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Experimental Methods and Data Evaluation Procedures for the Determination of Radical Copolymerization Reactivity Ratios from Composition Data

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UMR 5629, 33607 Pessac Cedex, France; ⁵Department of the Built Environment, Eindhoven University of Technology, Den Dolech 2, 5612 AZ Eindhoven, The Netherlands; ⁶Department of Chemical Engineering, Queen's University, Kingston ON K7L 3N6, Canada; ⁷Department of Materials Science, Nara University of Education, Takabatakecho, Nara, 630-8301, Japan; ⁸School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom; ⁹Department of Chemistry and Polymer Science, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa; ¹⁰School of Physical and Chemical Sciences, University of Canterbury, Private Bag 4800, Christchurch 8140, New Zealand *Corresponding author: a.m.v.herk@tue.nl and a.m.v.herk@outlook.com The working group in the composition as shown above has been active between October 2019 and April 2024. Abstract: This recommendation defines the preferred methodology for determining reactivity ratios from copolymer composition data using the terminal model for radical copolymerization. The method is based on measuring conversion (X) and copolymer composition (F) of three or more copolymerization reactions conducted with different initial monomer compositions (f_0) . Both low and high conversion experiments can be combined, or alternatively only low conversion experiments can be used. The method provides parameter estimates, but can also reveal deviations from the terminal model and the presence of systematic errors in the measurements. Special attention is given to error estimation in F and construction of the joint confidence interval for the reactivity ratios. Previous experiments measuring f_0 -F (i.e., copolymer composition as a function of varying f_0) or f-X (i.e., how f varies with X in an experiment) can also be analyzed with this IUPAC-

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recommended method. The influence of systematic errors in the measurements on the reactivity ratio determinations is addressed. The document has a broad significance in that it seeks to eradicate the use of incorrect methods and common mistakes in determining reactivity ratios in radical copolymerizations. Keywords: errors in measurements; joint confidence interval; radical copolymerization; reactivity ratios; terminal model 1. Introduction Several kinetic representations have been proposed to describe the incorporation of monomers into copolymer chains during radical copolymerization (1). Of these, the terminal model, where only the last unit in the chain affects the reactivity of a chain-end radical, is by far the most widely applied to relate the copolymer composition to the composition of the monomer in the reacting mixture. Other models include the penultimate model (2), in which the penultimate unit also affects the reactivities, and the non-terminal model, where there is no difference in reactivity for the monomers toward the propagating species, which thus only applies to the special case of ideal copolymerization (3). Still other representations consider complexation between monomers (the complex participation model) or complexation between monomer and copolymer chain end (the bootstrap model) (4). Copolymerization models serve to create mechanistic understanding of copolymerization reactions, but are ultimately most important in modelling of composition in manufacturing of copolymers. A high conversion is typically pursued for commercial manufacturing of copolymers where then composition drift

can occur, i.e., monomer and copolymer compositions shift with increasing conversion due to
the differences in monomer consumption rates.

The core assumption of the widely-used terminal copolymerization model is that the reactivity of the growing chains is entirely determined by their final monomer unit. Thus, a copolymerization of two monomers, M_1 and M_2 , contains two types of growing chains, and a total of four propagation reactions, as shown in Scheme 1 (5). Reactivity ratios (1), r_i , are defined as the ratio of the rate coefficients of propagation k_{ij} and k_{ij} , corresponding to homopropagation and crosspropagation of chains containing a terminal unit M_i .

 $-M_{1} \bullet + M_{1} \xrightarrow{k_{12}} -M_{1} \bullet \qquad r_{1} = \frac{k_{11}}{k_{12}}$ $-M_{1} \bullet + M_{2} \xrightarrow{\rightarrow} -M_{2} \bullet \qquad r_{2} = \frac{k_{11}}{k_{12}}$ $-M_{2} \bullet + M_{1} \xrightarrow{k_{22}} -M_{1} \bullet \qquad r_{2} = \frac{k_{21}}{k_{21}}$ $-M_{2} \bullet + M_{2} \xrightarrow{m_{2}} -M_{2} \bullet$ Scheme 1: Terminal model for copolymerization of two monomers M₁ and M₂.

