Kinetics of the Hydrolysis of Bisphenol F Diglycidyl Ether in Water-Based Food Simulants. Comparison with Bisphenol A Diglycidyl Ether†

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We studied the first-order degradation kinetics of Bisphenol F diglycidyl ether (BFDGE) in three water-based food simulants [3% (w/v) acetic acid, distilled water, and 15% (v/v) ethanol] at various temperatures. BFDGE and its first and second hydrolysis products were determined by reversed phase high-performance liquid chromatography with fluorescence detection. Nonlinear regression was used to fit the experimental data at 40, 50, and 60 °C with the proposed kinetic equations; the Arrhenius equation was then fitted to the rate constants obtained, and the kinetic models were tested by comparing experimental data obtained at 70 °C with the kinetic curves calculated using the rate constants predicted for this temperature. The half-life of BFDGE was longest in ethanol and shortest in acetic acid. The difference between the hydrolysis rates of BFDGE and Bisphenol A diglycidyl ether may be due to 10% of the BFDGE used being in $n = 1$ monomer form. The results imply that resins which comply with existing legislation on the migration of unreacted monomer may still contaminate foodstuffs.

INTRODUCTION

Bisphenol A diglycidyl ether [BADGE, 2,2′-[(1-methylethylidene)bis(4,1-phenyleneoxymethylene)]bisoxirane; relative molecular mass 340; see Figure 1] and Bisphenol F diglycidyl ether (BFDGE, Figure 1), like other epoxy compounds, are alkylating agents with cytotoxic effects in tissues with high rates of cell division. Their toxicity depends mainly on the concentration of epoxy groups, although the sensitization of surface tissues caused by BADGE is most probably due to toxic agents derived from byproducts (May, 1988). Since epoxy resins derived from BADGE and BFDGE are used in coatings for food containers (Tice and McGuiness, 1987; Tice, 1988), legal limits on the migration of BADGE and BFDGE into food and food simulants have been proposed (Scientific Committee for Food, 1987) or enacted (*Official Journal of the European Communities*, 1990). However, under standard test conditions (10 days at 40 °C), BADGE undergoes hydrolysis, with a half-life of less than 2 days (Tice and McGuiness, 1987; Tice, 1988; Paseiro-Losada et al., 1992).

In the work reported here, we investigated the degradation kinetics of BFDGE in three water-based food simulants, using RP-HPLC with fluorescence detection to separate and quantify BFDGE and its hydrolysis components. Results were compared with the degradation kinetics of BADGE in the same simulants (Paseiro-Losada et al., 1992).

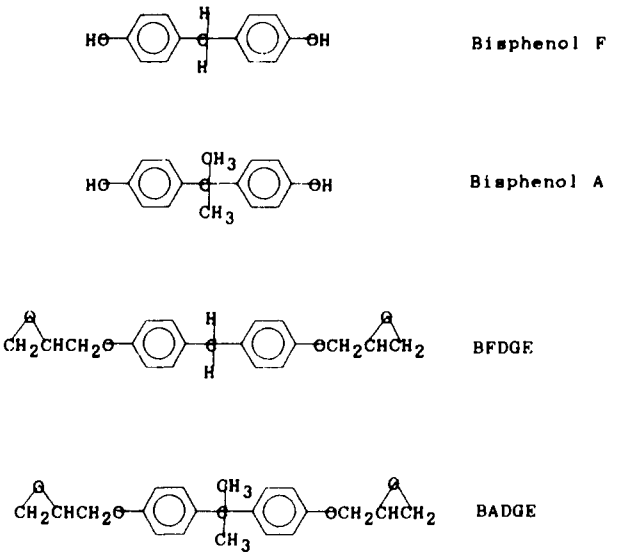

Figure 1. Molecular structures of Bisphenols A and F and their diglycidyl ethers.

