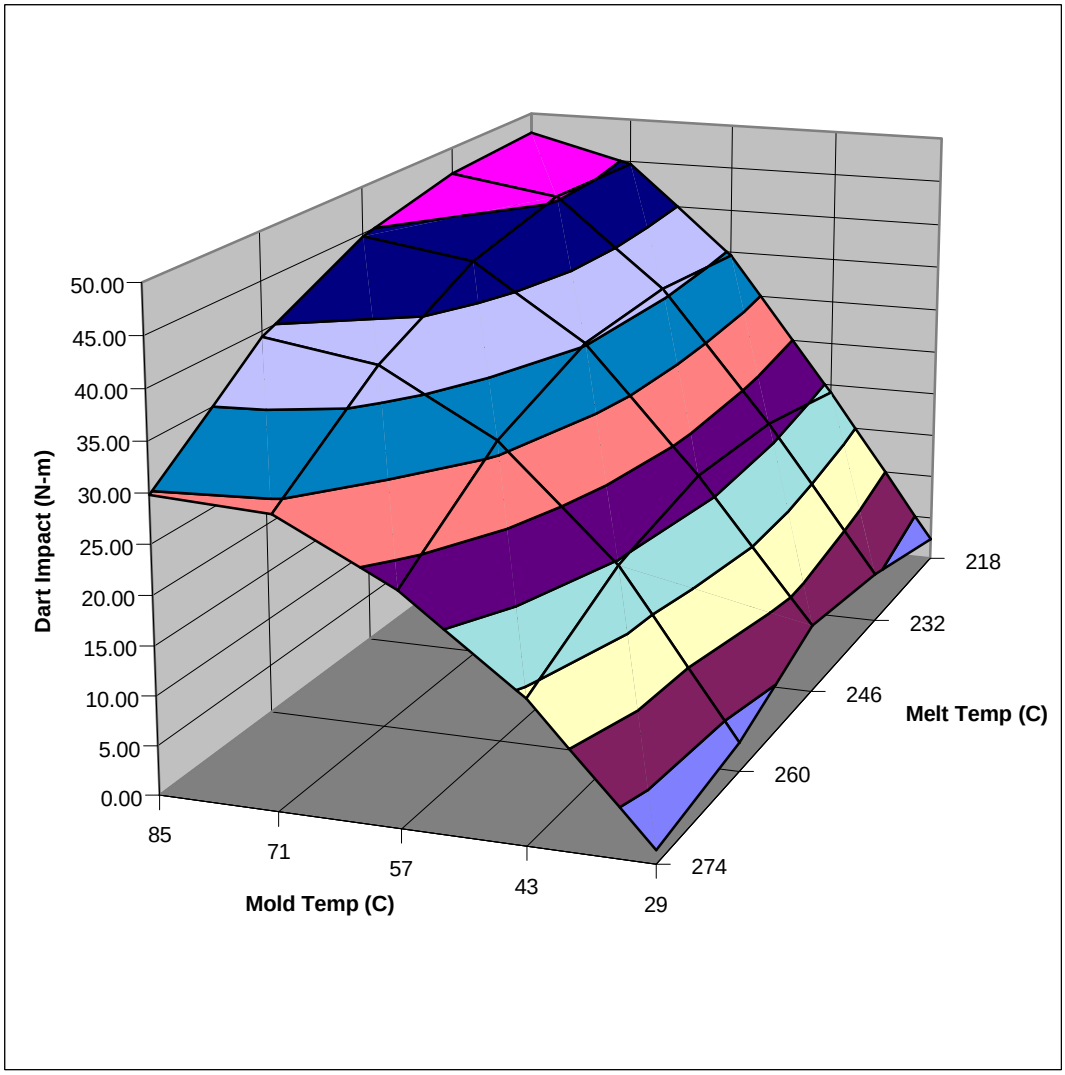
5.2 Impact of processing versus impact of radiation

The physical performance properties of many polymeric materials are affected by processing variables substantially more than by radiation damage. This can be understood in light of some basic bulk polymer processing principles, particularly the trade-off between output versus quality economics. Injection molding, extrusion and calendering processes are similarly affected by the economics of processing. For example, unless directed otherwise in order to comply with component specifications, an injection molding cycle will usually be optimized for maximum output of parts rather than optimization of physical properties. As the overall cost of a molding cycle predominantly is dictated by the time required to remove heat and for the molten polymer to become a solid, running a cycle with lower than ideal mold and melt

temperatures is attractive. This, however, ensures that part quality will be compromised and such a compromise can be critical in the case of health care products intended for radiation sterilization.

"Quality" optimized processing parameters, based on quality improvements, often result in reduced overall costs, despite output reduction. Increasing mold temperature, for example, has been shown to improve physical properties such as impact strength by a factor of 10 or more (which is significantly greater than any effect on impact strength resulting from radiation processing). The substantial and dominating effects of other material processing variables could explain the inconsistencies in the literature on the radiation compatibility of some materials. See figure 1.

Figure 1—Impact of process variables on physical properties—ABS



Condition A: Melt 274° C, Mold 29° C, Impact 1.35 N-m

Condition B: Melt 274° C, Mold 85° C, Impact 29.8 N-m

Shows impact strength increase by a factor of 22 times in an ABS material by simply raising the mold temperature from 29 to 85° C.

6 Material testing

Tests for product functionality and biocompatibility shall include tests to evaluate specific properties essential to the intended function of the product.

6.1 Definition of functional requirements

6.1.1 Product functionality

Tests should challenge dominant and/or critical failure modes of the product. The failure modes should be identified through a documented reliability analysis plan as part of the design or redesign process. The plan should take into consideration field experience and complaint files on related products, product design specifications, and common product use. Another valuable method for identifying potential failure modes is to challenge samples to failure. For example, a product is exposed to radiation overdosing (e.g., 100 kGy), then the product's failure modes are investigated. It is important to identify critical failure modes prior to beginning shelf-life testing. Without this knowledge, aging studies might not be meaningful or efficient.

6.1.2 Materials qualification dose

A maximum acceptable dose shall be established for each product. This dose would not be expected to be exceeded for any product undergoing routine sterilization processing. The maximum acceptable dose should be based on the following considerations: minimum sterilization dose (ANSI/AAMI/ISO 11137, 6.2.2, Sterilization dose selection), maximum to minimum dose ratio (ANSI/AAMI/ISO 11137, 6.4.2, Product dose mapping), maximum potential bioburden variability, maximum processing variability, desired flexibility in family groupings, and the number of times the product may be reprocessed. Products shall be qualified for function and safety after exposure to a radiation dose equal to or greater than this maximum dose.

Delivery of the maximum dose for qualification tests requires that production processing conditions be simulated. Considerations include process temperature and dose rate.

NOTE—Seasonal temperature variations must be considered, as extreme process temperature swings may affect a polymer response to radiation.

For a given materials qualification dose (see 3.3.1), material qualification performed at a low dose rate (gamma and x-ray) may reveal greater degradation (e.g., embrittlement) compared to a high dose rate (electron beam) irradiation as a result of enhanced oxidative effects (Cleland et al. 1993; Ishigaki and Yoshii, 1992; Williams, 1995; Farrell and Hemmerich, 1995). Consequently, a material formerly qualified at a low dose rate will typically require minimal qualification to demonstrate material compatibility at a higher dose rate. Conversely, a material formerly qualified at a high dose rate may require more substantial qualification in the low dose rate application. This is important to consider for materials that oxidatively degrade (e.g., polypropylene and aliphatic nylon) or for materials used in applications with large surface-to-mass ratios (e.g., films, fibers, adhesives, etc.).

In the event that a product destined for distribution to the market is irradiated at a dose exceeding the established maximum dose, the product should be revalidated by appropriate challenge testing for function and safety at the higher radiation dose prior its release to the market.

6.2 Definition of challenge tests and acceptance criteria

6.2.1 Device and package integrity

a) Utilize tests that specifically challenge the identified dominant or critical failure modes (see 6.1.1). Refer to ANSI/AAMI/ISO 11607 for package integrity challenge tests and validation guidance. See table 4 for a list of selected standard test methods that may apply to product functional testing.

NOTE It is necessary to design tests to challenge the specific failure mode of the product in a given application.

Table 4—Physical and functional test methods for plastic material evaluation*

Test Method	Test Reference†
Test for embrittlement:	
1. *Tensile properties*	
a) Tensile strength	ISO R527:1966
b) Ultimate elongation	ISO R527:1966
c) Modulus of elasticity	ISO R527:1966
d) Work	ISO R527:1966
e) Package seal strength	1994 ASTM Standards, Vol. 15.09; F-88-94
2. *Flexural properties*	
a) Flange bending test	"Stability of Irradiated polypropylene. 1. Mechanical Properties," Williams, Dunn, Sugg, Stannet, Advances in Chemistry Series, No. 169, Stabilization and Degradation of Polymers, eds. Allara, Hawkins, pp. 142-150, 1978.
b) Flexbar test	ISO 178: 1975
3. *Impact resistance*	1985 ASTM Standards, Vol. 08.01-Plastics, D-1822-84
4. *Hardness*	
a) Shore	ISO 868: 1985
b) Rockwell	1985 ASTM Standards, Vol. 08.01-Plastics, D785-65
5. *Compressive strength*	ISO 604: 1973
6. *Burst strength*	1985 ASTM Standards, Vol. 08.01-Plastics (Tubing), D-1180-57
a) For package seal strength	1996 ASTM Standards, Vol. 15.09; F-0114-96
7. *Tear strength*	1985 ASTM Standards, Vol. 08-01-Plastics, D-1004-66, and ISO 6383/1-1983
Test for discoloration:	
1. Yellowness index	1985 ASTM Standards, Vol. 08-02-Plastics, D-1925-70
2. Optical spectrometry	1985 ASTM Standards, Vol. 08-02-Plastics, D-1746-70

* Primary source: INTERNATIONAL ATOMIC ENERGY AGENCY. *Guidelines for industrial radiation sterilization of disposable medical products, Co 60 gamma irradiation.* TEC DOC-539. Vienna: IAEA, 1990.