Defining f_i as the mole fraction of M_i in the monomer mixture $(f_i = \frac{[M_i]}{[M_1] + [M_2]})$

and F_i^{inst} as the mole fraction of M_i that is instantaneously being incorporated into the copolymer $F_i^{\text{inst}} = \frac{d[M_i]}{d([M_1] + [M_2])}$ gives the well-known Mayo-Lewis (6) copolymer composition equation (Eq. 1): $F_1^{\text{inst}} = \frac{r_1 f_1^2 + f_1 f_2}{r_1 f_1^2 + 2f_1 f_2 + r_2 f_2^2} (\text{Eq. 1})$ Differentiating f_1 with respect to the total monomer concentration (Eq. 2) and integration after separation of variables leads to the Skeist equation (7) (Eq. 3) relating total monomer conversion, X, to the change in monomer composition: $= \frac{d}{d[M]} \left(\frac{[M_1]}{[M]} \right) = \frac{1}{(M)} \left(\frac{d[M_1]}{d[M]} - \frac{[M_1]}{[M]} \right) = \frac{1}{[M]} \left(F_1^{\text{inst}} - f_1 \right) (\text{Eq. 2})$

$$\ln(1-X) = \int_{f_{10}}^{f_1} \frac{1}{F_1^{\text{inst}} - f_1} df_1(\text{Eq.3})$$

The Skeist equation may be solved numerically. Alternatively, an analytical solution to this equation was provided by Meyer and Lowry (8) (Eq. 4). It relates the conversion *X* to the current

89 monomer composition f_i and the initial monomer composition f_{i0} .

$$1 - X = \left(\frac{f_1}{f_{10}}\right)^{\alpha} \left(\frac{f_2}{f_{20}}\right)^{\beta} \left(\frac{f_{10} - \delta}{f_1 - \delta}\right)^{\gamma} (\text{Eq. 4})$$
$$\alpha = \frac{r_2}{1 - r_2}, \qquad \beta = \frac{r_1}{1 - r_1}, \qquad \gamma = \frac{1 - r_1 r_2}{(1 - r_1)(1 - r_2)}, \qquad \delta = \frac{1 - r_2}{2 - r_1 - r_2}$$

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It should be noted that this equation contains singularities at $r_1 = 1$, $r_2 = 1$, and $r_1 + r_2 = 2$, and these can complicate its utilization (for specific solutions at the singularities, see Autzen et al. (9). Finally, the cumulative monomer composition, F_1^{cum} can be obtained from equation 5.

 $F_1^{\text{cum}} = \frac{f_{10} - (1 - X).f_1}{X}$ (Eq. 5)

If a sample of copolymer taken during a copolymerization is analyzed, it is the cumulative copolymer composition that has been determined, which from now on will be denoted as F. A key point to understand is that Eq. 1 only rarely gives so-called azeotropic conditions, which are that $F_1^{\text{inst}} = f_1 = \delta$, and thus both stay the same throughout a copolymerization. Far more commonly it is the case that $F_1^{\text{inst}} \neq f_1$, and thus both values start changing as soon as any copolymerization occurs, which is termed composition drift. The magnitude of this drift is described by Eqs. (4) and (5), and it is pivotal in determining how data should be analyzed. Reactivity ratios play a central role in equations 1–4, but as the equations are non-linear, it is not immediately evident how to determine these reactivity ratios from experimental data. Several methods have been proposed over the last 75 years, many of which involve linearization of the copolymer composition equation. Widely used linearized methods such as Fineman-Ross (10) and Kelen-Tüdős (11) distort the error structure of the experimental data, however, and can lead to biased and imprecise results (9). For this reason, non-linear least-squares fitting (NLLS) (9) or visualization of the sum of squares space (VSSS) (9, 13) is greatly preferred. For more background on the above preferences we refer to the basis for this recommendation in the full research paper from the same authors (9). Further problems are

