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Development of decision tools to assess the migration from plastic materials in contact with food

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12 Abstract

13 Testing the specific migration limits of all substances intentionally added to polymer material
14 according to European Union (EU) regulation is a tedious and expensive task. Although
15 mathematical modeling offers an interesting alternative, it can significantly overestimate the
16 migration in situations, which are strongly conservative due to significant uncertainty in
17 transport properties. In addition, its application is of little use for end-users or enforcement
18 laboratories, which do not have access to the formulation. This paper revises the paradigm of
19 migration modeling by combining modeling with deformation experiments and iterative
20 modeling in the framework of decision theory. The complete approach is illustrated for
21 polyolefins in contact with 50% ethanol for eight typical migrants, including hindered
22 phenolic antioxidants and low molecular weight surrogates. Results from a French ACTIA

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3 23 project on the identification of formulation fingerprints and on the prediction of partition
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5 24 coefficients with alcoholic and aqueous stimulants is described. When the true migration was
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8 25 close but still lower than the limit of concern, the proposed compact decision tree, including
9
10 26 up to four sources of uncertainty, showed that the chance of demonstrating compliance was
11
12 27 about 3:4 in the presence of one source of uncertainty, whereas it fell below 2:4 and 1:4 with
13
14
15 28 two and three sources of uncertainty respectively. The recommendations for further food
16
17 29 packaging safety surveys and future developments are discussed.
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20 30

21
22 31 **Key words:** food contact materials, migration modeling, compliance testing, sanitary survey.
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25 32