† These documents are the most current versions available at the time this guidance was approved. The user should always determine whether later versions are available that supersede those listed above.

b) Whenever possible, design tests to yield variable data rather than attribute data. Variable data are required to iterate an aging factor (see 7.5.2) or to utilize most advanced methods for estimating shelf life. Zero failure test results should be avoided when possible as understanding of ultimate product performance and failure modes is diminished.

c) Test units should consist of product constructed of the same or equivalent components or subassemblies and manufactured by the same or equivalent manufacturing processes as those used for routine production. Variability in raw materials, manufacturing processes, and storage conditions should be addressed during qualification. The test units should be finished devices in the final package. Subassemblies and even specially prepared test samples are satisfactory in certain cases; a justification should be documented.

d) Define acceptance criteria for all tests. The criteria chosen should be reflective of essential customer functional requirements or safety requirements per design specifications as opposed to arbitrary levels that provide unnecessary restraints on the validation process. The criteria should also be a function of the variability and criticality of the attribute being tested.

e) Select a sufficient number of product samples so that the acceptance criteria can be achieved in a statistically valid manner. (See ISO/TR 8550:1994.)

f) Develop a written test protocol specifying the accelerated aging conditions (e.g., temperature, humidity, heat cycling), transportation simulation considerations, time intervals, sample sizes, and specific tests and acceptance criteria to be undertaken at each test time interval. Thermal cycling is particularly valuable in assessing designs involving differentials in expansion coefficients, especially with adhesive bonding. Relatively large sample sizes may be required, and proper resource planning must be executed to ensure adequate accelerated aging oven space, ambient storage, manpower, and test equipment. Adequate controls should be designed into the protocol (e.g., using one batch for all samples or randomizing samples) so that appropriate comparisons can be made between time intervals.

g) Manufacture and irradiate samples per protocol.

h) After irradiation, wait until the majority of intermediate radiation by-products have decayed to final decay products; forty eight hours (see NOTE below) is a reasonable period of time for most materials. Initiate aging, remove samples from the aged and control groups at the appropriate times, and conduct testing as specified in the protocol.

NOTE Degradation reaction rates during the first 48 hours after irradiation are typically much higher than rates following this period. Indeed, radiation-induced degradation is largely complete during this period for many materials. The time frame for the high reaction rates is dependent on the characteristics of the material under investigation (see 7.2).

i) Evaluate the product test results with appropriate statistical methods to determine whether the product meets the acceptance criteria for each test interval.

6.2.2 Material biocompatibility

Evaluation of materials and products for biocompatibility is accomplished by material toxicity testing in conjunction with material characterization (see 7.2). Material characterization and screening tests for candidate materials can be accomplished early in the design process and may identify potential biosafety

issues that could lead to unnecessary redesign expense later in the process. Physiochemical, cytotoxicity, and hemolysis are examples of screening tests that are sensitive, inexpensive, and rapid. Material supplier biocompatibility and environmental data are good sources of information for use in evaluating candidate component materials. In addition, many useful databases are available to evaluate candidate materials. See the informative references in the bibliography (Annex F).

Chemical characterization of the materials involved also plays an important role in attempts to screen materials by identifying and quantifying the bioavailable physico-chemical constituents of the device. This would include characterization of:

a) the base material (e.g., molecular weight, polydispersity, linear or branched, crosslinked, composition);

b) additives such as colors, antioxidants, and plasticizers;

c) processing aids that remain as part of the device and are potentially leachable (e.g., internal lubricants);

d) trace components of toxicological concerns (e.g., monomers of known toxicity, heavy metals, transition metal catalysts);

e) any other questionable biological/toxicological components (e.g., particulates, pyrogens).

Evaluation of biocompatibility is performed according to ANSI/AAMI 10993-1, *Biological evaluation of medical devices—Part 1: Guidance on selection of tests*.

7 Accelerated aging programs

7.1 Introduction

7.1.1 Accelerated aging theory

A brief discussion of accelerated aging theory is provided in annex C.

7.1.2 Rationale

Health care product manufacturers shall demonstrate the quality, safety, and performance of each device and its packaging throughout its shelf life. One method is to age the product under rigorous real time storage conditions for the intended shelf life. Since the testing should be completed prior to release, this approach would delay, unnecessarily in many cases, the introduction of potentially valuable technology to the market with a concomitant loss of benefit to the patient. Avoiding unnecessary delays in bringing technology to market is the reason for developing and utilizing accelerated aging programs.

Due to the complexity of aging processes, however the use of accelerated aging programs is not without risk. The manufacturer is exposed to risk of unnecessary product obsolescence from conservative aging programs that predict a shorter shelf life than needed. In addition, as accelerated aging is often critical for market release, overly conservative aging programs increase the time required to collect aging data and delay the release of products for patient use. On the other hand, overly aggressive aging programs expose

patients to unacceptable risks associated with a predicted shelf life that is longer than the product performance warrants.

In order to minimize this safety risk, conservative aging factors (AFs) initially are recommended when little information is known about the product under investigation (see 7.5.1, "Fixed AF method"). With more information about the system under investigation and after collecting data to demonstrate the correlation between real time performance and accelerated aging performance, more aggressive and accurate AFs may be defined. (See 7.5.2, "Iterative AF method" and 7.5.3, "Advanced aging methods.")

7.1.3 Aging program options

a) Fixed AF (aging factor) method—This method is detailed in 7.5.1 and outlined in figure 2. A worked example is given in annex D. Guidance is provided for selecting and verifying an appropriately conservative aging factor when little information is known about the product under investigation. The method will often predict unduly short shelf life and cause unnecessary delays of product introductions. This is necessary to minimize patient safety risk as the information necessary to obtain a more accurate and aggressive shelf life prediction is not available.

b) Iterative AF method—This method is detailed in 7.5.2 and outlined in figure 3. A worked example is given in Annex E. Guidance is provided for collecting data that correlates real time and accelerated aging data in order to determine more accurate and aggressive aging factors.

c) Advanced aging methods—Advanced aging methods are introduced in 7.5.3. References from the literature provide additional methods for correlating real time and accelerated aging data (see the bibliography, Annex F).

d) Early product release by extension dating—A common practice used for introducing new pharmaceuticals when stability and potency over time have yet to be established is to use extendible expiration dating ("extension dating") supported by real time aging. This method allows release of product after as little as 30 days of real time aging at the manufacturer's recommended storage conditions. The manufacturer and the customer, however, accept the limitation that shelf life will be extended only as long as the product continues to meet the specified acceptance criteria. Extension dating requires that the customer cooperate by withdrawing products that no longer meet acceptance criteria and by switching to a fresh batch when notified.

7.2 Characterization of materials

In order to be responsible in the application of any of the above methods, an understanding of the materials of the product under investigation is necessary. Items to be considered include:

a) characteristics of the material itself
- chemical structure (aliphatic, aromatic, repeating units, repeating unit sequence, end groups, side chains)
- molecular weight and molecular weight distribution
- thermal transitions (e.g., melt and glass transitions)

NOTE Other transitions also apply to polymeric systems, for example, the alpha transition of semicrystalline polymers. This is the transition at which the crystalline regime relaxes and experiences increased mobility prior to the melt transition.

b) characteristics and impact of additives
- additives, processing agents, catalysts, lubricants, solvents, fillers, etc.

c) Processing history (see 5)
- resulting morphology (percent crystallinity, residual stresses, etc.)

7.3 Defining an aging factor for related products

Based on thorough material characterization (see 7.2), products with equivalent materials, manufacturing, sterilization processing, and clinical application may be grouped into product families and the same aging factors may be used. The rationale for the groupings shall be documented.

7.4 Aging factor (AF) estimates

It is the responsibility of the health care product manufacturer to define responsible aging factors for aging programs. The rationale shall be documented.

7.4.1 AF boundaries

Boundaries based on the characterization of the materials utilized should be considered in order to assure that initial, conservative aging factors are applied appropriately.

7.4.1.1 Ambient temperature (T_{RT})

Select an ambient storage temperature representative of actual product storage and use conditions (normally between 20–25° C). A temperature of 25° C is conservative and may be appropriate when detailed information about the storage environment is not available. However, any temperature that represents the storage conditions for the product can be selected (e.g., 22° C).