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2 3 4	112	encountered when the assumptions of the models are violated: for example, by applying
5 6 7	113	equation 1 to copolymerizations with non-negligible conversion, where equation 4 would be
8 9	114	more appropriate. These incorrect procedures can lead to significant errors in the estimation of
10 11 12	115	reactivity ratios.
13 14	116	2. Experimental Methods
15 16 17 18	117	2.1. Copolymer composition vs comonomer composition at low conversion (f_0 - F)
19 20 21	118	The most common method for determination of reactivity ratios involves collecting
22 23	119	copolymer composition data (F) (for example with NMR, gas chromatography or infrared
24 25	120	spectroscopy) at low conversion across a range of initial monomer composition (f_0). At
20 27 28	121	sufficiently low conversion, the change in monomer composition (f) during copolymerization is
29 30	122	negligible, and the cumulative and instantaneous copolymer compositions can be assumed to
31 32 33	123	be equivalent, allowing direct fitting of the Mayo-Lewis equation (Eq. 1).
34 35 36	124	There is, however, no unique interpretation of "low conversion" in the f_0 -F method; as with
37 38	125	disparate reactivity ratios (i.e., $r_1 >> 1$ and $r_2 << 1$), strong composition drift can occur even at
39 40 41	126	conversions below 5%. This may introduce significant errors in <i>F</i> (see Fig. 1).
42 43	127	The working group investigated several methods to correct for shifts in <i>F</i> at lower
44 45 46	128	conversions including, amongst others, using the average monomer composition over the
47 48	129	conversion range instead of f_0 . However, all these approximate correction strategies require
49 50 51	130	knowledge of the conversion, suggesting that direct application of an integrated form of the
52 53	131	copolymer equation such as the Meyer-Lowry equation (Eq. 4) is then possible. In such a case,
54 55 56 57 58	132	application of the integrated expression is preferable.
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Fig. 1. Cumulative copolymer composition (F_1) versus conversion (X) at different monomer-1 starting fractions (f_{10}). The blue dotted line represents the cumulative copolymer composition at 100% conversion, which equals f_{10} . This data has been calculated using $r_1 = 23$ and $r_2 = 0.02$, as these exemplify well the discussed ideas. Indicated in the graph: low conversion experiments (*, f_0 -F) with the f_0 -F curve in dashed green, which is method 2.1 of the text; following conversion and $f(*, f_0 - f - X)$, (f not shown in graph), which is method 2.2; starting from several f_0 values and monitoring the copolymer composition with conversion (*, f_0 -X-F), which is method 2.3, the IUPAC-recommended method. Reproduced with permission from Autzen et al. (9).

2.2. Conversion vs monomer composition (f_0 -f-X)

An alternative approach to the use of low conversion data is to measure the change in monomer composition across a range of conversions. The Meyer-Lowry equation (Eq. 4) relates the conversion X to the monomer composition f and therefore one most commonly fits X vs f and not vice-versa. This is how historically most fits are done, making X the dependent variable. This approach lends itself to online monitoring (for example with NMR, gas chromatography or infrared spectroscopy) and in principle would allow determination of both reactivity ratios from

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156 a single copolymerization, monitored from low to high conversion. In practice, however, the 157 use of a single copolymerization is highly susceptible to systematic errors, for example resulting 158 from errors in the initial monomer composition, and furthermore it is generally not possible to 159 find a single initial monomer composition that gives accurate estimates of both reactivity ratios. 160 These problems can be alleviated by carrying out multiple f_0 -f-X experiments starting from 161 different initial monomer compositions. Random errors are also likely to be high as changes in f162 are small and relatively insensitive to the copolymer composition at low conversions, while at 163 high conversions there remains little monomer to be measured, leading to a low signal-to-noise 164 ratio. Very accurate measurements are thus required in order to obtain estimates of reactivity ratios of useful precision. 165

166 2.3. Copolymer composition vs conversion and f_0 (f_0 -X-F)

