

# Comparison of the Effect of Ethylene Oxide and $\gamma$ -Irradiation on Selected Tyrosine-Derived Polycarbonates and Poly(L-lactic acid)

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**ABSTRACT:** Tyrosine-derived polycarbonates are a new class of degradable polymers that have possible biomedical applications. In this study, the effect of the two most common sterilization techniques, ethylene oxide and  $\gamma$ -irradiation (0.3, 1.1, 3.9, 6.4, 10.6 Mrad), was evaluated for a family of four structurally related tyrosine-derived polycarbonates and for poly(L-lactic acid) (PLLA). The four polycarbonates were poly(DTE carbonate), poly(DTB carbonate), poly(DTH carbonate), and poly(DTO carbonate) and differed only in the length of the pendent chain. Ethylene oxide exposure had little effect on molecular weight, surface composition, mechanical properties, or degradation rate of all test polymers except for poly(DTO carbonate). Poly(DTO carbonate) was unique since following ethylene oxide exposure it degraded faster than did the nonsterilized control.  $\gamma$ -Irradiated tyrosine-derived polycarbonates retained over 81% of their initial molecular weight when exposed to a clinically relevant dose of 3.9 Mrad and retained still 58% of the initial molecular weight when exposed to the highest test dose of 10.6 Mrad. No changes in surface composition and only slight changes in yield strength and the Young's modulus were detected for any of the tyrosine-derived polycarbonates following  $\gamma$ -irradiation. *In vitro*, irradiated films of poly(DTE carbonate), poly(DTB carbonate), and poly(DTH carbonate) degraded at approximately the same rate as did the nonsterilized films regardless of irradiation dose. Only poly(DTO carbonate), irradiated at high doses, degraded faster than did the control. Medical-grade PLLA was tested under identical conditions. Ethylene oxide exposure of PLLA did not affect the molecular weight, surface composition, mechanical properties, or *in vitro* degradation rate. However, upon irradiation at 10.6 Mrad, PLLA retained only 29% of its initial molecular weight; a dose of 3.9 Mrad resulted in retention of 49% of the initial molecular weight. In correspondence with earlier publications, irradiation of PLLA induced significant losses in the Young's modulus, % strain at break, and changes in the postirradiation rate of degradation in some specimens. Compared to PLLA, tyrosine-derived polycarbonates are significantly more stable to  $\gamma$ -irradiation and can be sterilized by conventional  $\gamma$ -sterilization techniques. © 1997 John Wiley & Sons, Inc. *J Appl Polym Sci* **63**: 1499–1510, 1997

**Key words:** degradable polymers; biomaterials; tyrosine; polycarbonate;  $\gamma$ -irradiation; ethylene oxide; sterilization; poly(L-lactic acid); tyrosine-derived polycarbonates

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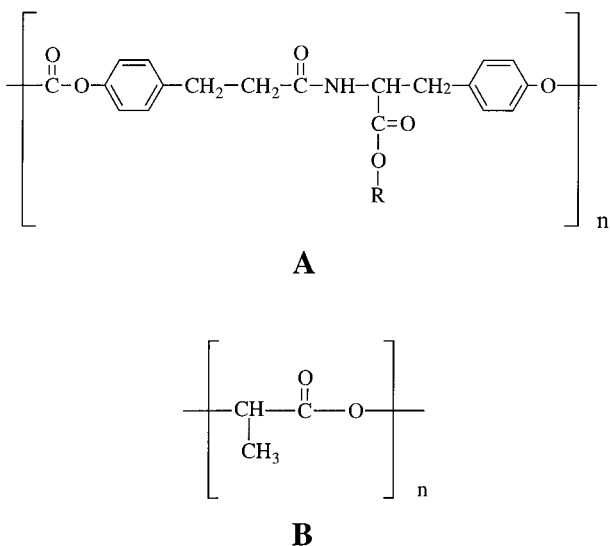
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**Figure 1** (A) Structure of tyrosine-derived polycarbonates: R = ethyl, poly(DTE carbonate); R = butyl, poly(DTB carbonate); R = hexyl, poly(DTH carbonate); R = octyl, poly(DTO carbonate). (B) PLLA.

## INTRODUCTION

Tyrosine-derived polycarbonates are a family of degradable polymers that were designed for biomedical applications. Like clinically used poly(L-lactic acid) (PLLA) and poly(glycolic acid) (PGA), tyrosine-derived polycarbonates are derived from nontoxic materials which are found naturally in the body. However, tyrosine-derived polycarbonates are distinct because the alkyl pendent chain can be varied to produce polymers with a range of material, chemical, and physical properties (Fig. 1).<sup>1</sup> Previous work has established the promise of tyrosine-derived polycarbonates as potential materials for biomedical applications including implantable drug delivery devices<sup>2</sup> and bone fixation devices.<sup>3,4</sup>

To further evaluate tyrosine-derived polycarbonates for clinical use, the ability of the polymers to maintain their properties following sterilization must be determined. Since these materials, like PGA and PLLA, undergo hydrolytic degradation when exposed to a hot, moist environment, autoclaving is not an option. UV exposure and germicidal solution methods do not effectively kill enough spores to be acceptable for sterilization of polymeric implant materials and may alter the

chemistry of the polymer.<sup>5</sup> Hence, the only currently possible sterilization methods are ethylene oxide and  $\gamma$ -irradiation.<sup>6-9</sup> Ethylene oxide exposure is a reliable, relatively cost-effective method to sterilize most polymeric devices, although poststerilization aeration of the samples to remove toxic residues and microbial testing to verify sterility is required.<sup>5,10</sup> Recently, overexposure to ethylene oxide has been linked to genetic damage, neurologic effects, and tissue irritation.<sup>11,12</sup> The National Institute for Occupational Safety and Health therefore recommends that ethylene oxide be handled as a mutagen and potential carcinogen to humans and that unnecessary use be eliminated.<sup>5</sup> These government regulations may become stricter as more information on the effect of occupational exposure to ethylene oxide is collected and may mandate the use of alternative sterilization techniques in the future.