26 27 33 **Introduction**

28
29 34 For the last three decades, consumer exposure to chemicals from food packaging materials
30
31 35 has attracted much public attention and interest of European regulatory authorities. Thus,
32
33 36 although the EU regulation is still in a consolidation phase, 502 substances (including 230
34
35 37 monomers and 272 additives) among the 937 which are positively listed in EU directives on
36
37 38 plastics in contact with food (European Commission, 2008), are subjected to specific
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39 39 migration limits (SML) due to toxicological concern. The recent authorization of substances
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41 40 not belonging to the positive list, when they are located behind one or more layers, the so-
42
43 41 called functional barrier, which prevents their migration into foods or food simulants above a
44
45 42 detectable level (European Commission, 2007), complicated the assessment of compliance
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47 43 testing and requirements of traceability (European Commission, 2004). The introduction of
48
49 44 modeling in directive 2002/72/EC (European Commission, 2002) as an alternative to time
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51 45 consuming migration testing was an appropriate response to the increasing sophistication of
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53 46 plastics materials on the market including multilayer materials, active or intelligent
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55 47 packaging, recycled polymers, nanocomposites... Despite significant collaborative work on
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3 48 the collection of diffusion coefficients (Begley *et al.*, 2005; Dole *et al.* 2006), the whole
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5 49 approach remains highly semi-empirical and insufficiently described in the literature
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8 50 according to the application context. Most of studies are focused on demonstrating that
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10 51 predictions based on worst-case scenarios overestimate the real migration (Franz and Welle,
11
12 52 2008). As a result, in the current framework, either worst-case modeling does demonstrate the
13
14 53 compliance or migration testing must be performed. In practice, the highly asymmetric
15
16 54 know-how and information along the food-packaging chain from the producer to consumer is
17
18 55 responsible for considerable uncertainty on the consumer side, which lessen drastically the
19
20 56 interest of modeling for end-users, enforcement authorities (Petersen *et al.* 2005) and
21
22 57 authorities responsible for food safety surveillance.
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26
27 58 The very low utility of current predictive approaches, expressed as a probability to
28
29 59 demonstrate the compliance, is illustrated as a decision diagram in Figure 1, where a
30
31 60 probability of acceptance is associated with each alternative. Reference probabilities, gathered
32
33 61 in Table I, were assigned according to the expertise obtained at the Laboratoire National de
34
35 62 métrologie et d'Essais (LNE) and at the Institut National de la Recherche Agronomique
36
37 63 (INRA). The current utility for a national reference laboratory as LNE is estimated lower than
38
39 64 3:1000 for most of monolayer cases. The main limiting factors are the identity of substances
40
41 65 and their amounts in the starting materials. Additional limitations arise from the lack of
42
43 66 realistic estimates of transport coefficients (diffusion coefficients and partition coefficients) in
44
45 67 the conditions of storage. The combined effect of several sources of uncertainty including on
46
47 68 composition and transport coefficients has been studied extensively for monolayer materials
48
49 69 (Vitrac and Hayert, 2005) and extended to multilayer materials and multimaterials (Vitrac and
50
51 70 Hayert, 2007) via a stochastic description of the contamination of food and an interval
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53 71 approach, respectively. They showed that the expected utility collapsed rapidly as soon as
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55 72 more than two sources of uncertainty were combined. Full modeling approaches independent
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3 73 on specific experiments has been applied on finished food products on the market (Vitrac *et*
4
5 74 *al.*, 2007) and on consumer exposure (Vitrac and Hayert, 2007) only in rare occasions where a
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8 75 significant expertise on physicochemical properties of packaging materials was available.
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11
12 77 This paper proposes to revise the paradigm of migration modeling by introducing modeling
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15 78 along with deformation experiments and refined prediction scenarios, recently made
16
17 79 available. The main objective was to combine several rapid experimental and numerical
18
19 80 techniques to improve the expected utility value up to 1:3 (Table I), in order to justify the
20
21 81 additional costs induced by modeling (software licenses, training...). The final approach will
22
23 82 be integrated in an expert system developed by INRA including databases and simulation
24
25 83 tools. In this new framework, the issue is not to minimize the deviation between the predicted
26
27 84 value and the real one, but determining the fastest decision path among possible alternatives
28
29 85 to demonstrate the compliance in the first place. The demonstration relies either on a
30
31 86 predicted value lower than SML or to a maximum initial concentration value in the polymer
32
33 87 (MIC), acknowledged by the supplier to be higher than the true amount (Figure 1). The
34
35 88 proposed four steps algorithm is particularly comprehensive for monolayer materials as few
36
37 89 input parameters, denoted x_i , and including initial concentrations, partition coefficients and
38
39 90 diffusion coefficients, are involved:
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- 45
46 91 - Step 1: finding the most influencing set of inputs, $X = [x_1 \ x_2 \ \dots \ x_n]$ for the considered
47
48 92 conditions of migration (food packaging geometry, contact time and temperature...).
- 49
50 93 - Step 2: finding the optimal set x° , which leads to migration = SML (idem with MIC).
- 51
52 94 - Step 3: for all inputs in the set, finding all conditions " $x_i < x_i^\circ$ " or " $x_i > x_i^\circ$ " to guarantee
53
54 95 migration < SML.
- 55
56 96 - Step 4: check whether all conditions are likely according to values available in
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58 97 databases, additional modeling or to experiments.
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3 98 The first step is the most critical because the number of influencing inputs, n , and their
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5 99 identities are not a priori known. Our objective was to analyze all four steps for polyolefins in
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7 100 contact with 50% ethanol as simulant of dairy products (European Commission, 2007). This
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9 101 situation was of significant concern as polyolefin materials represent nearly one third of all
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11 102 food packaging applications and currently no specific guidance exists to predict the migration
12
13 103 in such a food simulant. Additional interest in such semi-crystalline materials was triggered
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15 104 by the recent validation of several alternatives to conventional migration testing.
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17 105 Overestimates (Begley *et al.*, 2005) and likely estimates (Vitrac *et al.*, 2006) of diffusion
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19 106 coefficients have been published for all substances, which do not cause blooming effects. The
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21 107 French national project ACTIA RA 0522 “decision tools for compliance testing” (ACTIA,
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23 108 2005) contributed to generate missing steps in the predictive approach of the migration from
24
25 109 polyolefins starting from the diagram depicted in Figure 1: i) rapid deformation of materials
26
27 110 from Fourier Transform Infrared spectroscopy (FTIR) absorption spectra of polymer extracts
28
29 111 (Gillet *et al.*, 2009a), ii) prediction of partitioning between polyolefins and most simulants
30
31 112 (alcohols, water and water-ethanol mixtures) from molecular simulations of molecular pair
32
33 113 interactions (Vitrac and Gillet, 2008; Gillet *et al.*, 2009b and 2009c). The importance of
34
35 114 deformation to identify possible migrants and their extent has been already discussed in the
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37 115 conclusions of the EU AIR research program CT94-1025 (Feigenbaum *et al.*, 2002). For
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39 116 polymer additives comprising several repeated chemical patterns, e.g. di-tert-butylphenol in
40
41 117 hindered phenolic antioxidants, FTIR offers additional worst-case scenarios based on an
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43 118 equivalent amount patterns, considered as high diffusing individual molecules. The direct
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45 119 calculation of activity coefficients at atomistic scale for both flexible migrants and hindered
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47 120 migrants in various food simulants and in polyolefins widens dramatically the range of
48
49 121 applicability of modeling for monolayer and multilayer materials (Gillet *et al.*, 2009b; Gillet
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51 122 *et al.*, 2009c; Vitrac and Gillet, 2008; Vitrac and Gillet, 2009). As the approach was validated
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3 123 in more than 51 different conditions and did not require any fitting procedure, it would
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5 124 replace advantageously both rough estimations suggested in the “practical guide” to European
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8 125 Directives (European Commission, 2003) and the semi-empirical group contribution devised
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10 126 for the partitioning of volatile substances (Baner and Piringer, 1991). Besides, direct
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12 127 calculations provided two important insights at molecular scale, which were underestimated
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14
15 128 in previous works (Gillet *et al.*, 2009b). On one hand, additives comprising a repeated pattern
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17 129 have a higher chemical affinity than their constitutive patterns for simulants. This entropic
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19 130 effect, which does not depend on chemical composition effects, was related to the increased
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21
22 131 number of micro-configurations to recreate simulant-simulant interactions (e.g. hydrogen
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24 132 bonding) when a large guest molecule was inserted among smaller host ones. The practical
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26 133 consequence is that the partitioning of large additives cannot be extrapolated from volatile
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28
29 134 substances. On the other hand, strong deviations from ideality in water-ethanol mixtures were
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31
32 135 found to be responsible for highly non-linear variations of partitioning with the volume
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34 136 fraction in ethanol, and where in contradiction from prior extrapolations in pure water. The
35
36 137 practical consequence is that the lowest chemical affinity for the simulant is expected to be
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38 138 obtained with 20%-30% ethanol rather than in pure water Gillet *et al.* (2009c).
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42
43 140 The paper is organized as follows. The first section details the methodologies,
44
45 141 assumptions and scenarios to assess the compliance according to the decision tree depicted in
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47 142 Figure 1 and the proposed four steps algorithm. As a quantification of the initial amount may
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49 143 be required, a fast extraction technique under pressure was compared with the conventional
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51 144 reflux method on a typical high density polyethylene (HDPE). Eight typical migrants of
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53 145 polyolefins were particularly considered. The photo-initiator used in printing inks, 2-
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55 146 isopropylthioxanthone (2-ITX), was included because it was recently found in several food
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58 147 products including dairy ones in spite of not being authorized in EU (Bagnati *et al.*, 2007; Sun
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3 148 *et al.*, 2007; Rothenbacher *et al.*, 2007). The main experimental and simulated results are
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5
6 149 presented in the second section. Biases due to possible incomplete extractions of semi-
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8 150 crystalline polymers, which are insoluble in solvents, were tabulated according to the number
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11 151 of extraction steps as suggested by Choller *et al.* (2003). The effect of combined sources of
12
13 152 uncertainty was analyzed by ranking all prediction scenarios according to their ability to
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15 153 demonstrate the compliance and according to the number of uncertain inputs. The main
16
17 154 interest of the approach is that the typical generated diagrams can be used to extrapolate the
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19 155 effect of uncertainty for migrants different from those studied by simple geometric
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22 156 constructions. The findings and provides recommendations for its generalization in good
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25 157 manufacturing practices and quality auditing purposes are summarized in the last section.
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29 159 **Materials and methods**