167 The recommended approach by the authors of this paper for data collection is to measure 168 both cumulative copolymer composition (for example with NMR or infrared spectroscopy) and 169 global monomer conversion, starting from multiple initial monomer compositions (f_0). One of 170 the first reports on this approach was in 1979 by the group of Hamielec (12). The resulting 171 dataset can then be fitted using an integrated form of the copolymer composition equation (Eq. 172 4). The way copolymerization experiments are performed does not change with this approach, 173 but the measured conversion is now taken explicitly into account. In other words, this is the 174 method of Section 2.1, except that X is measured rather than being assumed to be (effectively) 175 zero. Thus, there is no longer any real difference between low and high conversion 176 experiments, as in both cases copolymer composition and conversion are measured, starting from a particular f_0 . Low and higher conversion data may be mixed to calculate reactivity ratios. 177

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178 This is illustrated in Fig. 1, where data points (the green stars) are fitted on a f_0 , X, F surface. 179 Other methods using low conversion data or measuring *f*-*X* data can still be seen as special 180 cases of this more general preferred method. It is also very important to have error estimates 181 for the F value, either directly measured or calculated from changes in monomer 182 concentrations (13, 14). As discussed below, the error in F is very different depending on 183 whether it was measured directly or calculated from changes in f. 3. Data Evaluation 184 A thorough consideration of measurement errors is important in three ways: 1) they can be 185 used to weight the data; 2) they determine the size of the joint confidence interval (JCI) (when 186 187 the errors are well known); and 3) they can be used to determine whether the fit is adequate by 188 comparing the actual fitting residues with the estimated errors. 189 Both F and X may be expected to be subject to experimental errors, and as such the error in 190 variables method (EVM) is preferred (15). However, in many cases, it is likely that errors in 191 determination of X will be small relative to errors in determination of F, as the measurement of

192 X is more straightforward. In these cases, X can be treated as the error-free independent

193 variable for the purposes of fitting. Looking at the individual fit residuals (calculated *F* minus

194 measured F i.e. F_{calculated} – F_{measured}), it is possible to detect trends (*e.g.* deviations at high

195 conversion, deviations at low or high f_0).

196 Besides comparing the errors per datapoint, the overall error estimated by the user and the

197 overall error obtained from the fit (s_F) can also be compared using a Fisher test (13).

198
$$S_F = \sqrt{\frac{ss_{min}(r_1, r_2)}{n-2}}$$
 (Eq. 6)
199 where $ss_{min}(r_1, r_2)$ is the sum of squares of the residuals at the minimum, and *n* is the number of
200 datapoints. The theoretical overall error is obtained when replacing $ss_{min}(r_1, r_2)$ in Eq. 6 by the
201 summation of the squares of the estimated errors by the user (13).
202 In the case where *f* is monitored as a function of conversion (for example with in-situ NMR
203 (16)), these values can easily be converted to f_0 -*X*-*F* data via mass balance (Eq. 5). In this
204 conversion, the errors assumed in *f* and *X* are then converted to errors in *F* through Gaussian
205 error propagation (note, a random error in f_0 is not included in this equation):

$$\Delta F_1 \approx \sqrt{\left(\Delta f_1 \frac{\partial F_1}{\partial f_1}\right)^2 + \left(\Delta X \frac{\partial F_1}{\partial X}\right)^2} = \sqrt{\left(\frac{(1-X)\Delta f_1}{X}\right)^2 + \left(\frac{(f_1 - f_{1,0})\Delta X}{X^2}\right)^2} (\text{Eq. 7})$$

We recommend that errors in the measurements be expressed in absolute terms rather than as a percentage of the measured value (relative error) (9) because a relative error structure is not often seen in experimental copolymerization data, and the results obtained using a relative error structure differ depending on how the monomers are labeled (9).