$\gamma$ -Irradiation does not require any poststerilization treatment of the samples and can sterilize in a measurable, predictable manner.<sup>5</sup> However, the high energy of  $\gamma$ -irradiation can lead to degradation or crosslinking of the polymer, affecting the surface and bulk properties.<sup>10</sup> In a preliminary study, tyrosine-derived polycarbonates retained more than 60% of their initial molecular weight upon irradiation at 1.0, 2.5, and 4.0 Mrad.<sup>1</sup> The preliminary study provided no data on the effect of  $\gamma$ -irradiation on mechanical strength, surface composition, and the rate of degradation.

In this study, the effect of ethylene oxide and  $\gamma$ -irradiation sterilization on a series of tyrosine-derived polycarbonates was assessed in a detailed, systematic fashion. Specifically, correlations between the polymer structure and the effect of the sterilization method on the molecular weight, radiation chemical yields for scission [ $G(S)$ ] and crosslinking [ $G(X)$ ], surface composition, mechanical properties, and degradation rate *in vitro* were investigated. To evaluate the effect of  $\gamma$ -irradiation dose on each polymer, five irradiation doses were used (0.3, 1.1, 3.9, 6.4, and 10.6 Mrad). PLLA was included as a control.

## EXPERIMENTAL

### Materials

Tyrosine-derived polycarbonates [poly(DTE carbonate), poly(DTB carbonate), poly(DTH car-

**Table I Properties of Solvent-cast Films of Tyrosine-derived Polycarbonates and PLLA**

Polymer	Molecular Weight <sup>a</sup> (Weight Average)	Polydispersity <sup>a</sup> ( $M_w/M_n$ )	Glass Transition Temperature (°C) <sup>b</sup>
Poly(DTE carbonate)	160,000	1.6	87
Poly(DTB carbonate)	118,000	1.6	72
Poly(DTH carbonate)	150,000	1.8	61
Poly(DTO carbonate)	128,000	1.9	51
PLLA	185,000	1.5	58

<sup>a</sup> Mean of three measurements.

<sup>b</sup> Values determined at the midpoint of the base-line shift are higher than are the onset values reported previously.<sup>1</sup>

bonate), and poly(DTO carbonate)] were synthesized according to published procedures.<sup>13,14</sup> The polymers were purified by precipitation into ether followed by a second precipitation into water to remove low molecular weight species. Medical-grade PLLA was obtained from Boehringer-Ingelheim in pellet form. Phosphate-buffered saline (PBS) was obtained from Sigma (St. Louis, MO). Pouches for  $\gamma$ -irradiated samples were donated by Technipaq Inc. (Crystal Lake, IL). All solvents were HPLC grade and were used as received.

## Methods

### Preparation of Solvent Cast Films

Polymer, 1.5 g, was dissolved in 25 mL (6% w/v) of methylene chloride. The solution was filtered through a Teflon syringe filter (0.45  $\mu$ m pore diameter) and poured into a leveled glass mold. The solvent was evaporated from filter paper covered molds in a dry nitrogen atmosphere glove bag for 24 h. The films were dried under vacuum for at least 1 week and stored at 0°C prior to sterilization. Properties of the solvent cast films are listed in Table I.

### Sterilization

Ethylene oxide treatment was performed using an Anprolene sterilization tray system Model AN72C (Andersen Products; Haw River, NC). Sterility was verified with a Steritest Spore Strip (Andersen Products). The samples were degassed for 2 weeks prior to analysis, and <sup>1</sup>H-nuclear magnetic resonance (NMR) verified the absence of detectable levels of ethylene oxide in the samples.  $\gamma$ -

Irradiation of samples in air at ambient temperature was performed by Isomedix Operations (Morton Grove, IL). Samples were placed on a rotating platform and exposed to a Co<sup>60</sup> source until the desired doses were obtained (0.3, 1.1, 3.9, 6.4, and 10.6 Mrad). Dosage was determined using Harwell Red perspex dosimeters. After sterilization, samples were stored at 0°C prior to analysis.

### Gel Permeation Chromatography (GPC)

Molecular weights of polymers were determined on a chromatographic system consisting of a Waters Model 510 pump, a Waters Model 410 refractive index detector, and a Digital Venturis 466 computerized data station equipped with Millennium software (Waters). Two PL-gel GPC columns (pore size 10<sup>5</sup> and 10<sup>4</sup> Å, 30 cm in length) were operated in series at a flow rate of 1 mL/min in tetrahydrofuran (THF). Samples were filtered through a 0.45  $\mu$ m Teflon membrane filter prior to injection. Molecular weights were reported as weight averages ( $M_w$ ) relative to polystyrene standards (Polymer Laboratories). The accuracy of the GPC measurements was confirmed using Wyatt Technologies MiniDawn low-angle laser light scattering (MiniDawn, Wyatt Technologies, Santa Barbara, CA).

### Spectroscopy

Attenuated total reflectance–Fourier transform infrared spectroscopy (ATR–FTIR) was recorded on a Matson-Cygnus 100 spectrometer equipped with a flat zinc–selenium crystal. All spectra were obtained from 200 scans at 2 cm<sup>-1</sup> resolution. Following correction for atmospheric water and car-

bon dioxide absorption, the spectra were resolved into individual components (Gaussian and Lorentzian mix) by means of an iterative least-squares method (GRAMS 386 software; Galactic Industries).  $^1\text{H-NMR}$  spectra of polymer solutions in deuterated chloroform ( $\text{CDCl}_3$ ) were recorded on a Varian Gemini VXR-200 spectrometer.