EXPERIMENTAL PROCEDURES

1. **Apparatus.** The following apparatus were used: Spectra-Physics SP8700 XR extended range LC pump; Spectra-Physics SP8750 organizer; Perkin-Elmer PE LS 40 fluorescence detector; Spectra-Physics SP4290 integrator and SP WINNER software, version 4.00; SELECTA air oven, Model 206; AFORA stoppered Pyrex graduated cylinders and volumetric flasks.

2. **Reagents.** The following reagents were used: helium N-50 from the Sociedad Española de Oxígeno (SEO), for degassing the mobile phases; water, demineralized Milli-Q quality (Millipore Corp.); acetonitrile, gradient grade, LiChrosolv(R) (Merck, ref 30); tetrahydrofuran, HPLC grade, Analyticals(R) (Carlo Erba, ref 412452); absolute ethanol (Merck, ref 983); acetic acid (Merck,

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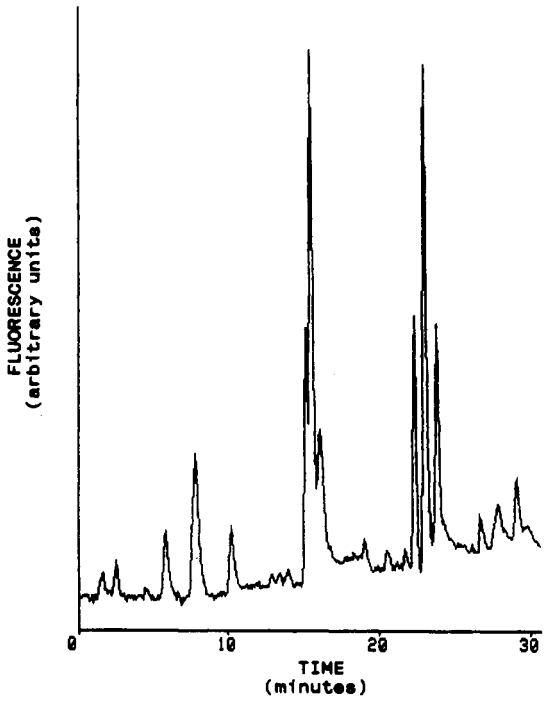


Figure 2. Chromatogram obtained midway through BFDGE hydrolysis. Compounds, in order of elution, are the second degradation product of BFDGE, the first degradation product, and BFDGE; each compound elutes as a triplet of peaks, one for each positional isomer. The group of three smaller peaks immediately following each triplet of larger peaks is due to the corresponding $n = 1$ oligomer.

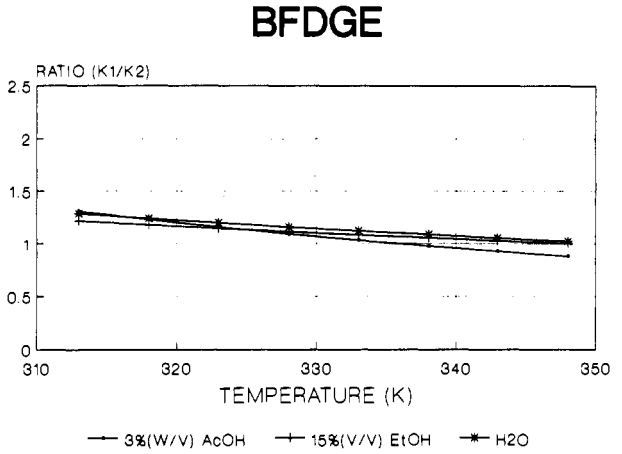


Figure 3. k_1/k_2 ratios for the hydrolysis of BFDGE in different simulants, plotted against assay temperature.

art. 63); Bisphenol F diglycidyl ether, Araldit XPY-306 (Ciba Geigy).