We believe the best option is to do the calculations with f_0 -*X*-*F* data (not directly with the f_0 -*f*-*X* data), because in the end, we are interested in using the reactivity ratio estimates for predicting copolymer compositions, and this is the more robust approach in the data evaluation. Another advantage is that in the conversion from f_0 -*f*-*X* to f_0 -*X*-*F* both the random errors in *f* (and if needed f_0) and in *X* can be propagated to give a well estimated random error in the calculated *F* (Eq. 7), and thus more realistic error estimates for the reactivity ratios. A potential problem is

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that some of the monomer can evaporate if the reactor is not a closed system, so even if f data are converted into F data, it is advised to measure at least the final average composition of the copolymer to check for internal consistency.

Note that this is not a full errors-in-variables method as the result is only optimized on the copolymer composition *F*. Proper weighting of those data can however take place (13). In the case of using EVM, there is no significant difference between the two approaches. It is likely that the analysis of f_0 -*f*-*X* data and the analysis of those data converted into f_0 -*X*-*F* might give slightly different results if EVM is not used (9). This is due to the fact that in the f_0 -*f*-*X* approach, fitting is often of the conversion data, *X*, while in the f_0 -*X*-*F* approach, fitting is on the composition data, *F*.

27 For parameter estimation, the best experiments are those that are most sensitive to parameter variation, for example, according to the well-known criteria of Tidwell and Mortimer 28 29 for the terminal model at low conversion (17). However, this assumes that the model is known. 30 Thus, this IUPAC method highly advises variation in initial monomer compositions (f_0) as well as conversion (X), in order to check for deviations from the terminal model (5) as well as 31 32 systematic errors in the measurements. In other words, we have combined parameter 33 estimation with investigation of whether the (terminal) model is adequate for compositional 34 data in this IUPAC recommended method. 35 A requirement of the technique is that the conversion is measured for each experiment, 36 which largely improves on the quality of the data in all cases. In the case that only low 37 conversion data is used, it is again important to carefully compare the estimated errors in F

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3 4	238	with the fit residuals (looking at individual datapoints and also utilizing the Fisher-test described
5 6 7	239	in equation 6). If in doubt, the f_0 -X-F method should be used.
8 9 10	240	In the event that the errors are known, for example, through an error propagation exercise
10 11 12	241	or through replicate measurements, the errors can be used to construct the joint confidence
13 14	242	interval using the \mathbf{x}^2 distribution (18) with ss $(r_1, r_2)_z$, the boundary of the JCI at level z (for
15 16 17	243	example a 95% probability):
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19 20 21 22	244	$ss(r_1,r_2)_z \le ss_{min}(r_1,r_2) + \sigma^2 \chi^2_z(p)$ (Eq. 8)
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24 25 26	245	Here σ^2 corresponds to the average absolute variance of the dependent variable (in this case F)
26 27 28	246	and is calculated from the known errors as entered by the user. The $ss_{min}(r_1,r_2)$ is the sum of
29 30	247	squares of residuals at the minimum and with p degrees of freedom (p equals two in the present
31 32 22	248	cases). If the errors are only estimates (which is often the case), the JCI at level z is constructed
33 34 35 36	249	through the following equation:
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38 39 40	250	$ss(r_1,r_2)_z \le ss_{\min}(r_1,r_2)(1+p/(n-p)F_z(p,n-p))$ (Eq. 9)
41 42		
42 43 44	251	Here, $F_z(p,n-p)$ represents a value from the Fisher-distribution at level z (for example at 90 or 95
45 46	252	% probability) with p and n-p degrees of freedom (p equals two in the cases at hand), n data points,
47 48	253	and $ss_{min}(r_1, r_2)$ sum of squares of residuals at the minimum. (Note that this use of F is distinct from
49 50 51	254	its use for copolymer composition.)
52 53	255	It is important to note that these procedures are developed assuming random errors in the data.
54 55 56	256	As soon as systematic errors appear, the JCI will no longer give a useful reflection of reality. In
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particular, if the true f_0 is significantly different from the reported value, all the data from that experiment are systematically biased. So although the error in f_0 is random, it results in a systematic error in that particular series of f_0 -X-F data (see Eq. 5). For this reason, it is recommended that several different starting values for f_0 are used. If each of these f_0 sets (e.g., the different curves in Fig. 1) have different systematic errors, the overall fit with all the different f_0 values and associated systematic errors is more likely to transpose to a random error (9). The sum of squares of residuals at the minimum will be larger than for the individual f_0 sets, and $ss_{min}(r_1, r_2)$, through equations 8 or 9, will increase the size of the JCI (9).