### Mechanical Testing

Pieces of sterile films were tested on a Sintech 5/D tensile tester at room temperature using a gauge length of 50 mm and a crosshead speed of 2 mm/min. Sample width (ca. 5 mm) and thickness (ca. 0.1 mm) were averaged from four measurements taken prior to analysis. The reported values of yield strength, the Young's modulus, and % strain at break were derived from the stress-strain curves and averaged from four separate runs. Statistical significance was determined using an unpaired  $t$ -test at 95% significance level (StatView 4.02; Abacus Concepts, Inc.).

### Thermal Analysis

A differential scanning calorimeter (DSC) TA Instruments Model 910 calibrated with indium was used to measure the glass transition ( $T_g$ ) of the polymers. Each specimen was subjected to two consecutive DSC scans. After the first scan, the specimen was quenched with liquid nitrogen and a second scan was performed immediately thereafter at the rate of  $10^\circ\text{C}/\text{min}$ . The  $T_g$  was determined in the second scan by the midpoint of the endothermic changes associated with the glass transition.

### Degradation Studies

Samples of the sterilized polymer films were incubated at  $37^\circ\text{C}$  in 20 mL of 0.1M PBS (pH 7.4) for 5 months. Each week, the samples were transferred into fresh buffer. At preselected time points, the samples were removed, rinsed in deionized distilled water, and dried under vacuum. The samples were then analyzed for molecular weight retention relative to unsterilized samples being incubated under identical conditions.

## RESULTS

Solvent-cast films of tyrosine-derived polycarbonates and PLLA were sterilized by ethylene oxide

and  $\gamma$ -irradiation. All polymers had initial molecular weights greater than 100,000 Da and polydispersities ( $M_w/M_n$ ) between 1.5 and 1.9 (Table I). Five doses of  $\gamma$ -irradiation (0.3, 1.1, 3.9, 6.4, and 10.6 Mrad) were used to evaluate the effect of radiation dose. While irradiation at 6.4 and 10.6 Mrad had no clinical relevance, these high doses were needed to estimate the radiation chemical yields.

### Exposure of Tyrosine-derived Polycarbonates to Ethylene Oxide

#### Physical Changes

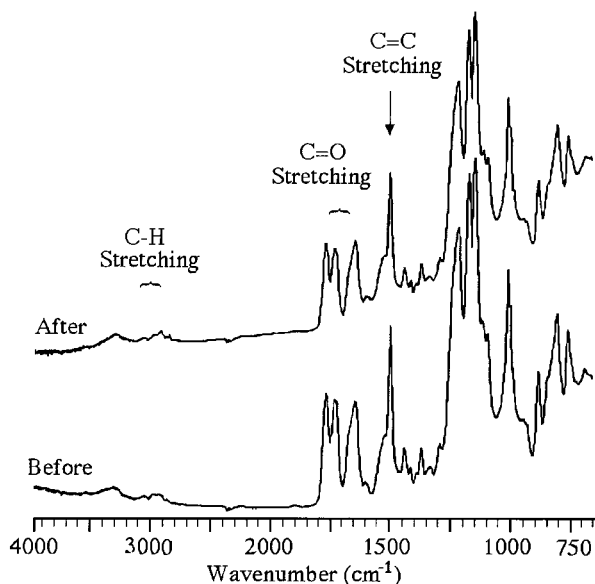
Following ethylene oxide exposure, there was no detectable change in the color, clarity, or physical appearance of any of the tyrosine-derived polycarbonate samples.

#### Molecular Weight Retention

The changes in molecular weight and polydispersity ( $M_w/M_n$ ) were evaluated by GPC. All four of the tyrosine-derived polycarbonates retained 99% of their initial molecular weight with no change in polydispersity following exposure to ethylene oxide.

#### Surface Chemical Composition

Since ethylene oxide can alter the surface properties of polymers, ATR-FTIR was used to evaluate the chemical surface characteristics of the exposed polycarbonates. Qualitative examinations of the spectra of ethylene oxide-exposed polycarbonates revealed no chemical changes in the surface relative to nonsterile control films (Fig. 2). Semiquantitative surface analysis of the sterilized polycarbonate films was performed using the phenyl C=C stretching peak as the internal reference. The integrity of the pendent chain ester bond was monitored using the area of the ester carbonyl stretching at  $1736\text{ cm}^{-1}$ . The integrity of the alkyl groups in the pendent chain was analyzed using the combined area of the aliphatic CH stretching peaks ( $\text{CH}_2$  at  $2870\text{ cm}^{-1}$ ,  $\text{CH}_3$  at  $2930\text{ cm}^{-1}$ , and  $\text{CH}_{\text{asymmetric}}$  at  $2980\text{ cm}^{-1}$ ). The integrity of the carbonate and amide bonds were monitored using the area of the carbonate stretching at  $1774\text{ cm}^{-1}$  and the amide I and II regions of the ATR-FTIR, respectively. Among the nonsterilized samples of the four tyrosine-derived polycarbonates, area ratios of the carbonate and amide absorp-



**Figure 2** ATR-FTIR spectra of poly(DTE carbonate) before (bottom curve) and after (top curve) ethylene oxide sterilization.

tions to the phenyl absorptions are all very similar, which is indicative of the identical backbone structure of the polymers. With increasing pendent chain length (from ethyl to octyl), the ratio of the area of aliphatic stretching to the area of phenyl stretching increased from 0.2 to 1.3, which is consistent with the chemical structure of the polycarbonates. Exposure to ethylene oxide had no effect on the ratios of the peak areas corresponding to aliphatic CH stretching, ester carbonyl stretch, carbonate carbonyl stretch, and amide stretching relative to the phenyl C=C stretching peak, indicating that no detectable changes in the surface chemical composition were associated with the exposure of these materials to ethylene oxide.