31 160 *Tested substances*

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34 161 Tested substances are listed in Table II. They were chosen to be representative of most
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36 162 technological functions in polyolefins. Irganox 1330 and Irganox 3114 were proposed as
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38 163 typical phenolic hindered antioxidants including a repeated chemical pattern. As they include
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40
41 164 three BHT patterns, they can be easily mistaken for dispersed BHT molecules in FTIR
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43 165 spectroscopy, with an equivalent concentration assessed three times higher than the true one.
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46 166 Erucamide is an unsaturated long chain carboxylic acid amide used as slip agent or lubricant
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51 167 in plastic films. At concentrations above 10^3 mg·kg⁻¹ in polyolefins, it is only partly
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59 168 compatible with polyethylene (Gillet *et al.*, 2009c), its migration does not obey to Fickian
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169 diffusion and migration modeling cannot be applied. As a result, it was only used in

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3 170 extraction experiments as a prototype of substance poorly dispersed in polyolefins. Two
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6 171 typical low molecular weights surrogates, which are not intentionally added substances into
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8 172 plastics, were also included: 2-ITX and diphenylmethane. The latter was introduced as
9
10 173 partitioning data have already been published by Baner and Piringer (1991).
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14
15 175 *Evaluation of extraction methods*
16

17 176 Extraction methods were evaluated on HDPE films formulated with Irganox 1076, Irgafos
18
19 177 168 and Erucamide. Dried polymer flakes were formulated during a first extrusion step prior
20
21 178 to final processing at a semi-industrial scale. Both extrusions were performed at 200°C in a
22
23 179 bi-screw extruder (model BC-21 Cleextral, France) and the material was finally calendered as
24
25 180 0.15 m wide ribbons. The final density and the crystallinity were of 940 kg·m⁻³ and 70 %
26
27 181 respectively, with a melting point of 136°C. Plastic additives were provided by CIBA (Basel,
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29 182 Switzerland) except for Erucamide, which was obtained from CRODA (Vimodrone, Italy).
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31 183 Raw HDPE was obtained from ATOCHEM (Paris, France).
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36 184 Two common extraction methods were considered: a conventional 40 h reflux extraction
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38 185 method in dichloromethane and a 40 min pressurized solid-liquid extraction (model ASE 200,
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40 186 Dionex, USA) in a 75:25 v/v mixture of isopropanol-dichloromethane at 105°C and 10.3
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42 187 MPa. The latter conditions were similar to ones described by Coulier *et al.* (2005) and were
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44 188 applied to 600 mg of samples mixed with sand in 11 ml extraction cells. Two static cycles of
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46 189 15 min each were applied to achieve complete extraction. To prevent the degradation of
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52 190 additives during extraction, 100 µL·L⁻¹ of tri-ethylphosphite (Sigma-Aldrich, USA) was
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191 added to solvents for both methods.

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3 192 Determination of concentrations in extracts was done by high-performance liquid
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5 193 chromatography (HPLC) with diode array and evaporative light scattering detection. The
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8 194 HPLC system consisted in a Waters 717plus autosampler, a Waters 600 controller equipped
9
10 195 with a thermostatted column compartment and an in-line degasser AF (Waters, USA). The
11
12 196 protocol described by Garrido-López (2005) was used. Separation was achieved on a Xterra
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14
15 197 C8 column (150mm×3.0mm; 5µm particles; Waters , USA) operated at 60°C.
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18 198

19
20 199 *Migration modeling*
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22 200 Migration modeling was performed under the same assumptions described by Vitrac and
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24 201 Hayert (2006) and by Vitrac *et al.* (2007) for similar applications. Migration in food or in a
25
26 202 food simulant was assumed to be one-dimensional without any reaction and mass losses with
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28 203 surroundings. The material was considered to be homogeneous and the relaxation of polymer
29
30 204 chains was assumed unaffected by the desorption process. The concentration profile in
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36 205 substance i , $C_i(Fo, x)$, along the packaging thickness, with SI units in $\text{kg}\cdot\text{m}^{-3}$, evolved
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46 206 therefore with the dimensionless diffusion time, denoted Fo , as:
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$$\frac{\partial C_i(Fo, x)}{\partial Fo} = \frac{\partial^2 C_i(Fo, x)}{\partial x^2} \quad (1)$$

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208 Where $Fo = D_{i,p} \cdot t / l_p^2$ and x is the dimensionless position between 0 and 1 within the film.

209 $D_{i,p}$ is the diffusion coefficient with SI units in $m^2 \cdot s^{-1}$; l_p is the packaging thickness and t is

210 the contact time. Only a pervious contact is assumed on food side, at $x=1$:

$$211 \quad \left. \frac{\partial C_F}{\partial Fo} \right|_{Fo} = - \left. \frac{\partial C_i}{\partial x} \right|_{x=1, Fo} = Bi \cdot [K_{i,F/P} \cdot C_i(x=1, Fo) - C_F(Fo)] \quad (2)$$

212 where Bi is the mass Biot number assigned to 10^3 to prevent a significant mass transfer
213 resistance at the interface, as the liquid simulant was stirred.