3. Procedure. *3.1. BFDGE Degradation.* A solution of 100 mg of Araldit XPY-306 in 50 mL of tetrahydrofuran was diluted 50-fold with tetrahydrofuran, and 1-mL samples of the resulting solution were in turn diluted 50-fold with water-based food simulant [3% (w/v) acetic acid, distilled water, or 15% (v/v) ethanol] at the working temperature, giving a final BFDGE concentration in the simulants of 800 $\mu g\ L^{-1}$ [800 ppb (w/v)].

3.2. BFDGE Determination. HPLC was performed on 0.5-mL samples immediately after the simulant was added and thereafter at intervals depending on the working temperature until degradation of BFDGE was complete. Experiments were performed at 40, 50, 60, and 70 °C. The chromatographic conditions were as follows: column, 15 cm × 5 mm i.d., stainless steel; packing, 5 μm Pecosphere CRT C18 RC (guard columns (C18) were used to protect the packing in analytical columns); injection, 50-μL loop in a Rheodyne valve, filled with a Hamilton syringe; flow, 1.5 mL/ min; gradient elution, 5-min isocratic elution with acetonitrile–water (25:75), 10-min linear gradient to 50% acetonitrile, 5-min isocratic elution at 50% acetonitrile, 5-min linear gradient to 60% acetonitrile, 5-min isocratic elution at 60% acetonitrile, 5-min linear gradient to 100% acetonitrile, and 5-min isocratic elution at 100%; detection, attenuation factor 16 with auto-zero, response, 4 (response time, 2.8 s), excitation wavelength 275 nm, emission wavelength 300 nm, photomultiplier voltage 750 V; integrator attenuation, 4.

Table I. Half-Lives of BFDGE under the Conditions Described

aq simulant	temp, °C	BFDGE $t_{1/2}$, h
3% (w/v) AcOH	40	6.5
	50	3.8
	60	2.0
distilled H_2O	40	51.5
	50	22.9
	60	11.6
15% (v/v) EtOH	40	73.8
	50	36.1
	60	18.3

A typical chromatogram is shown in Figure 2. Under the assumption that the chromatographic response was the same for all peaks, BFDGE and its hydrolysis products were quantified as the total area of the corresponding triplet, expressed as a percentage of the total area of the three major triplets.

3.3. Calculation of Kinetic Parameters. The hydrolysis of BFDGE takes place in accordance with the scheme

$$\text{BFDGE} \xrightarrow{k_1} \text{B} \xrightarrow{k_2} \text{C}$$

where B and C are, respectively, the results of hydrolyzing one and two oxirane rings. The corresponding rate equations are

$$d[A]/dt = -k_1[A]$$

$$d[B]/dt = k_1[A] - k[B]$$

$$d[C]/dt = k_2[B]$$

The rate constants k_1 and k_2 were optimized by fitting the integrated rate equations to the HPLC data by nonlinear regression using the SPSS/PC version 3.0 software package. The Arrhenius constant and the activation energy for the hydrolysis of BFDGE were then calculated by fitting the Arrhenius equation to the rate constants at 40, 50, and 60 °C by linear regression employing the same software package. Theoretical rate constants at 70 °C calculated from the Arrhenius equation were employed to generate kinetic curves, which were compared with the HPLC data obtained at this temperature to evaluate the proposed kinetic model.

RESULTS AND DISCUSSION

The half-life of BFDGE calculated from k_1 was longest in ethanol and shortest in acetic acid and decreased with increasing temperature (Table I); BADGE behaves similarly, although its hydrolysis is faster (Paseiro-Losada et al., 1992). The temperature dependence of the ratio k_1/k_2 for BFDGE was similar in the three simulants (Figure 3); for BADGE, k_1/k_2 in acetic acid differs from its values in ethanol and distilled water, which has been explained in terms of acidity and the formation of adducts with water and ethanol (Paseiro-Losada et al., 1992). This apparent difference between BFDGE and BADGE may be due to the $n = 1$ BFDGE oligomers that make up 10% of Araldit XPY-306 (Figure 4). If the reactivities of the two oxirane rings differ in the $n = 0$ monomers due to the presence of the $n = 1$ oligomer, acidity and adduct formation may no longer control the rate of hydrolysis. In keeping with this, the pre-exponential factors of the hydrolysis reactions