### Mechanical Properties

The mechanical properties of ethylene oxide-exposed tyrosine-derived polycarbonates were evaluated. Yield strength, the Young's modulus, and % strain at break were determined from a stress-strain curve to elucidate changes in polymer strength, stiffness, and elongation, respectively. Poly(DTE carbonate) exposed to ethylene oxide showed a small, significant reduction in the yield strength and stiffness relative to the control. The other three polycarbonates exposed to ethylene oxide showed no significant difference in yield

strength, the Young's modulus, or % strain at break relative to the nonsterilized control (Table II).

### Degradation

Samples of sterilized polymer films were incubated in PBS at 37°C for 5 months to determine the effect of ethylene oxide exposure on the post-sterilization degradation rate. The molecular weights of all samples were monitored at 1, 3, 4, and 5 months. For poly(DTE carbonate), poly(DTB carbonate), and poly(DTH carbonate), the difference in the  $M_w$  remaining after 5 months between ethylene oxide-exposed samples and unexposed controls was within  $\pm 10\%$  (Fig. 3). Since these small variations were within the instrumentation error of the GPC, one can conclude that ethylene oxide sterilization had no detectable effect on the subsequent degradation of these polymers. However, poly(DTO carbonate) exposed to ethylene oxide degraded faster than did the control; after 5 months *in vitro*, it retained only 45% of the initial  $M_w$ , whereas the nonsterilized control retained 59% (Fig. 3).

### Exposure of PLLA to Ethylene Oxide

PLLA was evaluated as a control. Ethylene oxide exposure did not cause a color change in the films, and 97% of the initial molecular weight was retained. The polydispersity did not change. Qualitative comparison of the ATR-FTIR spectra of exposed and unexposed PLLA films did not reveal the disappearance or emergence of any peaks; thus, no detectable changes in the surface chemical composition were produced by exposure to ethylene oxide. Since PLLA does not provide a distinct absorption that can be used as an internal reference in the calculation of peak areas, it was impossible to perform the semiquantitative analysis of the ATR-FTIR spectra. PLLA exposed to ethylene oxide retained its strength and % strain at break, but experienced a statistically significant decrease in the Young's modulus (Table II). Following incubation in PBS for 5 months, no significant differences in the poststerilization degradation rate were evident (Fig. 3).

### Exposure of Tyrosine-derived Polycarbonates to $\gamma$ -Irradiation

#### Physical Changes

$\gamma$ -Irradiation of tyrosine-derived polycarbonates up to 6.4 Mrad did not produce any change in the physi-

**Table II** Effect of Ethylene Oxide Exposure on Mechanical Properties of Tyrosine-derived Polycarbonates and PLLA

Polymer	Dose	Yield Strength <sup>a</sup> (MPa)	Young's Modulus <sup>a</sup> (MPa)	% Strain at Break <sup>a</sup>
Poly(DTE carbonate)	Control	53.2 ± 1.8	1937 ± 62	478 ± 152
	Exposed	47.0 ± 1.7 <sup>b</sup>	1594 ± 160 <sup>b</sup>	558 ± 124
Poly(DTB carbonate)	Control	44.7 ± 2.3	1552 ± 56	579 ± 107
	Exposed	46.4 ± 2.7	1513 ± 108	566 ± 147
Poly(DTH carbonate)	Control	39.7 ± 1.1	1416 ± 71	422 ± 180
	Exposed	40.8 ± 2.8	1483 ± 115	620 ± 165
Poly(DTO carbonate)	Control	36.2 ± 2.4	1015 ± 129	842 ± 111
	Exposed	37.0 ± 1.0	1182 ± 156	635 ± 183
PLLA	Control	59.5 ± 6.3	2689 ± 153	112 ± 59
	Exposed	56.7 ± 0.9	2355 ± 144 <sup>b</sup>	119 ± 82

<sup>a</sup> Mean ± standard deviation; *n* = 4 or 5.

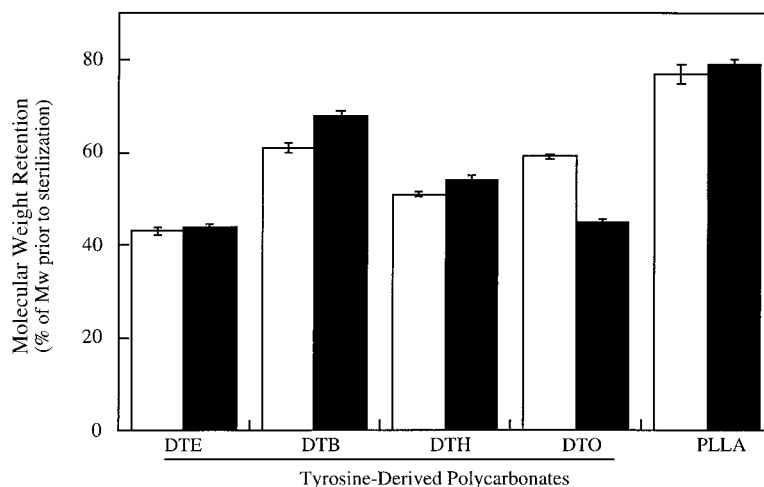
<sup>b</sup> Significantly different relative to control.

cal appearance of the films. However, after exposure to 10.6 Mrad, tyrosine-derived polycarbonates were noticeably more yellow in color. The color change was expected since the tyrosine-derived polycarbonates have a backbone structure that is similar to poly(bisphenol A carbonate) which is discolored by irradiation in the range of 0–50 Mrad.<sup>15</sup>