214 $K_{i,F/P} = C_{i,F}(Fo \rightarrow \infty) / C_{i,P}(x=1, Fo \rightarrow \infty)$ is the partition coefficient between the food product or
215 food simulant, denoted F , and the packaging material, denoted P . The concentration in food
216 or in food simulant, $C_F(Fo)$, was obtained from the mass balance $t=0$ and t by assuming a
217 uniform initial concentration profile equal to $C_{i,P}^0$:

$$218 \quad L_{F/P} \cdot C_F(Fo) = C_{i,P}^0 - \int_0^1 C_i(x, Fo) \cdot dx \quad (3)$$

219 where $L_{F/P} = V_F / (A \cdot l_p)$ is the volume dilution ratio. V_F and A are respectively the volume of
220 F and the contact surface area between P and F . Equations 1-3 were integrated in time using a
221 finite volume technique documented and implemented online in QSPR-MS tools of the Safe
222 Food Packaging Portal (INRA 2008). All simulations results were exported as datasheets to
223 be further interpreted.

225 *Migration scenarios*

1
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3 226 Ten scenarios with different sources of uncertainty were considered for five additives as
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5
6 227 plotted in Figure 2. For each quantity X required for modeling, two values were considered: a
7
8 228 likely value \bar{X} and a robust overestimate X^+ such that $\bar{X} < X^+$. The corresponding values are
9
10 229 gathered in Table III for each substance and in Table IV for each scenario. A similar $\bar{D}_{i,P}$
11
12 230 value was assigned to Irganox 1330 and Irganox 3114 as they had a very similar chemical
13
14 231 structure and as the expected difference is lower than the common experimental error as
15
16 232 assessed in (Vitrac *et al.* 2006). $\bar{K}_{i,F/P}$ values were calculated in the framework of a
17
18 233 generalized Flory-Huggins theory at atomistic scale as discussed in Vitrac and Gillet (2008)
19
20 234 and in Gillet *et al.* (2009b and 2009c). Desorption was assumed to occur in water-ethanol
21
22 235 (50:50 v/v) to simulate a contact with a dairy product (European Commission 2007). As a
23
24 236 possible worst case of packaging materials in contact with a dairy product, additives were
25
26 237 assumed to be used in a rigid container of 200 μm thickness and in contact with a low volume
27
28 238 of food of 100 mL. The conditions of test corresponded to a contact of 10 days at 40°C. By
29
30 239 contrast, low molecular weight contaminants were assumed to be located in thin 50 μm liner
31
32 240 in contact with a product of 1 L. To simulate more realistic conditions in the latter case, a
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34 241 contact with a dairy product at 4°C during 90 days was assumed.

41 242 The scenarios numbered from 1 to 8 were located at the vertices of a cube (Figure 2). The
42
43 243 face 1,4,7,3 corresponded to uncertainties on transport properties. The opposite face 2,6,8,5
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45 244 combined in addition uncertainty on composition, $C_{i,P}^0$. In absence of a transport property, a
46
47 245 robust overestimate was used instead. As no recommendation has been specifically proposed
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49 246 for 50% ethanol used as simulant, an upper bound of 10^3 was chosen for $K_{i,F/P}^+$ instead of the
50
51 247 unitary value recommended for simulant D (olive oil) in the “Practical Guide” (European
52
53 248 Commission 2003) as extreme worst case. This choice was consistent with experimental $K_{i,F/P}$
54
55 249 values found higher than 1 between polyolefins and ethanol (Vitrac *et al.* 2007, Gillet *et al.*
56
57 250 2009c). As detailed in table II, in absence of data on initial concentrations for migrants used
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3 251 as additives (Irganox 1330, Irganox 3114, BHT), maximum values recommended by the
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5 252 providers were used. For low molecular weight contaminants (2-ITX and diphenylmethane),
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8 253 concentrations in agreement with the extensive study of Rothenbacher *et al.* (2007) were
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10 254 used.

11
12 255 Scenarios 9 and 10 were special cases where the identity of the migrant *i* was unknown. In
13
14 256 this work, they were applied to phenolic antioxidants similar to those previously studied
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16 257 (Irganox 1330, Irganox 3114 and BHT) but for which only an estimate of the concentration in
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18 258 di-tert-butylphenol (BHT pattern) was assumed to be known, as detailed in Table IV. This
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20 259 situation was consistent with a concentration determination by FTIR (Gillet *et al.*, 2009a).
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26 261 **Results and discussion**

27 262 *Extraction yields*

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29 263 A list of substances, which may migrate from the contact material to the food, is
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31 264 conventionally required before starting any assessment of specific migration limits. This
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33 265 approach is well suited for substances, which are intentionally added to materials in contact
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35 266 with food. This information is obtained either by partial disclosure of confidential information
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37 267 or by a reformulation step. For practical cases taken in consideration by the Laboratoire
38
39 268 National d'Essais in France, the formulation is transmitted for less than 5 % of tested samples
40
41 269 (Table I). As a result, reformulation appears currently as the most robust approach to start the
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43 270 decision tree depicted in Figure 1. To be cost-efficient, this additional step must be rapid and
44
45 271 predictive. The difficulty arises with semi-crystalline materials such as polyolefins, which
46
47 272 cannot be dissolved in most of solvents below their melting point. Figure 3 presents the
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49 273 estimated concentration in *P* after successive extractions during a long-term extraction by
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51 274 reflux (extraction time 48 h) and using a pressurized cell (extraction time 40 min). The data
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3 275 were obtained for two typical antioxidants, Irganox 1076 and Irgafos 168, well dispersed in
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5 276 the bulk and a slip agent, Erucamide, mainly located at the external surface of *P*.
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10 277 Differences between methods and substances (including 3 extractions×3 concentrations
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19 278 measurements) were almost insignificant. As only leaching was required to extract Erucamide
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21 279 from HDPE, the extraction was complete in one step. For additives dispersed in the bulk, 95
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23 280 % extraction was reached after the first step. The bias related to a single extraction was
24
25 281 therefore minimal. Although the extraction bias (systematic error) could be corrected with the
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27 282 extraction yield, the experimental error (random error) was much higher. The overall relative
28
29 283 experimental error was assessed up to 20 % and did not decrease with the considered number
30
31 284 of extraction steps, since the extracted amounts were cumulated and not averaged. The
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33 285 magnitude of the extraction error was directly correlated to the accuracy of sampling and
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35 286 concentration measurements.
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42 288 *Migration kinetics*