This effect has been shown clearly in a simulated *X* vs *f* dataset generated with $r_1 = 0.4$, $r_2 = 0.6$ and $f_{10} = 0.5$ (9). When only changing the f_{10} value (i.e., introducing a systematic error) in fitting this simulated data, the effect on output reactivity ratios is shown in Fig. 2.



Fig. 2. Results obtained from fitting of simulated *X* vs *f* data obtained with $r_1 = 0.4$, $r_2 = 0.6$ and $f_{10} = 0.5$. Random noise of ±0.005 in *X* was applied to the simulated data, which was then fitted using different values of f_{10} , as per the abscissa, in order to mimic the effect of systematic error. Output values of r_1 (blue), r_2 (orange), and SSR (sum of squares of residuals; grey) are

1 2		
- 3 4	273	shown. For f_{10} = 0.5 the true results are obtained (r_1 = 0.4, r_2 = 0.6, SSR = 0.0539), but otherwise
5 6 7	274	there is distortion of r_1 and r_2 . Reproduced with permission from Autzen et al. (9).
8 9	275	It can be seen that a change in f_{10} of –0.001 shifts r_1 from 0.4 to 0.424 and r_2 from 0.6 to
10 11 12	276	0.64, while larger changes in $f_{ m 10}$ give progressively stronger distortions. The typical random
13 14	277	error in NMR for f_{10} is most likely larger than 0.001, so the effect is significant. This means that
15 16 17	278	even with a very accurate value of f_{10} , one might wish to optimize this value rather than assume
18 19	279	it is rigidly correct. Software to investigate these small variations in $f_{ m 10}$ has recently become
20 21 22	280	available (19–21). Then, as per our recommendation, combining different sets with different f_{10}
23 24	281	values is further mitigating this issue as discussed before.
25 26 27	282	Design of experiments can also be applied on the IUPAC recommended method. In the case
28 29	283	of low conversion data, we recommend use of at least three different f_0 values, where two of
30 31 32	284	them $(f'_{10}, f''_{10} \text{ in Eq. 10})$ can be chosen through the Tidwell-Mortimer D-optimal design
33 34	285	criteria (17), requiring an initial estimate of the reactivity ratios (Eq. 10). We realize that the
35 36 37	286	Tidwell-Mortimer approach is only applicable to low conversion experiments and cannot be
38 39	287	extended to higher conversions.
40 41		$2 r_{2}$
42 43 44	288	$f'_{10} = \frac{2}{2+r_1}$, $f''_{10} = \frac{r_2}{2+r_2}$ (Eq. 10)
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46 47	289	The IUPAC recommended method has been tested extensively with a large body of
48 49 50	290	experiments, and the results are also compared with other methods (19). An extended discussion
51 52	291	on the importance of the knowledge of the experimental errors for this method is also published
53	292	(20).

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$$r_1$$
 and r_2 . Reproduced with permission from Autzen et al. (9).
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Design of experiments can also be applied on the IUPAC recommended method. In the case
of low conversion data, we recommend use of at least three different f_0 values, where two of
them (f'_{10} , f''_{10} in Eq. 10) can be chosen through the Tidwell-Mortimer D-optimal design
criteria (17), requiring an initial estimate of the reactivity ratios (Eq. 10). We realize that the
Tidwell-Mortimer approach is only applicable to low conversion experiments and cannot be
extended to higher conversions.
 $f'_{10} = \frac{2}{2+r_1}$, $f''_{10} = \frac{r_2}{2+r_2}$ (Eq. 10)
The IUPAC recommended method has been tested extensively with a large body of
experiments, and the results are also compared with other methods (19). An extended discussion
on the importance of the knowledge of the experimental errors for this method is also published