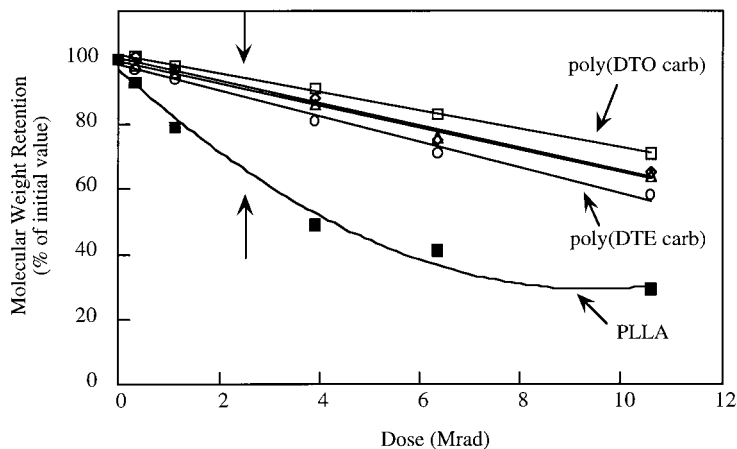
### Molecular Weight Retention

The effect of  $\gamma$ -irradiation on the molecular weight of tyrosine-derived polycarbonates is shown in Fig-

ure 4. Note that after irradiation to 10.6 Mrad, the highest test dose, poly(DTE carbonate) retained 58% of its initial molecular weight, while poly(DTO carbonate) retained 71% of its initial molecular weight. The molecular weight retention of poly(DTB carbonate) and poly(DTH carbonate) fell between the values of the ethyl and octyl derivatives. The polydispersity of all polycarbonates remained essentially constant (Table III). The observed minor variations are within the error of our instrumentation ( $\pm 0.2$ ).



**Figure 3** Effect of ethylene oxide sterilization on poststerilization rate of degradation. (Solid bar) Sterilized and (open bar) nonsterilized film samples were incubated under identical conditions for 5 months. Each bar represents the mean ± standard deviation of three measurements. Among all polymers tested; only poly(DTO carbonate) exhibited a statistically significant change in the degradation rate after exposure to ethylene oxide.



**Figure 4** Molecular weight retention (% of molecular weight prior to sterilization) of (open circle) poly(DTE carbonate), (open diamond) poly(DTB carbonate), (open triangle) poly(DTH carbonate), (open square) poly(DTO carbonate), and (solid square) PLLA as a function of  $\gamma$ -irradiation dose. Percent  $M_w$  retention was calculated relative to the  $M_w$  of the corresponding nonsterilized control film. Arrows correspond to a dose of 2.5 Mrad which is widely used for the sterilization of medical implants. Each point represents the mean of three measurements.

### Radiation Chemical Yields

$\gamma$ -Irradiation of polymers is known to induce structural changes such as chain scission and crosslinking. These changes can potentially lead to changes in mechanical strength, solubility, and degradation rate of polymers.<sup>16</sup> The number of molecules undergoing chain scission [ $G(S)$ ] and/or crosslinking [ $G(X)$ ] per 100 eV of absorbed energy for each polycarbonate was estimated using eqs. (1) and (2) in combination with the slope of plots of  $M_n^{-1}$  vs. dose and  $M_w^{-1}$  vs. dose (Fig. 5).<sup>17</sup> In the equations, the initial weight-average molecular weight is  $M_{w,0}$ , initial number-average molecular weight is  $M_{n,0}$ , the radiation dose is  $D$  (in eV/g), and Avogadro's number is denoted by  $N_A$ <sup>17,18</sup>:

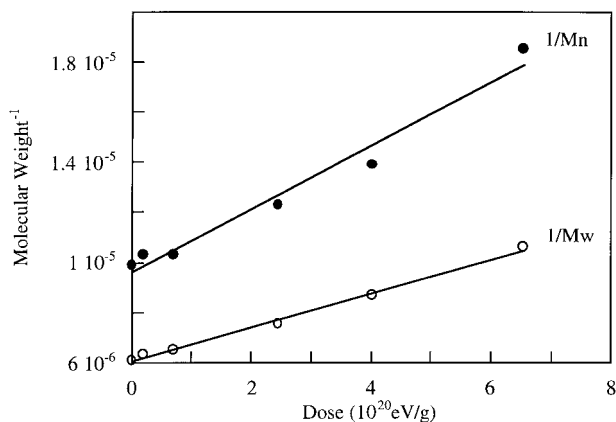
$$\frac{1}{M_{n,D}} = \frac{1}{M_{n,0}} + [G(S) - G(X)] \frac{D}{100N_A} \quad (1)$$

$$\frac{1}{M_{w,D}} = \frac{1}{M_{w,0}} + \left[ \frac{G(S)}{2} - 2G(X) \right] \frac{D}{100N_A} \quad (2)$$

The  $G$  values for tyrosine-derived polycarbonates are shown in Table IV. Poly(DTE carbonate) had the highest  $G(S)$  value, 0.74, and poly(DTO carbonate) had the lowest value, 0.1. Chain scission was the predominant mechanism of irradiation damage for the polycarbonates. The small  $G(S)$  values indicate that the amount of degradation is small which was expected due to the presence of "protective" aromatic groups in the backbone.<sup>15,17,19</sup> All the tyrosine-derived poly-

**Table III** Effect of Radiation Dose on Polydispersity of Tyrosine-derived Polycarbonates and PLLA

Polymer	$\gamma$ -Irradiation Dose (Mrad)					
	0.0	0.3	1.1	3.9	6.4	10.6
Poly(DTE carbonate)	1.6	1.6	1.6	1.7	1.6	1.7
Poly(DTB carbonate)	1.7	1.6	1.7	1.7	1.7	1.7
Poly(DTH carbonate)	1.8	1.8	1.8	1.8	1.8	1.8
Poly(DTO carbonate)	1.8	1.9	1.8	1.7	1.5	1.7
PLLA	1.4	1.5	1.4	1.5	1.7	1.8



**Figure 5** Representative plot of (open circle)  $M_w^{-1}$  vs. dose and (solid circle)  $M_n^{-1}$  vs. dose for poly(DTE carbonate).  $M_w^{-1}$  and  $M_n^{-1}$  increased linearly with dose.

carbonates had negative  $G(X)$  values, indicating that very little or no crosslinking had occurred.<sup>20</sup>

### Surface Chemical Composition

The surface properties of the irradiated polycarbonates were evaluated by ATR-FTIR as described for the ethylene oxide-exposed samples. Irradiation at each dose for each polycarbonate did not effect the ratios of peak areas corresponding to aliphatic CH stretching, carbonate carbonyl stretch, ester carbonyl stretch, and amide stretching relative to the phenyl C=C stretching peak. This demonstrates that no detectable alterations in the surface chemical composition were associated with irradiation of these materials at any dose.