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44 289 Figure 4 plots the dimensionless kinetics corresponding to the most complete scenario (i.e.
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46 290 with the lowest uncertainty), ranked 1 in Figure 2, for three antioxidants initially included in a
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48 291 200 µm thick film in contact with 50% ethanol ($L_{FP}=50$) at 40°C. The dimensionless
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50 292 diffusion time corresponding to a conventional contact time of 10 days at 40°C, denoted F_{O10} ,
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52 293 is also depicted. Although most of decision-makers would not start with this scenario, it is
53
54 294 particularly useful to illustrate the migrant based reasoning. Diffusion behavior of BHT was
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56 295 highly distinct of additives including several BHT patterns with a F_{O10} value close to 6
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5 296 against a value of $4 \cdot 10^{-2}$ for Irganox 1330 and Irganox 3114. Concentration values at
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15 297 equilibrium, $C_{i,F}^{(F_0 \rightarrow \infty)}$, given by the overall mass balance defined in Equation 4, were also
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17 298 highly different:
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$$C_{i,F}^{(F_0 \rightarrow \infty)} = \frac{1}{L_{F/P} + 1/K_{i,F/P}} \cdot C_{i,P}^0 \quad (4)$$

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24 300 As a same dilution ratio, $L_{F/P}$, and a same initial concentration, $C_{i,P}^0$, were applied to all
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26 301 migrants, the differences in calculated migration rates were only related to partitioning
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28 302 between HDPE and 50% ethanol, $K_{i,F/P}$ used as input. Despite all migrants consisted in the
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30 303 repetition of same BHT pattern, their chemical affinity for 50% ethanol varied significantly
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32 304 with their size. This effect has been extensively studied in Gillet *et al.* (2009b and 2009c) and
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34 305 has been proposed to explain the relative high chemical affinity of large additives for mixtures
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36 306 consisting in much smaller molecules. Similar considerations are detailed by Fill and
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38 307 Bromberg (2003). Accordingly, the effect of solute size on $K_{i,F/P}$ was related to a much higher
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40 308 dispersion of chemical interactions between the migrant and the simulant when the migrant
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42 309 was larger. Indeed, a large molecule as Irganox 3114 consisting in 3 BHT patterns exposed a
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44 310 much lower specific surface to simulant than a single BHT molecule and consequently
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46 311 perturbed less the cooperative network of hydrogen bonds in water-ethanol mixtures. It is
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48 312 underlined that the current approach neglects possible reactions, which could reduce the size
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50 313 of migrants and which could modify accordingly the chemical affinity of fragments for the
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52 314 simulant.
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3 316 In detail, the migration of large additives, Irganox 1330 and Irganox 3114, was controlled
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5 317 by both the migrant chemical affinity for 50% ethanol (which favors the migration
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7 318 comparatively to BHT) and by the limiting diffusion in the film. . The uncertainty effects
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10 319 were however not symmetric. As illustrated in Figure 4b, concentrations of Irganox 1330 and
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12 320 3114 in simulant were greater than 40 % of their equilibrium values, e.g. maximum possible
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15 321 concentration in simulant. Overestimating diffusion coefficients would therefore increase the
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17 322 concentration in food simulation at a maximum by a factor $1/0.4=2.5$. In contrast,
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19 323 overestimating the partitioning by several orders of magnitude might lead to a complete
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22 324 extraction, that is $1/50$ the initial concentration, that is overestimating the expected migration
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25 325 by one order of magnitude (Figure 4a).

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27 326 It is worth noting that such a very low partitioning (Table III) with the simulant requires a
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29 327 particular care in the writing of the boundary condition (Equation 2) and in the resolution of
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31 328 the complete set of transport equations. It is expected that the requested time to reach the
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34 329 equilibrium is lower when the chemical affinity is very low for F . Simply explained, the
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36 330 equilibrium was reached all the more rapidly when the amount of migrant to be desorbed to
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39 331 reach the equilibrium was lower. In the absence of chemical affinity of the simulant, the
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41 332 macroscopic equilibrium would be thus obtained instantaneously as soon as a single molecule
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43 333 would have left the polymer. These features, which may appear counter-intuitive, are
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46 334 discussed by Vitrac and Hayert (2006).

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48 335 The practical consequence was that the mis-identification in FTIR of Irganox 1330 as
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50 336 BHT, with a three times higher molar concentration (note that the mass concentration would
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52 337 remain unchanged), would not be necessarily a worst case as the affinity of Irganox 1330 for
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55 338 the simulant would be also higher.

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60 340 *Sensitivity diagrams to uncertainty*