7.4.1.2 Accelerated aging temperature (T_{AA})

Select a temperature for the accelerated aging tests based upon the materials used. As the aging temperature increases, the aging factor also increases and the aging duration decreases. The reduction in aging time obtained using a higher temperature should be balanced by the risks involved with extrapolating higher temperature properties to room temperature properties. Guidelines for selecting an aging temperature are as follows:

a) Keep T_{AA} below temperature at which the product distorts. Consider the major transitions of the materials under investigation as described in 7.2. For example, the choice of T_{AA} should be at least 10^{o} C less than the melt temperature, T_m.

b) Keep T_{AA} at or below 60^{o} C unless a higher temperature has been demonstrated to be appropriate. Temperatures higher than 60^{o} C are not recommended due to the higher probability in many polymeric systems of nonlinear changes, such as percent crystallinity and rates of radical reactions and peroxide degradation.

When elevated temperature aging is not feasible (e.g., for materials with very low heat distortion temperature or materials that undergo major morphological changes at even slightly elevated temperatures), other aging methods may be employed (see 7.6).

7.4.2 Initial aging factor (AF_0) estimates

From many years of experience with radiation sterilization and from the data available in the literature (Carfagno and Gibson, 1980), it is possible to provide guidance with respect to conservative estimates of aging factors that may be used initially. These estimates may be used to begin aging programs while real time data are being collected to verify or iterate the initial estimate. In accordance with the guiding principle of this document, the initial estimates suggested below are conservative in most cases when applied within reasonable boundaries (see 7.4.1).

7.4.2.1 $Q_{10} = 2$

Q_{10} is an aging factor for a 10^{o} C rise in temperature. $Q_{10} = 2$ is a common and conservative basis for calculating an aging factor for polymeric systems typically applied with health care products and their packaging. Much aging factor information for polymeric materials was generated for nuclear power and geosynthetic applications, e.g., pond liners. Compared to health care product applications, the requirements for polymeric materials used in these industries is far more severe in terms of both aging environment and length of aging time. Hence, aging factor estimates applied to health care products are often conservative. Even so, before $Q_{10} = 2$ can be applied, the user should show that the materials of the system under investigation fall within the appropriate boundaries (see 7.4.1).

An overall average initial aging factor estimate (AF_0) for a temperature range greater than 10^{o} C is calculated from a Q_{10} value by means of the following equation:

$$F = Q_{10}\hat{}[(T_{AA}-T_{RT})/10] \quad (1)$$

For example, if $Q_{10} = 2$, $T_{AA} = 55\,^{o}$C and $T_{RT} = 25\,^{o}$C, then AF = 2exp[(55-25)/10] = 2exp[3] = 8.

The aging factor is applied to calculate the time that product is required to be held in an accelerated aging oven (t_{AA}). The following equation is used:

$$t_{AA} = \frac{RTE}{AF} \quad (2)$$

where RTE is the desired time interval for testing. For example, if a 2-year shelf life is desired, RTE is equal to 2 years (24 months). Furthermore, for an AF of 8, t_{AA} = (24 months/8) = 3 months in the accelerated aging oven.

7.4.2.2 More aggressive aging factor from the literature

A more aggressive aging factor value found in the literature (e.g., $Q_{10} = 2.3$) may be applied if justified. An important aspect of this justification would be the demonstration that both the system under investigation and the system in the literature are well characterized (see 7.2). Another important aspect of the justification would be that the systems have similar designs and clinical applications. This is essential in order to assure that the aging factor found in the literature can be applied to the system under investigation within appropriate boundaries.

7.5 Aging programs

7.5.1 Fixed AF (aging factor) method

7.5.1.1 Introduction

This method uses the smallest number of samples and provides the most conservative aging factor. The basic concept involves the eight stages outlined in figure 2. Additional guidance with respect to stages 5–8 is provided below. A worked example is given in annex D.

The eight stages of the fixed AF method provide a simple and conservative technique for evaluating the long-term performance of a product. Like any responsible accelerated aging program, it confirms accelerated aging data with real time aging data.

Reasons for using this method include the following.

a) A desire to establish a product's shelf life by means of accelerated aging, when aging data or information for the product is limited.

b) Resources, including product samples, for designing and implementing iterative type studies are not available.

c) Variable data are not available. (Variable data is required for the iterative methods.)

d) The product shelf life is short; hence, there is not a driving force to invest in determining a more accurate and aggressive aging factor.

The disadvantage of this model is that it is often overly conservative, i.e., it can significantly underestimate the product's long-term performance and result in an inappropriately short predicted shelf life. Or, by corollary, it may unnecessarily extend the time needed to establish a given shelf life.

7.5.1.2 Protocol

See figure 2 for an outline of the eight stages and annex D for a worked example of the protocol.

Stages 1–4
Follow stages 1–4 outlined in figure 2.

Stage 5
Define aging time intervals corresponding to the desired shelf life. An example for a product with a 2-year shelf life is given in table 5.

The number of accelerated aged time intervals is, minimally, one. The one mandatory time interval is at the time equivalent to the desired shelf life (desired shelf life divided by aging factor). However, the practice of using only one accelerated time interval exposes one to the risk of failure without prior warning from an earlier accelerated aged time interval. This risk needs to be properly evaluated. Using only one data interval provides no information for data trending. The time zero point is valuable as a baseline for comparison to other time intervals.

Table 5—Time intervals for the fixed aging factor method

Table 5A: Real time (t_{RT}) intervals for product with 2-year shelf life	Table 5B: Real time equivalent (RTE) intervals for product with 2-year shelf life with corresponding accelerated aging (t_{AA}) time intervals.*	
RT (t_{RT}) weeks	**RTE weeks**	**$^{*}t_{AA}$ weeks**
[0]	[0]	[0]
[13]	[13]	[1.2]
[26]	[26]	[2.3]
[52]	[52]	[4.6]
104	104	9.2

NOTE: Time intervals in [brackets] are optional.
*t_{RT} = 25 °C; t_{AA} = 60° C and AF_0 = 11.3; t_{AA} = RTE/AF_0. For example, to calculate the time required to age a sample at 60° C to achieve an RTE of 104 weeks: t_{AA} RTE/AF_0 = 104 weeks/11.3 = 9.2 weeks.

Stage 6
Age samples at T_{AA}. In parallel, age samples at T_{RT}.

Use the defined accelerated aging temperature (see 7.4.1.2) for the appropriate period of time (see 7.4.2.1, equation 2).

NOTES

1) Humidity may be used in conjunction with temperature; see 7.6.
2) See 6 for discussion of manufacturing, irradiating, and conditioning samples.

Stage 7
Evaluate product performance after accelerated aging relative to the product specification.

a) If the accelerated aging results meet the acceptance criteria, the product's shelf life is tentatively established.

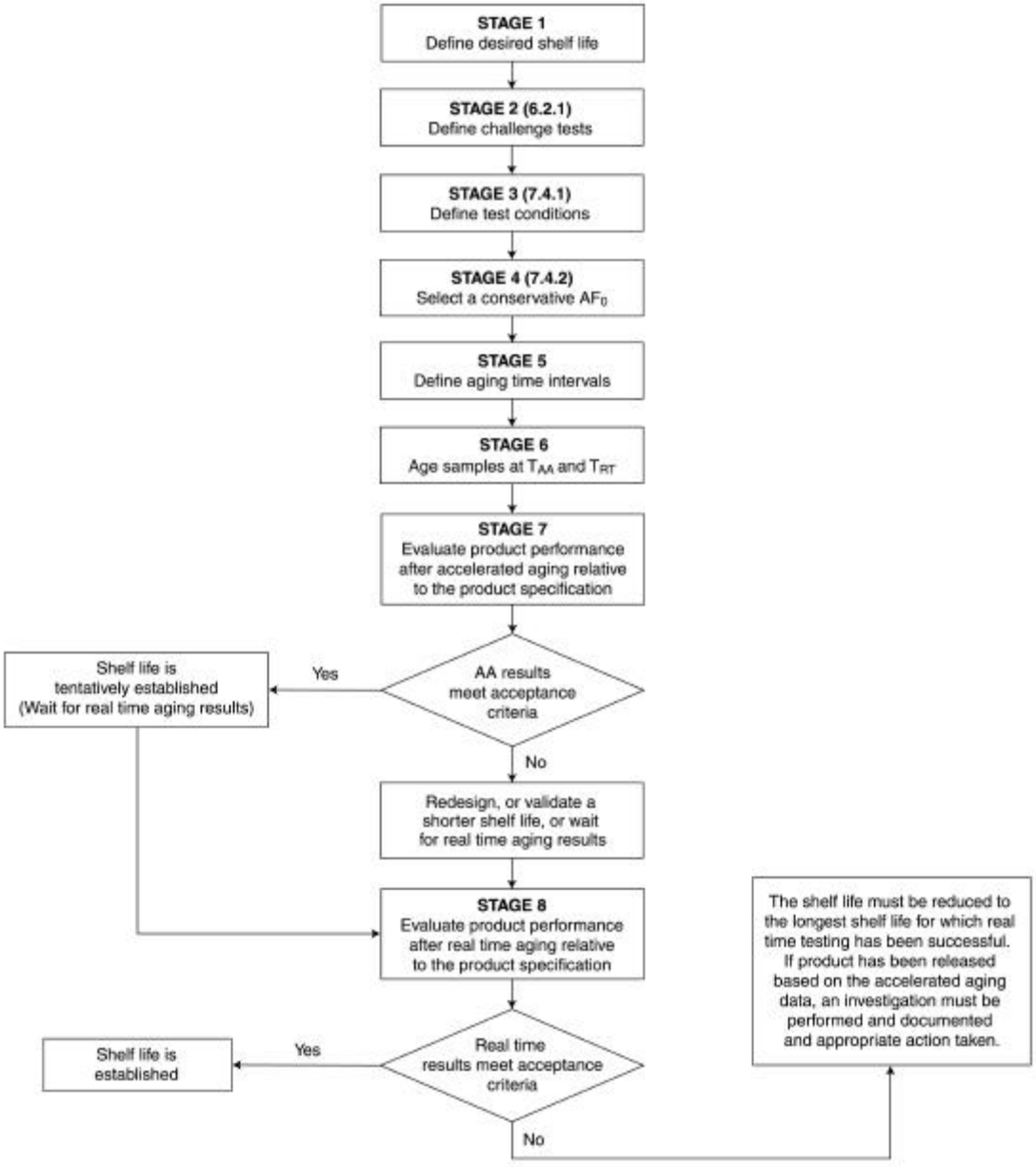
b) If the accelerated aging results fail to meet the acceptance criteria, either redesign the health care product (see 4 and 5 on material selection and processing), attempt to establish a shorter shelf life, or wait for real time aging results. The shelf life is established if real time aging results are acceptable; in this case, the aging program is more rigorous than real time aging.