### Mechanical Properties

The irradiated films were evaluated for the retention of mechanical properties. Polymer films irradiated at 6.4 and 10.6 Mrad were not included in these studies, since such high doses would not normally be used clinically. Poly(DTO carbonate) showed a significant decrease in % strain at break for all doses. The modulus increased with dose and a significant increase was found after radiation at 3.9 Mrad (Table V). Since poly(DTO carbonate) showed the smallest loss of molecular weight, the obvious embrittlement observed may be due to a small amount of crosslinking. For the other polycarbonates, the mechanical properties exhibited only slight changes that were marginally significant in a few cases without showing any clear, discernible trends (Table V). The gen-

eral lack of significant changes in their mechanical properties is in agreement with the fact that the polycarbonates retained much of their molecular weight.

### Degradation

Films of each of the four polycarbonates irradiated at 0.3, 1.1, and 3.9 Mrad were incubated at 37°C in PBS for 5 months to evaluate the effect of radiation on the rate of degradation. Films irradiated at 6.4 and 10.6 Mrad were not included in these studies as these doses are practically irrelevant. Of the tyrosine-derived polycarbonates, only poly(DTO carbonate) irradiated at 3.9 Mrad degraded faster than did the nonirradiated control (Fig. 6).

### Exposure of PLLA to $\gamma$ -Irradiation

After  $\gamma$ -irradiation at 10.6 Mrad, the PLLA film was clear and colorless, but had lost its mechanical strength and contained cracks throughout. PLLA was clearly degraded by irradiation (Fig. 4), retaining only 29% of its initial molecular weight after irradiation at 10.6 Mrad. The polydispersity of PLLA increased with dose (Table III). The  $G$  values for PLLA [ $G(S) = 2.39$ ;  $G(X) = -0.02$ ] indicate that PLLA experienced predominately chain scission and no crosslinking (Table IV). These results correspond to previously published results: Collett et al. reported  $G(S)$  values between 2.22 and 3.32 for semicrystalline PLLA irradiated at 2.5 Mrad under different water-vapor pressures.<sup>16</sup> Previous studies also reported the predominance of chain scission without crosslinking for PLLA irradiated at less than 25 Mrad.<sup>18</sup>

The effect of  $\gamma$ -irradiation on the surface chemi-

**Table IV** Estimated  $G$  Values of Scission and Crosslinking for Tyrosine-derived Polycarbonates and PLLA

Polymer	Estimated $G$ Values	
	$G(S)$	$G(V)$
Poly(DTE carbonate)	0.74	-0.02
Poly(DTB carbonate)	0.69	-0.03
Poly(DTH carbonate)	0.58	-0.04
Poly(DTO carbonate)	0.15	-0.10
PLLA	2.39	-0.02