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3 341 Introducing simultaneously a significant amount of uncertainty for the diffusion coefficient
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5 342 and partition coefficient, as it could be in practice, complicates arriving at clear conclusions
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7 343 regarding the possible exceedance of a given threshold. The effects of combined variations in
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9 344 $K_{i,FP}$ and $D_{i,P}$ values, corresponding to Figure 4, are illustrated as isocontours of $10^3 \cdot C_{i,F}^{(Fo)} / C_{i,P}^0$
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11 345 in Figure 5 for two dilution ratios: $L_{F/P}=50$ and $L_{F/P}=83$. These ratios matched the
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13 346 conventional assumption used in conservative consumer exposure assessment in EU
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15 347 (European Commission 2002): 1 kg on food in contact with 6 dm² of packaging material. In
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17 348 Figure 5, the values corresponding to scenarios numbered from 1 to 8 (see Table IV) are
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19 349 plotted at the vertices of a rectangle. The extents of variations represent the effects of
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21 350 overestimations when one or two input values were missing and when strong overestimates
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23 351 were used instead (see Table III).
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29 352 For a small migrant as BHT, equilibrium was reached in less than two days so that only
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31 353 uncertainty on partitioning was able to change the concentration in food simulant after 10
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33 354 days. By choosing $K_{i,FP}^+$ (scenarios 3,5,7,8), the extraction was almost complete and the
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35 355 concentration in simulant was solely controlled by the maximum permitted concentration in
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37 356 HDPE. The overestimation factor reached up two decades. The behavior was opposite for
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39 357 large antioxidants and their migration rates were almost independent of partitioning. The
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41 358 isocontours appeared therefore mainly parallel to $K_{i,FP}$ axis with a maximum overestimation
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43 359 factor of 5. According to Equation 4, it is worth to notice that decreasing $K_{i,FP}^+$ from 1000
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45 360 down to 1 (worst case recommended in “practical guide” (2003)) did not change previous
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53 361 conclusions as $L_{F/P}$ values higher than 10 led to almost complete extraction for any $K_{i,FP}^+ \geq 1$.
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3 362 $L_{F/P}$ introduced only some additional effects. They were related to two complementary
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5 363 contributions: i) lowering the effect of a poor chemical affinity for simulant at high $L_{F/P}$
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7 364 values and ii) increasing the dilution of the amount of migrated substances. Depending on the
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12 365 units used to express the specific migration limit (SML), in $\text{mg}\cdot\text{dm}^{-2}$ of packaging or $\text{mg}\cdot\text{kg}^{-1}$
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22 366 of packaging, the one or the other led to a more conservative assumption. As we expressed
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26 367 SML in $\text{mg}\cdot\text{kg}^{-1}$, $L_{F/P}=50$ was chosen in the remainder of the work as a worst case
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36 368 assumption. The conventional assumption 1 kg in contact with 6 dm^2 would lead to a
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38 369 concentration in food simulant down to twice lower.
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43 371 The effect of cumulating up to three sources of uncertainty made the utility of some
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45 372 scenarios questionable according to the expected migration limit of concern (SML or
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47 373 detection limit). To generate a practical sensitivity diagram depicting all combined sources of
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50 374 uncertainty, a simplified descriptor, derived from Equation 2, $F_{0_{10}} \cdot K_{i,F/P}$ was used instead of
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52 375 isocontours. For low molecular weight contaminants with a contact time of 90 days (Table
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55 376 III), a similar descriptor was proposed: $F_{0_{90}} \cdot K_{i,F/P}$. Values of $C_{i,F}^{(F_0=F_{0_{10}}, F_{0_{90}})}$ against the previous
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58 377 criteria are plotted in Figure 6 for $\bar{C}_{i,P}^0$ and $(C_{i,P}^0)^+$. Confidence intervals caused by
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60 378 uncertainties on transport properties, $\bar{K}_{i,F/P}$ and $\bar{D}_{i,P}$, are also presented to highlight that the

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3 379 decision of compliance should not be taken necessarily at the predicted value but should
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5 380 include an additional safety margin.
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8 381 Combining several sources of uncertainty showed that the hierarchy of scenarios to
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10 382 demonstrate the compliance was not intuitive as it depended on the considered case..
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12 383 Scenarios involving $K_{i,F/FP}^+$ values (3,5,7,8), as generally recommended for migration
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14 384 modeling, were able to demonstrate the compliance only when the migration limit was as high
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20 385 as the overall migration limit in EU regulation, $60 \text{ mg}\cdot\text{kg}^{-1}$, that is for Irganox 1330. By
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29 386 contrast, refined scenarios 1,2,4,6 involving at least one likely transport properties were
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31 387 always applicable to demonstrate compliance. Irganox 3114 and DPM were special cases,
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33 388 where compliance could not be determined when more than one source of uncertainty was
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36 389 included.
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41 391 *Decision diagrams in MIC*

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43 392 The usability of previous sensitivity diagrams by end-users, having not access to the initial
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45 393 formulation of their materials, was improved by replacing the concentration in food simulant
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47 394 by the equivalent maximum concentration in the packaging material, *MIC*, which matches the
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50 395 limit of concern. It was calculated as:
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$$MIC = \frac{C_{i,P}^0}{C_{i,F}^{(Fo)}} \cdot \text{limit of concern} \quad (5)$$

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57 397 *MIC* values are more practical as they can be calculated *a priori* for a given food
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59 398 packaging application and they can be compared subsequently with formulation data derived
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399 from general manufacturing practices or from a partial formulation disclosure (Figure 1). The

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3 400 interesting feature is that the provider needs only to acknowledge that it uses the substance at
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5 401 a lower concentration than *MIC*. To make robust conclusions, the uncertainty associated to
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8 402 each *MIC* estimates must be accounted. *MIC* values corresponding to Figure 6 are plotted in
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10 403 Figure 7 in increasing order. When implemented as decision diagram, each bin represents a
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12 404 condition node: is the initial concentration higher than the value above each bin? If the answer
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15 405 is yes, the question must be repeated with the next bin on the right. If the answer is no, the
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17 406 compliance is demonstrated. For large additives, the *MIC* values were progressively
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19 407 increasing as the migration model was sensitive to all sources of uncertainty. For low
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21 408 molecular weight contaminants and additives, changes between values were most abrupt.
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23 409 Ordering scenarios *a priori* guaranteed the decision-maker that acquiring new information
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25 410 will improve the decision. A strict improvement is obtained by merging scenarios with similar
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27 411 values. As it is physically expected, $\bar{K}_{i,F/P}$ was the most valuable information for small
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29 412 migrants while it was $\bar{D}_{i,P}$ for large additives including a repeated pattern.
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414 *Decision diagrams for phenolic antioxidants mistaken with BHT*