Stage 8
Evaluate product performance after real time aging relative to the product specification.

a) If the real time aging results meet the acceptance criteria, the product's shelf life is established.

b) If the real time aging results fail to meet the acceptance criteria even though accelerated aging results pass, the tentatively established shelf life is not valid. If no assignable cause can be determined for the real time aging failures, the shelf life shall be reduced to the longest shelf life for which real time testing has been successful. If product has been released to the market based on the accelerated aging data, an investigation should be performed, the risk to users should be evaluated and documented, and appropriate action should be taken.

Figure 2—Flowchart of the fixed aging factor method



In this scenario, the aging program is less rigorous than real time aging. Selecting and processing materials appropriately (see 4 and 5) can help one avoid this situation by assuring that materials are well characterized (see 7.2) such that appropriate boundaries are applied and a conservative initial AF_0 estimated.

7.5.2 Iterative AF method

7.5.2.1 Introduction

This method involves a more rigorous design of the aging protocol and uses a larger number of samples than the fixed AF method above. It also provides the opportunity to refine and confirm, through an

iterative technique, the initial conservative aging factor. The result is a more accurate and aggressive aging factor that extends the shelf life and reduces the time required for the accelerated aging portion of shelf life studies.

The basic concept involves the 11 stages outlined in figure 3. Additional guidance with respect to stages 5 through 11 is provided below. A worked example is given in annex E.

The 11 stages of the iterative AF method provide a technique for correlating accelerated aging data with real time data so that an accurate aging factor can be determined.

The major benefit of this method is the opportunity to reduce the time of shelf life studies or to extend the shelf life. The major drawbacks with the method are the increased number of samples and testing resources needed and the requirement for test methods that provide variable data.

The basic concept is to collect data early at a number of parallel real time aged and accelerated aged time intervals. A correlation between the two, therefore, can be developed so that the actual aging factor of the system under investigation can be defined. Hence, the initial conservative aging factor may be iterated to the actual aging factor. Real time data continue to be collected to confirm or reiterate the correlation at longer time frames

7.5.2.2 Protocol

See figure 3 for an outline of the 11 stages and annex E for a worked example of the protocol.

Stages 1–4
Follow stages 1–4 outlined in figure 3.

Stage 5
Define aging time intervals corresponding to the desired shelf life. The fixed method required only the final time interval for AA and RT. To apply the iterative method, these intervals should be used along with time zero and one additional AA and RT time interval. This allows for data trending and slope calculations. See example in table 6.

Stage 6
Age samples at T_{AA}. In parallel, age samples at T_{RT}.

Use the defined accelerated aging temperature (see 7.4.1.2) for the appropriate period of time (see 7.4.2.1, equation 2).

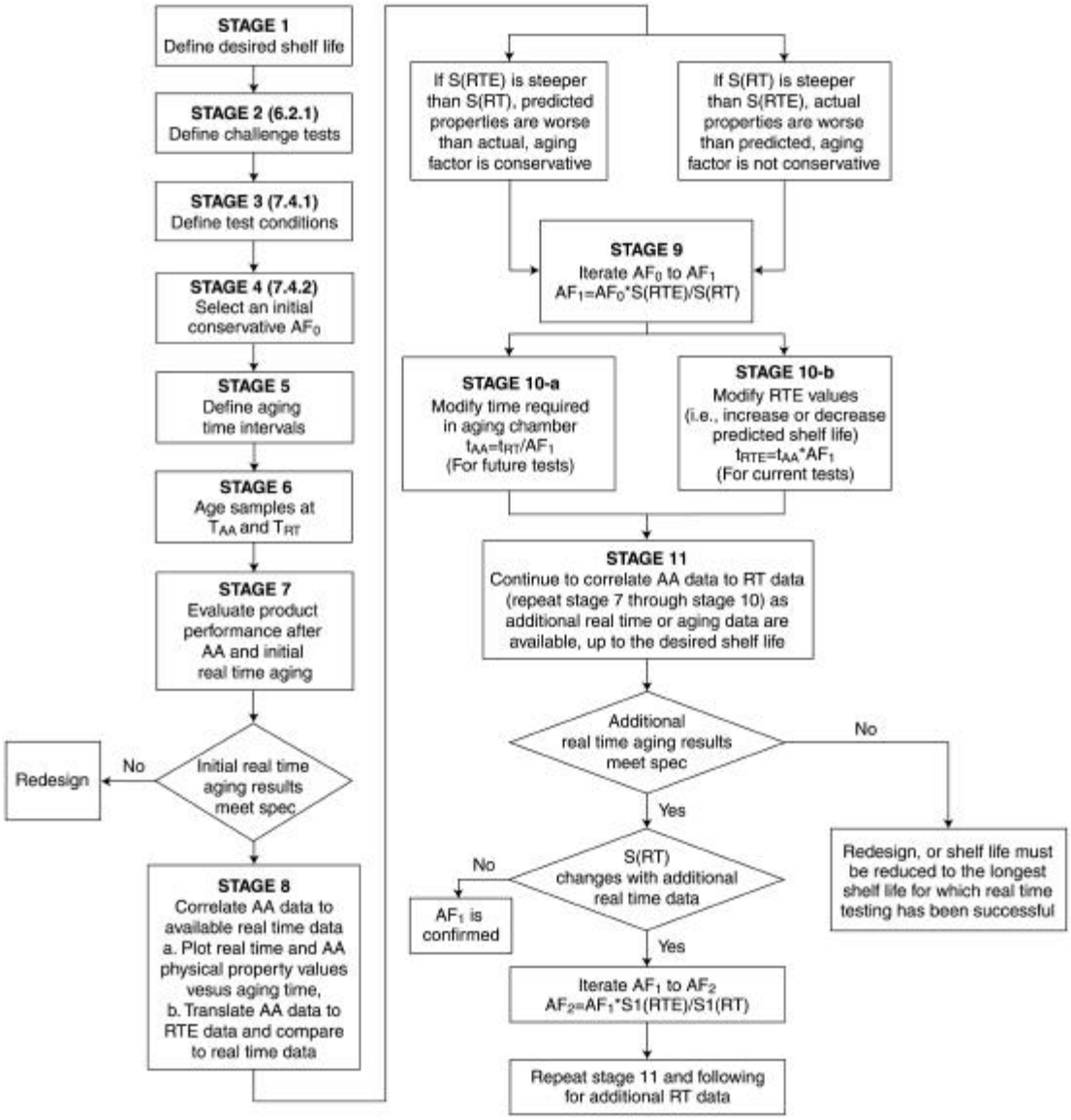
NOTES

1) Humidity may be used in conjunction with temperature (see 7.6).
2) See 6 for discussion of building, irradiating and conditioning samples.

Stage 7
Evaluate product performance after accelerated aging and initial or added real time aging:

a) If initial or added real time aging results meet acceptance criteria, proceed.

Figure 3—Flowchart of the iterative aging factor method



NOTE—S(RTE) = slope of RTE data; S(RT) = slope of RT data.

b) If initial real time aging results fail to meet the acceptance criteria and if no assignable cause can be determined for the real time aging failures, redesign the product (see 4 and 5 on material selection and processing).

NOTE If accelerated aging results have been collected and have passed acceptance criteria prior to collecting the initial real time aging results that have failed, the tentatively established shelf life is not valid. If product has been released to the market based on the accelerated aging data, an investigation should be performed, the risk to users should be evaluated and documented, and appropriate action should be taken.

Table 6—Time intervals for the iterative aging factor method

Table 6A: Real time (t_{RT}) intervals for product with 2-year shelf life.	Table 6B: Real time equivalent (RTE) intervals for product with 2-year shelf life with corresponding accelerated aging (t_{AA}) time intervals.*	
RT (t_{RT}) Weeks	**RTE Weeks**	***t_{AA} weeks**
0	0	0
13	13	1.2
[26]	[26]	[2.3]
[52]	[52]	[4.6]
104	104	9.2

NOTE: Time intervals in [brackets] are optional

* T_{RT} = 25°C; T_{AA} = 60°C and AF_0 = 11.3; t_{AA} = RTE/AF_0. For example, to calculate the time required to age a sample at 60°C to achieve an RTE of 13 weeks: t_{AA} = RTE/AF_0 = 13 weeks/11.3 = 1.2 weeks.