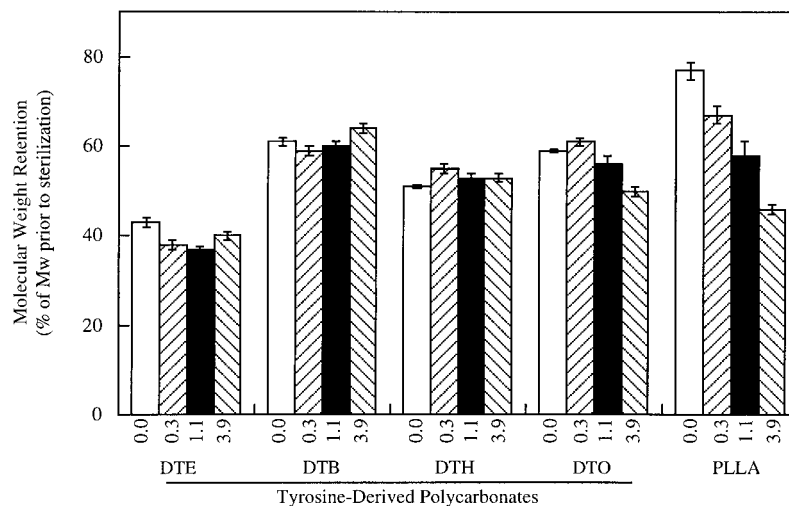


**Table V** Effect of Radiation Dose on Mechanical Properties of Tyrosine-derived Polycarbonates and PLLA

Polymer	$\gamma$ -Irradiation Dose (Mrad)	Yield Strength <sup>a</sup> (MPa)	Young's Modulus <sup>a</sup> (MPa)	% Strain at Break <sup>a</sup>
Poly(DTE carbonate)	0.0	53.2 $\pm$ 1.8	1937 $\pm$ 62	478 $\pm$ 152
	0.3	53.4 $\pm$ 3.0	1785 $\pm$ 343	288 $\pm$ 149
	1.1	44.9 $\pm$ 1.1 <sup>b</sup>	1910 $\pm$ 93	125 $\pm$ 73 <sup>b</sup>
	3.9	53.4 $\pm$ 1.6	1954 $\pm$ 103	298 $\pm$ 179
Poly(DTB carbonate)	0.0	44.7 $\pm$ 2.3	1552 $\pm$ 56	579 $\pm$ 107
	0.3	49.0 $\pm$ 2.8 <sup>b</sup>	1379 $\pm$ 188	538 $\pm$ 95
	1.1	47.4 $\pm$ 3.2	1332 $\pm$ 124 <sup>b</sup>	648 $\pm$ 115
	3.9	44.5 $\pm$ 1.6	1678 $\pm$ 73 <sup>b</sup>	713 $\pm$ 31
Poly(DTH carbonate)	0.0	39.7 $\pm$ 1.1	1416 $\pm$ 71	422 $\pm$ 180
	0.3	39.9 $\pm$ 2.2	1415 $\pm$ 85	529 $\pm$ 171
	1.1	42.8 $\pm$ 1.4 <sup>b</sup>	1424 $\pm$ 75	535 $\pm$ 194
	3.9	41.9 $\pm$ 2.2	1290 $\pm$ 70 <sup>b</sup>	587 $\pm$ 178
Poly(DTO carbonate)	0.0	36.2 $\pm$ 2.4	1015 $\pm$ 129	842 $\pm$ 111
	0.3	38.7 $\pm$ 1.4	1116 $\pm$ 103	631 $\pm$ 110 <sup>b</sup>
	1.1	36.6 $\pm$ 1.8	1096 $\pm$ 34	605 $\pm$ 124 <sup>b</sup>
	3.9	37.5 $\pm$ 2.1	1195 $\pm$ 115 <sup>b</sup>	679 $\pm$ 95 <sup>b</sup>
PLLA	0.0	59.5 $\pm$ 6.3	2689 $\pm$ 153	112 $\pm$ 59
	0.3	54.4 $\pm$ 0.6	2330 $\pm$ 51 <sup>b</sup>	128 $\pm$ 65
	1.1	55.0 $\pm$ 1.9	2174 $\pm$ 158 <sup>b</sup>	56 $\pm$ 47
	3.9	52.7 $\pm$ 2.1 <sup>b</sup>	2445 $\pm$ 150 <sup>b</sup>	4.9 $\pm$ 2.4 <sup>b</sup>

<sup>a</sup> Mean  $\pm$  standard deviation;  $n = 4$  or  $5$ .

<sup>b</sup> Significantly different relative to control.



**Figure 6** Effect of  $\gamma$ -irradiation on the poststerilization rate of degradation. (Open bar) Non-sterilized film samples and films irradiated at (hatched bar) 0.3 Mrad, (solid bar) 1.1 Mrad, and (hatched bar) 3.9 Mrad were incubated under identical conditions for 5 months. Each bar represents the mean  $\pm$  standard deviation of three measurements.

cal composition of PLLA was evaluated by ATR-FTIR. Qualitative analysis of the spectra of irradiated PLLA did not indicate any changes at any dose. Semiquantitative analysis could not be performed due to the lack of a  $\gamma$ -resistant bond in PLLA which could be used as an internal reference.

Irradiated PLLA films did show a loss in mechanical properties, losing approximately 10% of their yield strength when irradiated at 3.9 Mrad. There was a significant decrease in modulus at all doses relative to the nonsterilized control. Percent elongation at break was maintained at 0.3 Mrad, but decreased as the irradiation dose increased (Table V). The relatively low loss of strength for PLLA despite the 50% loss in molecular weight at 3.9 Mrad can be explained by its high initial molecular weight ( $M_w = 185$  kDa). Even after a reduction to only 50% of the original molecular weight, the degree of polymerization was still high enough to retain most of its original mechanical integrity.

Following irradiation, films of PLLA were incubated in PBS at 37°C for 5 months to analyze the effect of the radiation on *in vitro* degradation. PLLA irradiated at all doses degraded faster than did the nonsterilized control samples (Fig. 6).

## DISCUSSION

### Exposure to Ethylene Oxide

Data obtained in this study confirm that, as a general rule, both tyrosine-derived polycarbonates and PLLA can be exposed to ethylene oxide without detrimental changes in molecular weight, polydispersity, mechanical properties, surface chemical composition, and the degradation rate after sterilization. There were no obvious trends related to the backbone or pendent chain structure of the polymers.

In regard to the tyrosine-derived polycarbonates, the data obtained in this study showed slight deviations from Ertel's results,<sup>1</sup> which reported an average of 90%  $M_w$  retention after exposure to ethylene oxide, while in this study, no change in molecular weight (99%  $M_w$  retention) was observed. This difference is probably related to the different conditions used. Whereas in this study, polymers were exposed to ethylene oxide at 25°C for 24 h, Ertel sterilized at 32°C for 6 h.

An interesting phenomenon was observed in

the poststerilization degradation of poly(DTO carbonate). Whereas the other polymers exposed to ethylene oxide degraded at the same rate as did the nonsterilized controls when incubated in buffer under physiological conditions, poly(DTO carbonate) exposed to ethylene oxide degraded faster than the control (Fig. 3). One possible explanation is based on the observation made by Guess that polymer structure and pendent chain length can effect the diffusion coefficient and activation energy of diffusion of ethylene oxide gas. Comparing polyethylene, polypropylene, and polybutylene showed that ethylene oxide diffused more quickly from polyethylene than from polypropylene and polybutylene.<sup>21</sup> An additional observation relates to the fractional free volume in each of the four polycarbonates. Calculations by Suarez et al. clearly showed that poly(DTO carbonate) is not as tightly packed as are the other polymers.<sup>22</sup> Such an open packing structure favors ethylene oxide uptake, as shown by Sherstnev et al. for polyisoprene as compared to polystyrene.<sup>23</sup>

Accordingly, we hypothesize that the long pendent chain of poly(DTO carbonate) may have prevented the complete desorption of ethylene oxide with the residual amount of ethylene oxide leading to an increase in the rate of hydrolytic degradation. We attempted to confirm this hypothesis by testing all specimens for traces of ethylene oxide by NMR but were not able to detect the typical ethylene oxide absorption at 2.54 ppm in any of the polymer samples after degassing. Additional studies, using a more sensitive method for the detection of residual levels of ethylene oxide in degassed polymers, are needed to fully explain the unusual degradation behavior of ethylene oxide-sterilized poly(DTO carbonate).