39 415 When the identity of the substance was not known as it might occur in FTIR
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41 416 deformation, a large molecule (in this work a large hindered phenolic antioxidant) was
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43 417 replaced by much smaller one (BHT). This approximation suited particularly for Irganox
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45 418 1330 and Irganox 3114. Nevertheless two additional difficulties appeared: the initial
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47 419 concentration was expressed in equivalent concentration in BHT patterns and the limit of
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49 420 concern was assumed to be the SML of BHT. The reliability of such assumptions to
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51 421 demonstrate the compliance is depicted in Figure 8. As the SML of BHT was much lower
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53 422 than the one of real additives, the approximation guaranteed a conservative decision limit. By
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55 423 introducing the expected transport properties of BHT, $\bar{D}_{BHT,P}$ and $\bar{K}_{BHT,F/P}$, and an equivalent
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57 424 concentration in BHT pattern, the predictions of scenarios 9 and 10 were close to those of
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3 425 scenarios 1 and 2 respectively (Figure 5). As a result, the compliance could be demonstrated
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5 426 easily with scenario 9 and 10.
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8 427 The proposed approximation seemed valid when BHT replaces molecules based on the
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10 428 repetition of several BHT patterns. It should not be generalized to any series of additives. A
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12 429 more general estimate based on $D_{BHT,P}^+$ and $K_{BHT,F/P}^+$ was tested and plotted as scenarios 9' and
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14 430 10' in Figure 8. As it led to equivalent *MIC* values lower than 200, it was not suitable for
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16 431 antioxidants, which are conventionally used at concentrations much higher.
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22 433 *Shortest paths to demonstrate the compliance*
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25 434 From the point of view of decision-maker, the dependence diagram depicted in Figure 2
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27 435 should be started in the reverse order with the lowest knowledge level. For antioxidants, it
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29 436 could be started with scenarios 9 and 10 as a homologous molecule was available. For other
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31 437 molecules, it should be started with the scenario 8. The best scenario was the one, which
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33 438 made it possible to demonstrate the compliance and was connected with shortest path length
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35 439 (decision path length) to the initial scenario. In other words, the optimal scenario should
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37 440 minimize the extent of additional information necessary to demonstrate the compliance.
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44 442 Previous figures 5-6 cannot be used directly to determine the shortest path length as they
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46 443 focus on the values of physicochemical properties instead of on the amount of available
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48 444 information. In practice, the lengths of all possible paths (8) were read in Figure 2, they did
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50 445 not depend on the considered substance or on the considered problem. The efficiency of each
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52 446 corresponding scenario (ability to demonstrate the compliance) depends both on the
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54 447 considered case, e.g. substance, and on the decision limit value. In order to derive almost self-
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56 448 similar diagrams, i.e. reusable for other applications, where the shortest distance can be easily
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58 449 read, all scenarios were ranked according to their equivalent decision path length and plotted
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3 450 in Figure 9 as concentrations normalized according to the considered SML. Starting from the
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5 451 left, the shortest path length was consequently defined as the first abscissa with a normalized
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7 452 concentration lower than 1. Except when the SML was as high as the global migration limit
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10 453 (Irganox 1330), a path of length 4 was required, which indicated that no more than two
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12 454 sources of uncertainty could be combined. On one hand, it could be argued, as a rule of
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15 455 thumb, that when partial formulation disclosure is not accepted or available, at least one
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17 456 transport property must be known with enough accuracy. On the other hand, when the initial
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19 457 concentration is available, conventional overestimates, although inaccurate, are expected to be
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22 458 able to demonstrate the compliance not in all cases but with a significant expectation, between
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24 459 50% and 75%.

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27 460 For polyolefins (one third of total food contact applications), the current state of the art
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29 461 suggests that scenario 2 and possibly scenario 1 should be nearly available for all practical
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31 462 cases, while minimizing the risk of false negative (considered as “not able to demonstrate the
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33 463 compliance” when it is compliant). In addition, the risk of false positives would be very low
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36 464 while appropriate safety margin on likely transport properties are included in the decision.
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40 41 466 **Conclusions and future prospects**

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43 467 This paper addresses a general framework to combine migration modeling and experiments
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45 468 into the same decision tool to demonstrate the compliance of thermoplastics materials in
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47 469 contact with food with regulatory limits. The objective was to select the necessary
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49 470 experiments and simulation scenarios among several alternatives to make a decision: “it is
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51 471 compliant” or “the compliance cannot be demonstrated with this approach”. In comparison to
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53 472 conventional approaches used in migration modeling, the ambition was neither to assess the
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55 473 real migration nor to overestimate all uncontrolled factors but to dramatically increase the
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3 474 usability of modeling-based compliance testing. The improvements consisted mainly in
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5 475 designing an end user-oriented approach, which was:

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8 476 - more efficient (more robust, it takes less time to accomplish the demonstration, it requires
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10 477 fewer assumptions, formulation disclosure is not systematically required...);
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12 478 - easier to learn (based on simple diagrams, include a robust physical reasoning based in
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14 479 particular on minimal number of dimensionless quantities);
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17 480 - more satisfying to use (the method toggles when required from empirical models of
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19 481 transport properties to more sophisticated ones based on a molecular simulation).