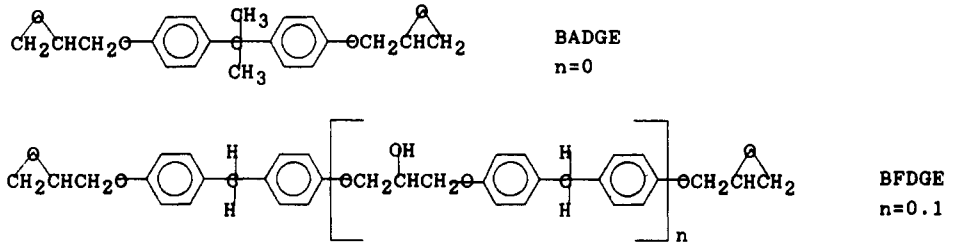
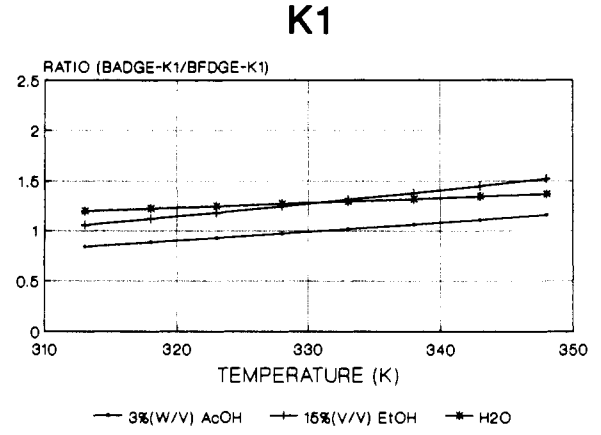


Figure 4. Structures of the diglycidyl ethers used.

Table II. Pre-Exponential Factors and Activation Energies of the Two Hydrolysis Reactions Calculated Using the Arrhenius Equation

		BFDGE		
simulant	k	A	E, kcal/mol	r
3% (w/v) AcOH	k_1	7.1E5	12	0.997
	k_2	2.8E7	15	0.993
distilled H_2O	k_1	1.4E7	15	0.999
	k_2	1.1E8	17	0.999
15% (v/v) EtOH	k_1	1.8E6	14	1.000
	k_2	1.0E7	16	1.000



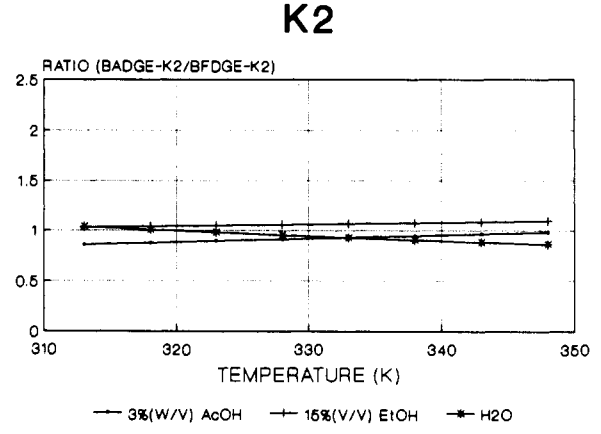


Figure 5. k_1(BADGE)/k_1(BFDGE) and k_2(BADGE)/k_2(BFDGE) ratios in the simulants vs assay temperature.

(except the second hydrolysis reaction in water) are lower for BFDGE (Table II) than for BADGE (Paseiro-Losada et al., 1992), particularly for the first hydrolysis. In spite of these differences, ratios k_1(BADGE)/k_1(BFDGE) and k_2(BADGE)/k_2(BFDGE) are near unity (Figure 5).