### Exposure to $\gamma$ -Irradiation

$\gamma$ -Irradiation of tyrosine-derived polycarbonates resulted in some decrease in the molecular weight for all polymers. The general trend was that the polymers seem to become more resistant to molecular weight loss as the number of methylene groups in the pendent chain increased (Fig. 3): Poly(DTO carbonate) retained most of its initial molecular weight, while poly(DTE carbonate) retained the least. This is also reflected in the correlation between  $G(S)$ , the amount of chain scission, and the number of methylene groups in the pendent chain. The  $G(S)$  value decreased as the

length of the pendent chain increased, indicating that the polymers with longer pendent chains experienced less chain scission than did those with shorter pendent chains. These results are reasonable in view of reports published by others.<sup>19,24</sup>

In addition, for each of the four polycarbonates, a linear relationship was observed between the molecular weight retention and the dose of  $\gamma$ -irradiation. As the dose increased, the % molecular weight retained decreased. Interpolation of the linear relationship between % molecular weight and dose predicts that tyrosine-derived polycarbonates will retain greater than 88% of their initial molecular weight upon exposure to the clinically used sterilization dose of 2.5 Mrad (Fig. 3). The relatively high stability of tyrosine-derived polycarbonates to  $\gamma$ -irradiation is an important advantage for their use in biomedical applications as the addition of radiation stabilizers could interfere with the biocompatibility of the polymers.

Data obtained in this study on the effect of  $\gamma$ -irradiation on the molecular weight retention for tyrosine-derived polycarbonates are in contrast to the observations published by Ertel and Kohn,<sup>1</sup> who observed a maximum retention of 76% of the initial molecular weight at 1 Mrad and 62% at 4 Mrad of  $\gamma$ -irradiation irrespective of pendant chain length. We have no explanation for this discrepancy and speculate that nonideal conditions of the initial pilot study may have contributed to the high loss of molecular weight observed.

Among all polycarbonates, only poly(DTO carbonate) exhibited a clearly defined change in mechanical properties. The modulus showed an upward trend with a statistically significant increase after radiation at 3.9 Mrad. Poly(DTO carbonate) also demonstrated a significant decrease in % strain at break for all doses. The embrittlement and increase in modulus of poly(DTO carbonate) following irradiation indicates that some crosslinking occurred; however, since the molecular weight and solubility properties did not change, the amount of crosslinking was small.

The difference in the behavior of poly(DTO carbonate) relative to the other tested polycarbonates can be explained based on the number of methylene groups present in the polymer. It is well established that polymers containing aromatic groups and oxygen do not crosslink when exposed to  $\gamma$ -irradiation, while polymers containing methylene groups experience crosslinking.<sup>16,17,24</sup> Therefore, for poly(DTE carbonate) having only two methylene groups in its pendent

chain, chain scission was the predominant mode of radiation damage. For poly(DTO carbonate), having eight methylene groups in the pendent chain, irradiation resulted in both chain scission and crosslinking. Dong et al. reported similar results. A poly(methyl acrylate) having a pendent chain with seven methylene groups showed both degradation and crosslinking whereas a poly(methyl acrylate) with a benzyl pendent chain did not crosslink.<sup>19</sup>

Poly(DTO carbonate) also experienced an unexpected increase in poststerilization degradation rate following  $\gamma$ -irradiation at 3.9 Mrad. Thus, it is important to note that among the tested polycarbonates the overall material properties of poly(DTO carbonate) were most significantly affected by  $\gamma$ -irradiation, even though this polymer showed the highest degree of molecular weight retention.

For PLLA, a polynomial correlation between dose and molecular weight was observed in which the molecular weight decreased with increasing dose of  $\gamma$ -irradiation. This was consistent with published results.<sup>16,18,25</sup> Interpolation of our data predicts that PLLA will retain 60% of initial molecular weight when irradiated at 2.5 Mrad, which corresponds to results published by Gilding and Reed.<sup>25</sup> Specimens of PLLA irradiated at 1.1 and 3.9 Mrad exhibited significant changes in their mechanical properties and degraded faster than did the nonsterile control incubating under the same conditions. Clearly, irradiation of PLLA leads to significant molecular damage affecting the entire spectrum of material properties.

## CONCLUSIONS

This study represents the first comprehensive evaluation of the sterilizability of tyrosine-derived polycarbonates using the widely investigated PLLA as a control and comparison material. Comparing the effects of ethylene oxide and  $\gamma$ -irradiation sterilization on the molecular weight, surface composition, mechanical properties, and *in vitro* degradation for tyrosine-derived polycarbonates and PLLA clearly indicates that ethylene oxide induces less structural damage to the polymers.

Both tyrosine-derived polycarbonates and PLLA can be sterilized by exposure to ethylene oxide, with the possible exception of poly(DTO carbonate). This material exhibited a higher degrada-

tion rate after ethylene oxide exposure than that of the nonexposed control.

Due to the presence of aromatic groups in the backbone, tyrosine-derived polycarbonates were significantly more resistant to  $\gamma$ -irradiation than was PLLA. Among the different tyrosine-derived polycarbonates, the polymers with pendent chains up to six carbons experienced chain scission, while poly(DTO carbonate) underwent both chain scission and a small amount of crosslinking. The results of this study indicate that, contrary to PLLA, tyrosine-derived polycarbonates can be sterilized by  $\gamma$ -irradiation.

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