NOTE This table is equivalent to table 5 for the Fixed AF Method except that two additional time intervals (0 and 13 weeks) are not optional. This provides an ability to correlate real time and accelerated aged time intervals.

Stage 8

Correlate accelerated aging data to available real time data:

a) Plot real time and accelerated aging physical property values versus aging time. Determine the best fit for the data (linear, log linear, "S") for both AA and RT data.

b) Translate accelerated aging data to real time equivalent data and compare to real time data
- Translate time in aging oven to RTE: RTE = t_{AA} x AF.
- Compare the slopes of RTE data to RT data (for linear data).

NOTE S(RTE) = slope of RTE data; S(RT) = slope of RT data.

- If S(RTE) is steeper than S(RT), the predicted properties are worse than the actual properties (i.e., the aging factor was conservative; it may be iterated to a more accurate and aggressive aging factor).
- If the S(RT) is steeper than S(RTE), the predicted properties are better than the actual properties (i.e., the aging factor was not conservative; it should be iterated to a more accurate and conservative aging factor).

Stage 9

Iterate AF_0 using available real time data; the conservative initial AF_0 may be replaced with the new AF_1 derived from the data.

a) Calculate the slope of the RT data: S(RT).

b) Calculate the slope of the RTE data: S(RTE)

c) Take the ratio of these two slopes to iterate AF_0 to a more accurate AF_1:

$$AF_1 = AF_0 \times [S_0(RTE)/S_0(RT)] \quad (3A)$$

Stage 10
Modify shelf life or aging time; based on AF_1. The following two courses of action are available:

a) Modify the time in the aging chamber to achieve subsequent AA time intervals.

NOTE Since AF_0 is designed to be conservative, the time to age samples is typically reduced as AF_0 is iterated to AF_1.

b) Modify RTE values, i.e., increase or decrease predicted shelf life.

Stage 11
Repeat stages 7 through 10 as additional real time data are available, out to the desired shelf life.

As additional iterations are made, AF_0 may be replaced with Fi and AF_1 may be replaced with AF_{i+1} in stages 8 through 10. Hence, equation 3A translates into:

$$AF_2 = AF_1 \times [S_1(RTE)/S_1(RT)] \quad (3B)$$

$$AF_{i+1} = AF_I \times [S_i(RTE)/S_i(RT)] \quad (3C)$$

a) If additional RT aging results fail to meet the acceptance criteria, and if no assignable cause can be determined for the real time aging failures, then the shelf life shall be reduced to the longest shelf life for which real time testing has been successful; redesign of the product may be appropriate (see 4 and 5). If product has been released to the market based on the accelerated aging data, an investigation should be performed, the risk to users should be evaluated and documented, and appropriate action should be taken.

b) If additional RT aging results meet acceptance criteria, proceed.

c) If the slope of the RT data line does not change with additional RT data intervals, the existing aging factor is confirmed. Continue collecting RT data out to the desired shelf life and evaluate data per a) and b) above.

d) If slope of the RT data line does change with additional RT data intervals, use the new slopes, S_1 (RT) and S_1 (RTE) to iterate AF_1 to a more accurate AF_2 per equation 3B above. With additional iterations, iterate AF_i to a more accurate AF_{i+1} per equation 3C above.

Continue collecting RT data until the desired shelf life and evaluate data per a) through d) of this stage.

7.5.3 Advanced aging methods

Numerous additional methods for predicting the shelf life of materials are reported in the literature (see bibliography Annex F). The prediction of shelf life is often accomplished through the correlation of accelerated aging data and real time data. These methods typically require the highest level of resources in terms of number of samples, amount of analysis, expertise, and time. The benefit is an accurate and aggressive estimate of shelf life.

An advanced method applied to polypropylene syringe aging data is given in Donohue and Apostolou, 1996. It requires significant resources, in that it calls for the collection of aging data at two elevated temperatures in addition to ambient temperature. However, it demonstrates the advantage of advanced methods in that a very aggressive aging factor is responsibly established. The aging factor correlates with a Q_{10} value of greater than 3.

7.6 Alternative aging methodologies

Conditions other than heat should also be considered, and in fact, may be the most appropriate for a given application (Woo, et al., 1996). Humidity, e.g., 60% RH, may be used in conjunction with elevated temperature in aging studies. It is particularly important in assessing materials that absorb or corrode, e.g., adhesives, glues, metals, and hygroscopic materials or coatings. The fluctuations in the amount of moisture in the product at the time of irradiation can lead to variable physical results due to radiolysis byproducts of water vapor, hydrogen, and free oxygen. Examples of other environmental variables that may be used to age health care products include the presence of salinity, blood, and high concentrations of oxygen. Needless to say, the permeability of the packaging plays an important role in all of these scenarios.

It should be recognized that in establishing the accelerated aging protocol, environmental conditions should be selected to avoid unrealistic failure conditions that would never occur in real time ambient aged conditions. For example, where there is evidence that an aging effect occurs only in the presence of heat (due to autocatalytic reactions that only occur at elevated temperatures), one should use environmental factors other than heat to age the product or perform aging under conditions of storage or use only. The fortunate aspect of such a situation is that, while a shelf life cannot be established due to the unrealistic failure conditions, an unrealistic shelf life cannot be established.

7.7 Biocompatibility considerations

In most cases, zero time biocompatibility testing will be the worst case scenario relative to radiation sterilization because, at that time, the highest level of potentially reactive species is usually available for biointeractions. In some scenarios, however (e.g., when enhanced leaching of additives is anticipated; see 4.2), it may be advisable to screen for biocompatibility (see 6.2.2) after aging or after the product and/or packaging has been exposed to other enhanced environmental factors, e.g., moisture. See ANSI/AAMI 10993-1:1992.

Annex A

Material radiation compatibility fundamentals

A.1 Polymers and polymerization

Polymers are long, chain-like molecules that are made up of repeating chemical units (monomers) that are bonded together to form a high molecular weight material. They can have a carbon or silicon backbone and exhibit strength along the chain length similar to that of metals and ceramics while the strength between chains is relatively low. The arrangement of an individual polymer or groups of polymers may be very structured (crystalline) or completely random (amorphous), or a polymer may have crystalline regions dispersed throughout the amorphous material (semicrystalline). In addition to the influence of chemical structure, processing conditions used to form the material may influence the degree of crystallinity. Polymers are classified into three primary groups: thermoplastics, thermosets, and elastomers. All are used extensively in medical applications.

In addition to the pure (neat) polymer, commercial polymer products contain other components to modify the polymer's performance or aid in processing and stabilization of the polymer. Common additives include antioxidants, ultraviolet light stabilizers, plasticizers, inert fillers, colorants, and processing aids. Additives are generally used in low concentrations (1% or less), although some additives acting as fillers (e.g., talc, barium) or reinforcing agents (e.g., glass) may be used in quantities up to 70% of the polymer's weight. Certain additives prevent radiation damage to plastics. These "antirads" are usually materials that also act as antioxidants. The action of these additives can be either that of a reactant that combines readily with radiation-induced free radicals or that of a primary energy absorber preventing radiation's interaction with the polymer.

A.2 Radiation chemistry

High energy radiation produces ionizations and excitations in polymer molecules. These energy-rich polymers can undergo a series of dissociation, abstraction, and addition reactions that ultimately lead to chemical stability. This stabilization process, which may continue weeks after irradiation, often results in physical and chemical changes in the polymers. The resultant changes may include embrittlement, discoloration, odor, stiffening, softening, chemical resistance, melting temperature, and toxicological response.

Molecular weight, chain length, entanglement, polydispersity, branching, and pendant and terminal chain functionality contribute to the polymer's structure/property relationship, and each of these characteristics may be modified with radiation. Understanding the direction and magnitude of these characteristics, as a function of radiation exposure (dose), is crucial to predicting the performance and utility of irradiated plastics.

The influence of radiation on the properties and performance of a polymer may also vary with location within the part. During irradiation, radicals are formed in the polymer proportional to the local dose. However, the associated chemical reactions that follow are also determined by the local concentration of reactants that may sharply vary through a part (e.g., oxygen concentration is higher near the exterior surfaces). In addition, orientation of molecular chains during processing (e.g., extrusion) can have a profound effect on radiation damage. Molecular structures that most commonly fail during irradiation are those under the greatest combined stress from environment (e.g., load, solvent, and residual molding stress).

Stabilizing reactions can be grouped into three classes:

- Recombination—No change of properties;
- Cross-linking—Increase in strength and decrease in elongation;
- Chain scission—Loss of strength and elongation.

Usually, all of these processes are taking place simultaneously during and after irradiation. The balance of the process depends on the chemical composition and morphology of the polymer, and its surrounding environment. Often the most significant mode of radiation-induced degradation is the embrittling chain scission reactions that result from interaction with oxygen. Free radicals oxidize easily, especially at the surface of the polymers where oxygen is readily available. In some cases inert gas (e.g., nitrogen and argon) or vacuum can be used to eliminate oxidation; antioxidants such as hindered amines are also useful in limiting oxidation. High dose rates available from electron beam irradiation systems can also limit oxidative degradation of polymers by increasing the free radical concentration, plus enhancing radical–radical reaction and minimizing radical oxygen reactions. The application of these techniques is particularly important for oxidation-sensitive materials, especially those containing thin profiles, such as coatings, films, and fibers.