The experimental and predicted kinetic data at 70 °C, and their differences, are shown in Figure 6. The discrepancies are greatest in ethanol, in which adduct

Table III. Statistical Analysis of y Residuals

		product		
simulant	y residual[a]	BFDGE	1-DEG	2-DEG
3% (w/v) AcOH	av	−2.209	−0.838	2.045
	SD	3.976	2.170	3.277
	exptl t[c]	2.003	1.392	2.250
	error,[b] %	−8.841	−4.596	3.602
distilled H_2O	av	−1.256	0.339	0.919
	SD	2.538	2.337	2.512
	exptl t[d]	2.100	0.615	1.552
	error, %	−4.490	1.790	1.731
15% (v/v) EtOH	av	−0.304	−2.012	2.316
	SD	1.928	2.989	4.426
	exptl t[e]	0.687	2.934	2.281
	error, %	−0.813	−8.611	5.904

[a] y residual = y exptl − y pred. [b] Error (%) = (Σ y residual/Σ y pred) × 100. [c] Theoretical $t(\alpha = 0.05, DF = 12)$: $t(1-\alpha/2) = 2.179$. [d] Theoretical $t(\alpha = 0.05, DF = 17)$: $t(1-\alpha/2) = 2.110$. [e] Theoretical $t(\alpha = 0.05, DF = 18)$: $t(1-\alpha/2) = 2.101$.

Table IV. Levels of BFDGE and Its Hydrolysis Products after 10 Days in Water-Based Food Simulants at 40 °C

aq simulant	2-DEG, %	1-DEG, %	BFDGE, %
3% (w/v) AcOH	100.0	0.0	0.0
distilled H_2O	74.0	22.8	3.2
15% (v/v) EtOH	62.3	27.7	10.0

formation appears not to depress the k_2 process at 70 °C as much as between 40 and 60 °C. No statistically significant differences between predicted and observed data were encountered for BADGE (Paseiro-Losada et al., 1992); however, they were found for BFDGE, especially in ethanol (Table III).

The EEC specifies conditions for migration tests of 10 days at 40 °C; the FDA specifies 49 °C (Till et al., 1987). In acetic acid at 40 °C the only substance remaining after 10 days was the second hydrolysis product of BFDGE (Table IV); in distilled water and ethanol both hydrolysis products remained (BFDGE levels in these two systems are not detected when the real migration levels of free residual BFDGE from epoxy resins into these simulants are considered). In none of the three simulants was any species but the second hydrolysis product present after 10 days at 50 (close to 49 °C) or 60 °C.

CONCLUSIONS

The analytical technique used for the assay of BFDGE and its two hydrolysis products allowed migration levels due to BFDGE to be expressed as BFDGE itself and BFDGE hydrolysis kinetics in various food simulants to be studied.

The kinetic model proposed for the hydrolysis of BFDGE is valid within the temperature limits used. The reaction consists of two consecutive first-order hydrolysis steps.