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2 3 4	293	4. Summary of Recommendations
5 6 7	294	The following is a summary of the recommendations coming out of our work:
8 9 10	295	-Either use low conversion f_0 - F data or conversion-dependent data in the form of f_0 - f - X or f_0 - X - F ,
10 11 12	296	in all cases with at least three different starting monomer compositions f_0 .
13 14 15	297	-Obtain the best possible information about the errors in the measurements, and utilize weighting
16 17	298	in the fit according to the errors in the dependent variable (in most cases F).
18 19 20	299	-Use only non-linear regression or the visualization of the sum of squares space.
21 22	300	-If the independent variable (usually f) has considerable error, use non-linear regression
23 24 25	301	combined with EVM.
26 27 28	302	-If using f_0 -f-X data without EVM, convert the f_0 -f-X data into f_0 -X-F with proper error
28 29 30	303	propagation, taking errors in f (also f_0 if needed) and X into account.
31 32 33	304	-If using low conversion f_0 -F data, check that no significant (i.e., more than the expected random
34 35	305	error) change in F has occurred due to composition drift. This can be done by using the
36 37 38	306	estimated reactivity ratios to calculate the predicted change in F with conversion. If this
39 40	307	indicates too much composition drift over the range of X used experimentally, then one should
41 42 43	308	go back and use the f_0 -X-F method instead.
43 44 45	309	-Be aware of errors in f_0 , especially in conversion-dependent experiments.
46 47 48	310	-Mitigate errors in f_0 through 1) measuring f_0 (e.g., through NMR), and/or 2) investigating limited
49 50	311	variations in f_0 though fitting f_0 - <i>f</i> - <i>X</i> single experiments, and/or 3) looking at the residuals in a
51 52 53	312	set of experiments and detecting systematic patterns – if there are such patterns, then vary f_0
54 55	313	again, i.e., step 2).
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-Investigate if the fit residuals exceed the expected errors; if they do, this usually indicates that
the terminal model is not valid for the copolymerization system under investigation and/or
that systematic errors are present.

-The obtained reactivity ratios should be reported with the correct number of significant digits
(typically 2) and an indication of the uncertainty in those values (preferably a joint confidence
interval).

320 5. Conclusions

321 The IUPAC working group on "Experimental Methods and Data Evaluation Procedures for the Determination of Radical Copolymerization Reactivity Ratios" has established a robust method 322 to determine reactivity ratios from composition data following the terminal model. The method 323 324 is based on measuring conversion (X) and (cumulative) copolymer composition (F) in a few copolymerization reactions at different starting monomer compositions (f_0), although a set with 325 326 only low conversion can also be used $(f_0$ -F). We make freely available the analysis software for this method, and we strongly recommend that it be used for reactivity ratio determination (21-327 23). The method not only provides parameter estimates but can also reveal deviations from the 328 329 terminal model and systematic errors in the dataset. It is shown that error estimation for the F-330 values is important for weighting the data, determining the size of the joint confidence interval (in the case of accurately known errors) and discerning whether the fit with the terminal model 331 is adequate. In principle, previous experiments measuring f_0 -F (if conversion is known or 332 333 sufficiently low) can still be analyzed with the IUPAC-recommended method. Special attention 334 has been given to the occurrence of systematic errors in the f_0 -X-F and f_0 -f-X experiments. It is 335 shown that the current statistical treatment is not able to properly accommodate systematic

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2 3 4	336	errors occurring within such experiments. However, with the analysis of the residuals space (f_{0} -
5 6	337	X-F), these errors can be identified and where possible corrected through optimization of f_0 as a
7 8 9	338	third parameter.
10 11 12 13	339	Acknowledgement
14 15 16	340	We thank the International Union of Pure and Applied Chemistry (IUPAC) for financial support (Project No.
16 17 18	341	2019-023-1-400) (24).
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