The rupturing of bonds that reduce the molecular weight and strength of the polymer (chain scission) and the linking of molecules that results in the formation of large three-dimensional networks (cross-linking) occur simultaneously, with one mechanism usually dominating. If chain scission dominates, polymers lose mechanical strength and low molecular weight fragments, gas, and unsaturated bonds often appear. However, if cross-linking dominates, the polymer increases in tensile strength, rigidity, and toughness, and decreases in elongation at break.

The balance of these competing reactions is critical and will vary from polymer to polymer and part to part, based on the chemical composition (e.g., aromatic), morphology of the polymer (e.g., percent crystallinity, molecular weight, density), the design of the part (thick versus thin sections), the total radiation dose absorbed, the rate at which the dose is deposited, and, to some degree, the postirradiation storage environment (temperature/oxygen). This balance can also be affected by process-induced stresses and the environment during irradiation (especially the presence or absence of oxygen).

Another deleterious effect is discoloration (usually yellowing) from the development of specific chromophores in the polymer. Color development, which occurs at widely differing doses in various polymers, may diminish or increase with storage time after irradiation. Often, discoloration appears prior to any measurable loss in physical properties. This is the case with PVC where radiation-induced yellowing from conjugated double bonds develops at a dose much lower than is necessary to cause any reduction in its physical properties.

Odor is another undesirable effect in some polymers and is the result of specific radio-stabilizing chemistries. The most common polymers that exhibit postirradiation odor are polyethylene, polyvinylchloride (rancid oil odor from oxidized soybean and linseed oils in the plasticizer), and polyurethane. If the reaction chemistries of the odors are understood, they can often be mitigated through the use of antioxidants, processing temperatures, or employment of a higher molecular weight polymer. Odor reduction can also be accomplished through the use of gas-permeable packaging (i.e., Tyvek™, paper) and elevated temperature conditioning.

Annex B

Material processing and product design guidelines

B.1 General processing guidelines to optimize material functionality

For injection molding, mold temperature, melt temperature, and mold filling rate can affect polymer physical properties (e.g., elongation, impact, and tensile strength) much more than radiation will affect physical properties. Therefore, it is important to monitor the control samples carefully, even noting mold cavity number as that often affects performance. Warm molds and easy filling rates produce ductile parts. Brittle parts are produced in cold molds with tortuous filling and poor venting. Table B.1 lists 14 ways to recognize cold-molded parts that are likely to reduce product performance capabilities.

Table B.1—How to recognize cold-molded parts

1	No flash
2	Poor gloss/Dull finish
3	No shrink marks
4	Dimensions are high tolerance or oversized
5	Packing rings (blush) at gate
6	Warping is reduced
7	Cloudy or loss of transparency
8	Crazed when contacting solvent
9	Visible weld line opposite gate
10	Part cracks when bent or flexed
11	Parts are heavier than standard
12	Parts stick in cavity but are free on cores
13	Parts distort when heated
14	Durometer readings are higher than standard (harder)

Polymers respond to the combined effect of the following stresses and environmental exposures. Like other engineered systems, polymeric molecules tend to fail at the point of greatest cumulative stress. Hence, in order to be successful in radiation material qualification, it is important to understand and control all of the variables affecting the polymers, such as:

- shrinkage stress;
- processed-in stress;
- applied stress;
- solvent/chemical attack;
- hydrolysis, inadequate drying;
- radiation;
- temperature;
- regrind;
- oxidation.

B.2 Product design

Product design can have a significant influence on the long term performance and reliability of a product or component. Radiation sterilization of poorly designed products can lead to premature part failure through increased sensitivity to environmental attack. In order to compensate for the effects of all stresses leading to losses in physical properties, appropriate design safety factors need to be incorporated.

For injection molding, notable design guidelines include the following:

a) Avoid abrupt thick to thin transitions.

b) Incorporate generous radii everywhere.

c) Avoid interference fits and long term creep loading exceeding 20% of yield strength.

d) Design molds for fast and easy filling with gates sized and located to minimize material flow pressures and paths. Also design part ejection to minimize ejection forces and molded-in stresses.

Follow material suppliers' design guidelines for each polymer that may be specific to its unique morphology and chemistry. Their guidelines may make the polymer less susceptible to various processing and environmental stresses.

Perform an appropriate reliability analysis to assure that critical failure modes are understood and addressed appropriately. Consider establishing functional safety factors (Stubstad and Hemmerich, 1994) for critical components to apply after all manufacturing, environmental, and sterilization processing is complete and the components have been aged.

Annex C

Accelerated aging theory

Accelerated aging theory allows prediction of future performance of critical product materials. Proper application of the theory takes into account the chemistry, morphology, manufacturing, and environmental factors that might affect the product under investigation. These factors are coupled into a single composite that can be evaluated in a systematic way. Depending on the complexity of the system under evaluation, the techniques used might be trivial or, on the other extreme, be insoluble.

The prediction techniques are guidelines. If applied in a thoughtful and systematic way, they will ensure long-term performance safety for the user. It is important to understand, however, that they are driven by the material under investigation, not the reverse. The improper application of a simple aging model to a complex system or the use of an inappropriate aging factor does not change the shelf life of the material. Instead, it simply produces inaccurate results that can ultimately lead to the premature failure of a product. Properly applied, however, these production techniques can permit the use of today's most advanced materials with security and safety.

One of the most widely used techniques for estimating the future properties of medical polymers is based on the work of Arrhenius (1889). He observed that the chemistry in dilute sugar-water solutions (in that case, the inversion of the sucrose) could be accelerated by raising the solution's temperature. In fact, for the systems studied by Arrhenius, the relationship between temperature and reaction rate can be represented by a very simple exponential function, often referred to as the Arrhenius equation.

The practical importance of this equation is the way in which it relates temperature and time. That is, the equation permits the user to calculate a material's properties at a future time or at a different temperature. Most important to the health care product industry, however, the equation also permits the user to raise a material's temperature, then, after one month, estimate what the room temperature properties of the material will be after one year.

Although the materials used by the health care product industry are much more complex than the sugar solutions studied by Arrhenius (making his simple exponential equation inappropriate for most polymer applications) it still represents a good first approximation for estimating a material's future performance. In fact the Arrhenius equation that yields the axiom, "the aging rate (Q) will double for every 10° C that the temperature is raised," is surprisingly accurate. It is this approximation ($Q_{10} = 2$) that is used in the simplest of the protocols for estimating a conservative aging factor.

Annex D

Worked example of fixed aging factor method

The eight stages of the fixed method protocol outlined in figure 2 and 7.5.1 are applied in this annex to an illustrative set of data.

	Description	Example
Stage 1	Define the desired shelf life of the product (from marketing needs, product needs, etc.).	9 years desired; 4 years minimum
Stage 2	Define challenge tests, sample sizes, and acceptance criteria.	• Ultimate tensile strength (UTS) • 4000 psi is the minimum specification
Stage 3	Define test conditions; define ambient (T_{RT}) and accelerated aging (T_{AA}) temperatures.	T_{RT} = 25° C; T_{AA} = 60° C
Stage 4	Select a conservative AF_0 estimate.	Assume Q_{10} = 2; AF_0 may be calculated using 25° C and 60° C: $AF_0 = 2^{[(60-25)/10)]} = 11.3$
Stage 5	Define aging time intervals corresponding to the desired shelf life.	See table D.1

Table D.1—Time intervals for example set of data—fixed aging factor method

Table D.1A: Real time (t_{RT}) intervals for product with 9-year shelf life		**Table D.1B: Real time equivalent (RTE) intervals for product with 9-year shelf life with corresponding accelerated aging (tAA) time intervals***	
RT (t_{RT}) years	**RT (t_{RT}) weeks**	**RTE weeks**	***t_{AA} weeks**
[0]	[0]	[0]	[0]
[1]	[52]	[52]	[4.6]
[2]	[104]	[104]	[9.2]
[3]	[156]	[156]	[13.8]
[4]	[208]	[208]	[19.4]
9	468	468	41.4

NOTE Time intervals in brackets are optional.

*$T_{RT = 25\ °C;}$ T_{AA} = 60° C, and AF_0 = 11.3; t_{AA} = RTE/AF_0. For example, to calculate the time required to age a sample at 60° C to achieve an RTE of 468 weeks: t_{AA} = RTE/AF_0 = 468 weeks/11.3 = 41.4 weeks.

	Description	Example
Stage 6	Age samples at T_{AA}. In parallel, age samples at T_{RT}.	AA and RT samples are aged for times defined in table D.1.
Stage 7	Evaluate product performance after accelerated aging relative to the product specification: a) If the accelerated aging results meet the acceptance criteria, the product's shelf life is tentatively established. b) If the accelerated aging results fail to meet the acceptance criteria, either redesign the product, attempt to establish a shorter shelf life, or wait for real time aging results. If real time aging results later prove to be acceptable, the aging program is more rigorous than actuality.	Table D.2 shows that the AA data meet specification up through 4 years but not at 9 years. This demonstrates that the shelf life is tentatively established at 4 years. If 9 years is critical for success of the project, the options are to redesign the product or to wait for real time data.