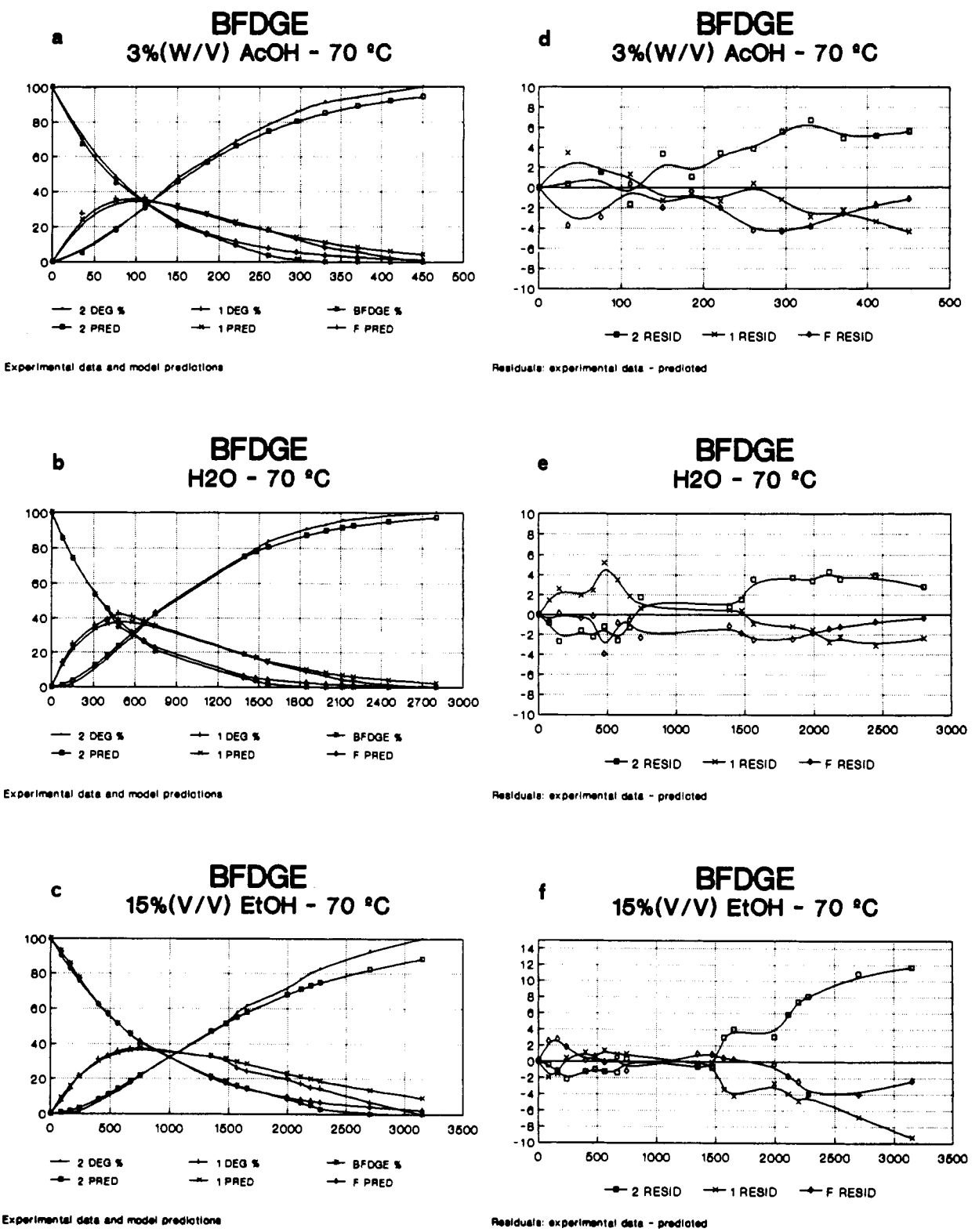


Figure 6. Experimental and predicted curves at 70 °C in (a) 3% (w/v) acetic acid, (b) distilled water, and (c) 15% (v/v) ethanol; residuals between the curves in (d) 3% (w/v) acetic acid, (e) distilled water, and (f) 15% (v/v) ethanol.

The fact that for the second hydrolysis the theoretical reaction rate is less than the experimental value suggests that the OH groups in the intermediate compound autocatalyze the second reaction. The ratios k_1(BADGE)/k_1(BFDGE) and k_2(BADGE)/k_2(BFDGE) are close to 1; i.e., the two compounds have similar hydrolysis rates.

We believe the study of the toxicity of the hydrolysis products of BFDGE is toxicologically important, rather than that of the parent compound, since the hydrolysis of BFDGE in water-based food under typical conditions is almost total.

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Registry No. BFDGE, 87110-76-7; EtOH, 64-17-5; AcOH, 64-19-7; BADGE, 1675-54-3.