Table D.2—Evaluation of AA data relative to product specification

AA @ 60° C (weeks)	RTE (y)	UTS (psi)	Meet spec?
0	0	7772	Yes
4.6	1	6784	Yes
9.2	2	6123	Yes
13.8	3	4997	Yes
19.4	4	4156	Yes
41.4	9	567	**No**

	Description	Example
Stage 8	Evaluate product performance after real time aging relative to the product specification: a) If the real time aging results meet the acceptance criteria, the product's shelf life is established. b) If the real time aging results fail to meet the acceptance criteria even though accelerated aging results pass, the tentatively established shelf life is invalid. If no assignable cause can be determined for the real time aging failures, the shelf life must be reduced to the longest shelf life for which real time testing has been successful. If product has been released to the market based on the accelerated aging data, an investigation must be performed, the risk to users should be evaluated, and documented and appropriate action should be taken.	Table D.3 shows that the RT data also meet specification up through 4 years but not at 9 years. This establishes the shelf life is established at 4 years. If 9 years is desired, the product must be redesigned.

Table D.3—Evaluation of RT data relative to product specification

RT (y)	UTS (psi)	Meet spec?
0	7772	Yes
1	7063	Yes
2	7045	Yes
3	6144	Yes
4	5063	Yes
9	2685	**No**

For illustrative purposes, the set of data in the table below is used to illustrate both the fixed AF method and the iterative AA method, i.e., the same set of data was used to illustrate both methods. The real time data for the example used in this presentation comes from D.C. Sun, et al., 1996. The accelerated aging data are not from that paper; they have been generated to better illustrate the methods of this document.

Table D.4—Illustration of the Fixed AF method and the Iterative AA method

t_{RT} (y)	UTS (psi)	t_{AA} (weeks @ 60° C)	UTS (psi)
0	7772	0	(same)
1	7063	4.6	6784
2	7045	9.2	6123
3	6144	13.8	4997
4	5063	19.4	4156
9	2685	41.4	567

Annex E

Worked example of iterative aging factor method

The 11 stages of the iterative method protocol outlined in figure 3 and 7.5.2 are applied below to an illustrative set of data.

	Description	Example
Stage 1	Define the desired shelf life of the product (from marketing needs, product needs, etc.)	9 years desired; 4 years minimum
Stage 2	Define challenge tests, sample sizes, and acceptance criteria	• Ultimate tensile strength (UTS) • 4000 psi is the minimum specification
Stage 3	Define test conditions; define ambient (T_{RT}) and accelerated aging (T_{AA}) temperatures	T_{RT} = 25° C; T_{AA} = 60° C
Stage 4	Select a conservative AF_0 estimate	Assume Q_{10} = 2; AF_0 may be calculated using 25° C and 60° C: $AF_0 = 2^{[(60-25)/10]} = 11.3$
Stage 5	Define aging time intervals corresponding to the desired shelf life	See table E.1

Table E.1—Time intervals for example set of data—iterative aging factor method

Table E.1A: Real time (t_{RT}) intervals for product with 9-year shelf life		**Table E.1B: Real time equivalent (RTE) intervals for product with 9-year shelf life with corresponding accelerated aging (t_{AA}) time intervals***	
RT (t_{RT}) Years	**RT (t_{RT}) Weeks**	**RTE weeks**	***t_{AA} weeks**
0	0	0	0
[1]	[52]	[52]	[4.6]
[2]	[104]	[104]	[9.2]
[3]	[156]	[156]	[13.8]
4	208	208	19.4
9	468	468	41.4

NOTE: Time intervals in [brackets] are optional.

* $T_{RT = 25\ °C;}$ T_{AA} = 60° C and AF_0 = 11.3; t_{AA} = RTE/AF_0. For example, to calculate the time required to age a sample at 60° C to achieve an RTE of 208 weeks: t_{AA} = RTE/AF_0 = 208 weeks/11.3 = 19.4 weeks.

NOTE This table is equivalent to table D.1 of annex D for the fixed AF method except that two additional time intervals (0 and 4 years) are not optional. This provides the ability to responsibly correlate real time and accelerated aged time intervals.

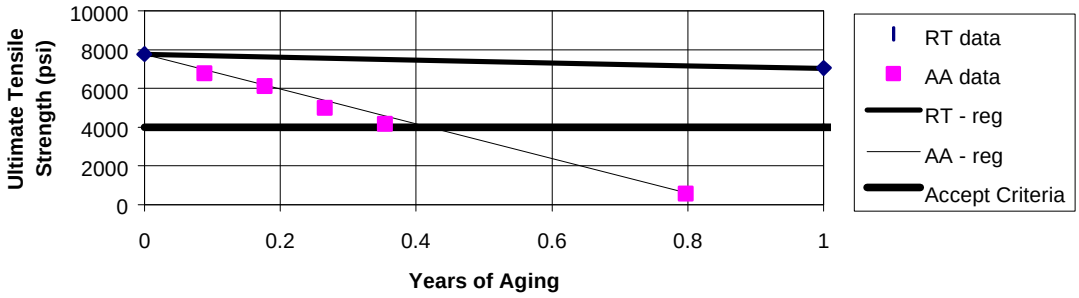
	Description	Example
Stage 6	Age samples at T_{AA}. In parallel, age samples at T_{RT}. NOTES 1) Perform transportation simulation and extreme conditioning (thermal cycling), if appropriate. 2) Humidity is often used in conjunction with temperature.	AA and RT samples are aged for times defined in table E.1
Stage 7	Evaluate product performance after accelerated aging and initial real time aging: a) If initial or added real time aging results meet acceptance criteria then proceed. b) If initial real time aging results fail to meet the acceptance criteria and if no assignable cause can be determined for the real time aging failures, then redesign the product.	Table E.2 shows the data that would be available after 1 year. Since the initial RT data passes specification, it is appropriate to continue with the iterative method.

Table E.2—AA data and initial RT data that are available after 1 year of aging. Evaluation of data relative to product specification

RT (y)	UTS (psi)	Meet spec?	AA @ 60° C (weeks)	RTE (y)	UTS (psi)	Meet spec?
0	7772	Yes	4.6	1	6784	Yes
1	7063	Yes	9.2	2	6123	Yes
			13.8	3	4997	Yes
			19.4	4	4156	Yes
			41.4	9	567	No

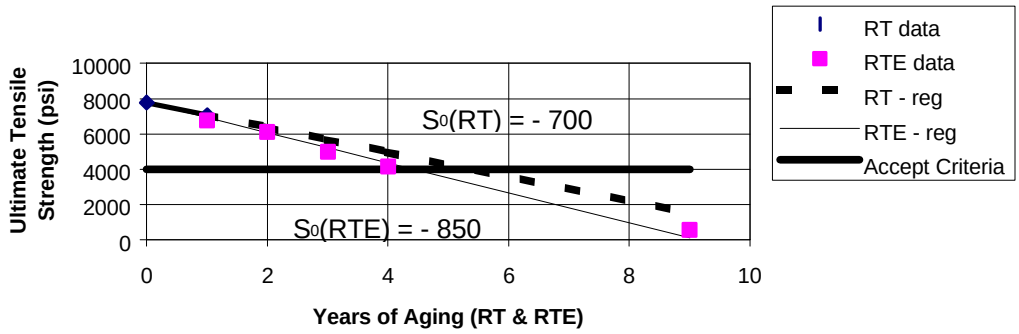
	Description	Example
Stage 8	Correlate accelerated aging data to available real time data. a) Plot real time and accelerated aging physical property values versus aging time. Determine the best fit for the data for both AA and RT data.	See fig. E.1—the data are fit by a linear model.

Fig E.1 UTS vs. Years of Aging (RT & AA)
RAW DATA



	Description	Example
Stage 8 (cont.)	Correlate accelerated aging data to available real time data (continued). b) Translate accelerated aging data to real time equivalent data and compare to real time data. A useful means of comparison is to plot the data and calculate slopes. NOTE: RTE = t_{AA} H AF.	See fig. E.2 S_0(RTE) is steeper than S_0(RT). Hence, the predicted properties are worse than the actual properties (i.e., the aging factor was conservative; it may be iterated to a more accurate and aggressive aging factor).

Fig E.2 UTS vs. Years of Aging (RT & RTE)
Q_{10} = 2; AF_0 = 11.3
TRANSLATE AA DATA TO RTE DATA

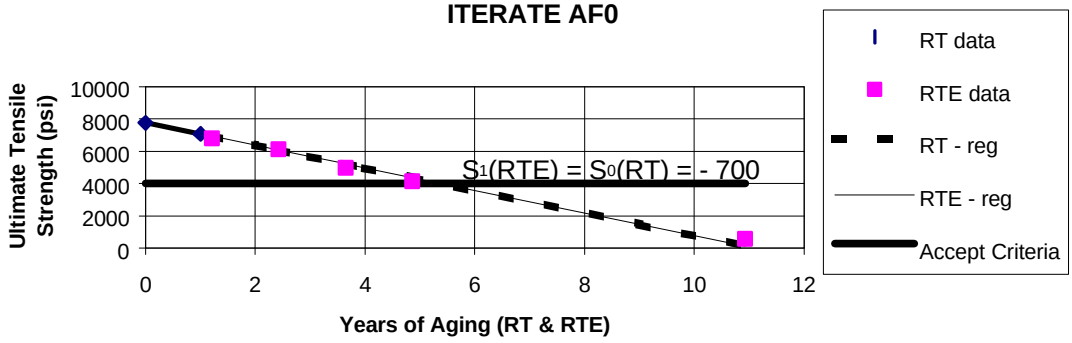


S_0(RTE) = slope of original RTE data; S_0(RT) = slope of initial RT data.

SHELF LIFE ESTIMATE IS 4 YEARS.

	Description	Example
Stage 9	Iterate AF_0 using available real time data; the conservative, initial, AF_0 may be replaced with the new AF_1 derived from the data. a) Calculate the slope of the initial RT data b) Calculate the slope of the RTE data c) Take the ratio of these two slopes to iterate AF_0 to a more accurate AF_1 (equation 1): $AF_1 = AF_0 \times [\, S_0(RTE)/\, S_0(RT)]$ (1)	a) $S_0(RT) = -700$ (see fig. E.2) b) $S_0(RTE) = -850$ (see fig. E.2) c) $AF_1 = 11.3 \times [(-850)/(-700)]$ $= 13.7$
Stage 10	Modify shelf life or aging time	See fig. E.3. Shelf life estimate is extended to 4.9 years.

Fig E.3 UTS vs. Years of Aging (RT & RTE)
AF1 = 13.7; Q10 = 2.11
ITERATE AF0



SHELF LIFE ESTIMATE IS EXTENDED TO 4.9 YEARS.

	Description	Example
Stage 11	Repeat Stage 7 through Stage 10 as additional real time data are available, up to the desired shelf life.	• See fig. E.4. Additional RT aging data at 2 and 3 years meet acceptance criteria; proceed. • Since the slope of the RT data line changes with 2 and 3 year RT data points, the new slope, S1 (RT) is used to iterate AF_1 to a more accurate AF_2 (7.5.2, equation 3B): $AF_2 = AF_1 \times [\ s_1(RTE)/\ s_1\ (RT)]$ $= 13.7 \times [(-700)/(-500)]$ $= 19.2$ • See fig. E.5. Shelf life estimate is extended to 6.8 years. • See figs. E.6 and E.7. Additional RT aging data at 4 years meets acceptance criteria; 9-year data do not. • The shelf life is again iterated based on the 4- and 9-year RT data; $AF_3 = AF_2 \times [\ S_2(RTE)/\ S_2\ (RT)]$ $= 19.2 \times [(-500)/(-575)]$ $= 16.7$ • The final shelf life is established at 5.9 years.

Fig E.4 UTS vs. Years of Aging (RT & RTE)
TWO NEW REAL TIME DATA POINTS

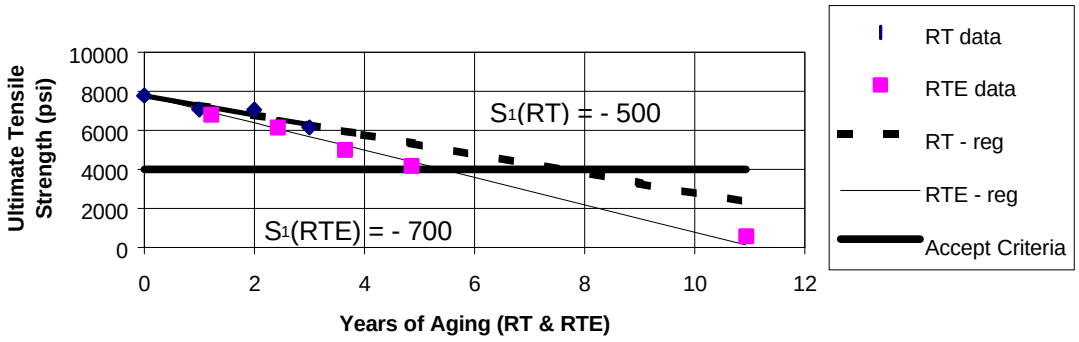
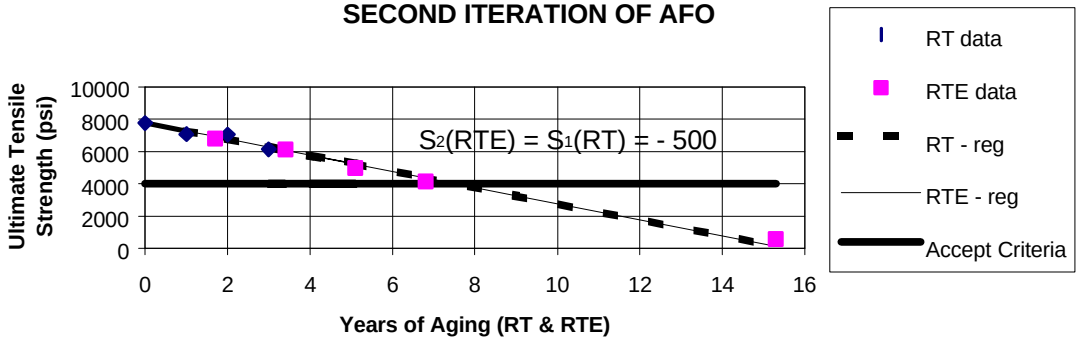


Fig E.5 UTS vs. Years of Aging (RT & RTE)
AF2 = 19.2; Q10 = 2.33
SECOND ITERATION OF AFO



SHELF LIFE ESTIMATE IS EXTENDED TO 6.8 YEARS.

Fig E.6 UTS vs. Years of Aging (RT & RTE)
TWO ADDITIONAL RT DATA POINTS

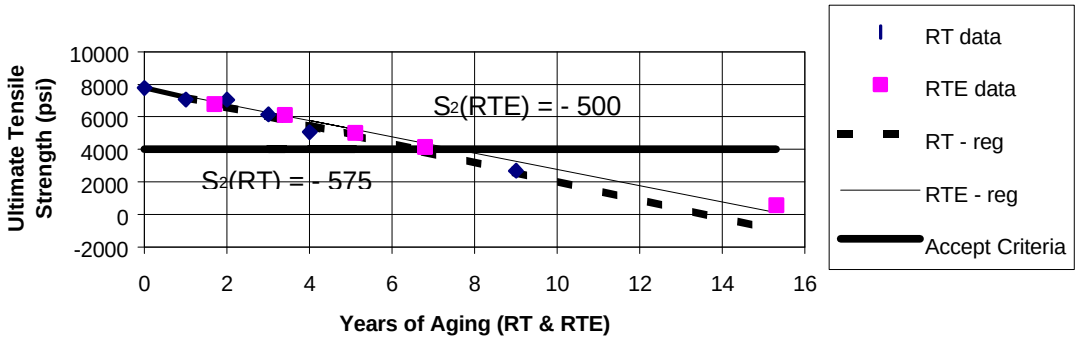
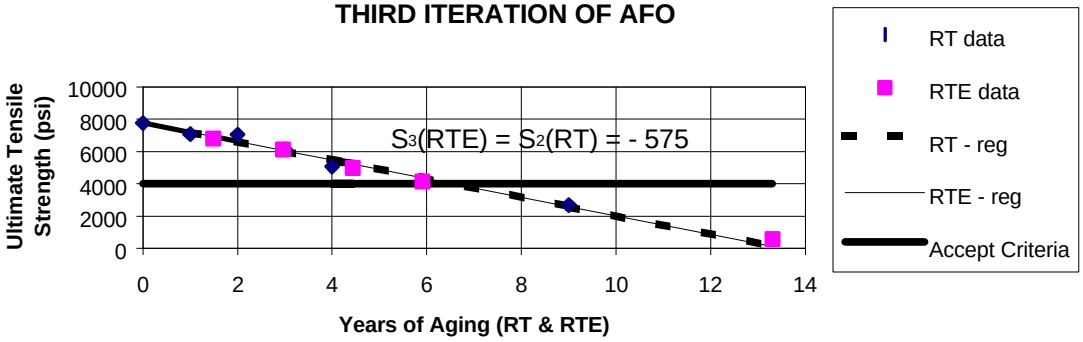


Fig E.7 UTS vs. Years of Aging (RT & RTE)
AF3 = 16.7; Q10 = 2.24
THIRD ITERATION OF AFO



SHELF LIFE ESTIMATE IS REDUCED TO 5.9 YEARS.

NOTE The overall impact of using the iterative method versus the fixed method in the example of annexes E and D, respectively, is to responsibly extend the shelf life estimate of the product from 4.0 years to 5.9 years. The uncertainty of the shelf life estimate is estimated to be 1 year. Statistical analysis is not included in this example.

For illustrative purposes, the set of data in the table below is used to illustrate both the fixed AF method and the iterative AA method, i.e., the same set of data was used to illustrate both methods. The real time data for the example used in this presentation comes from D.C. Sun, et al., 1996. The accelerated aging data are not from that paper; they have been generated to better illustrate the methods of this document.

Table E.3—Illustration of the fixed AF method and the iterative AA method

t_{RT} (y)	UTS (psi)	t_{AA} (weeks @ 60° C)	UTS (psi)
0	7772	0	(same)
1	7063	4.6	6784
2	7045	9.2	6123
3	6144	13.8	4997
4	5063	19.4	4156
9	2685	41.4	567

Annex F

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