20 482 The method was tested in complicated cases involving the migration of low molecular
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22 483 weight contaminants and hindered phenolic antioxidants into the simulant proposed for dairy
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24 484 products, 50% ethanol, for which the possibilities of modeling had not yet been examined.
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27 485 Although the current results might find an application in the previous 2-ITX crisis, the finality
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29 486 was mainly methodological. All ten scenarios incorporating up to three sources of uncertainty
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31 487 has been incorporated into an on line semi-supervised software on the SAFE FOOD
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33 488 PACKAGING PORTAL (INRA 2008). It generates all proposed diagrams in less than 3
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35 489 minutes so that the overall decision tree can be easily integrated along with the process of
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37 490 identification and quantification of substances and along with the audit of the provider.
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45 492 Apart from the decision tool concept, this work brought two important insights for both
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47 493 compliance testing and future sanitary survey. The migration of large additives such
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49 494 antioxidants is mainly controlled by the resistance of material to diffusion. This low effect of
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51 495 partitioning is exacerbated by their higher chemical affinity for food simulant consisting in
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53 496 much smaller molecules. As an example of consequence, long time contacts and heating
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55 497 should lead to higher contamination of food products by large additives than by smaller ones
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57 498 even if they had a similar chemical composition. As this description neglects a possible
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3 499 hydrolysis of additives, a dedicated experimental verification is encouraged. Finally, the
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6 500 results highlighted that the crude assumptions recommended in the current “Practical Guide”
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8 501 (2003) for modeling, based mainly on simulant D and strong overestimates of diffusion
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10 502 coefficients, failed to deserve the demonstration of compliance for intentionally added
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12 503 substances in most of tested cases. As modeling combined with fast deformation techniques
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15 504 appear to be the mainly independent approach to audit the compliance, further extension of
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17 505 this work to other polymers and multilayer materials is highly desirable.
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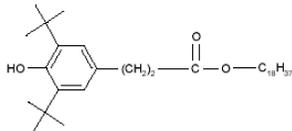
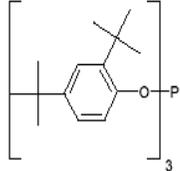
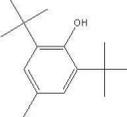
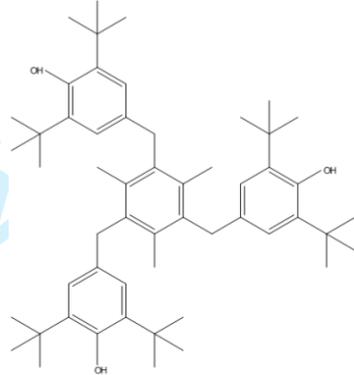
603 **Table I.** Transition and overall probabilities of the decision tree plotted in Figure 1. The final probability to demonstrate the compliance is
 604 denoted $p_{\text{compliance}}$. The values obtained with the current methodologies used at LNE (Laboratoire National de métrologie et d'Essais) and the
 605 expected values with the new proposed paradigm are compared.
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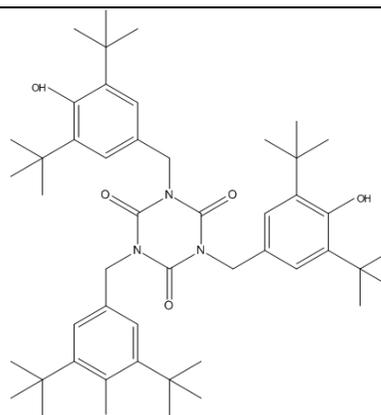
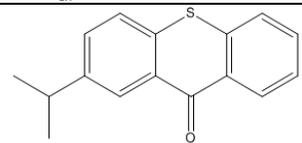
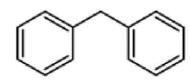
	Notations	Current state at LNE†	Expected value with the new methodology‡
Transition probabilities	a	5%	50%
	b	50%	75%
	c	10%	80%
	d_{SML}	90%	90%
	d_{MIC}	50%	50%
Overall probabilities	$p_1 = a$	5%	50%
	$p_{2,\text{SML}} = a \cdot b$	2.5%	37.5%
	$p_{3,\text{SML}} = a \cdot b \cdot c$	0.25%	30%
	$p_{4,\text{SML}} = a \cdot b \cdot c \cdot d_{\text{SML}}$	0.20%	27%
	$p_{2,\text{MIC}} = a \cdot (1-b)$	2.5%	12.5%
	$p_{3,\text{MIC}} = a \cdot (1-b) \cdot c$	0.25%	10%
	$p_{4,\text{MIC}} = a \cdot (1-b) \cdot c \cdot d_{\text{MIC}}$	0.13%	5%
	$P_{\text{compliance}} = p_{4,\text{SML}} + p_{4,\text{MIC}}$	0.33%	32%

607 †The values were in particular inferred from the number and type of compliance requests received by LNE during the last five years.

608 ‡The values were derived from blind samples tested during the project RA05.22

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613**Table II.** List of tested substances.

Category	Code	Chemical name	Function	CAS number	M (g·mol ⁻¹)	SML (mg·kg ⁻¹)	Chemical structure
Plastic additives	Irganox 1076	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl) propionate	radical scavenger	2082-79-3	530	6	
	Irgafos 168	Phosphorous acid, tris(2,4-di-tert-butylphenyl) ester	hydroperoxide decomposer	31570-04-4	647	60	
	Erucamide	Cis-13-docosenoamide	slip agent	00112-84-5	337	60	$\text{CH}_3-(\text{CH}_2)_7-\text{CH}=\text{CH}-(\text{CH}_2)_{11}-\text{C}(=\text{O})-\text{NH}_2$
	BHT	Butylated hydroxytoluene	radical scavenger	000128-37-0	220	3	
	Irganox 1330	1,3,5-Trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)benzene	radical scavenger	01709-70-2	774	60	

Category	Code	Chemical name	Function	CAS number	M (g·mol ⁻¹)	SML (mg·kg ⁻¹)	Chemical structure
	Irganox 3114	1,3,5-Tris(3,5-di-tert-butyl-4-hydroxybenzyl)-1,3,5-triazine-2,4,6(1H,3H,5H)-trione	radical scavenger	27676-62-6	784	5	
Low molecular weight contaminants	2-ITX	2-(1-methylethyl)-9H-Thioxanthen-9-one	Printing ink photoinitiator	5495-84-1	254	10 ⁻² ‡	
	DPM	diphenylmethane	reference†	101-81-5	168	10 ⁻² ‡	

614 † experimental partition coefficient between HDPE and ethanol is available (Baner *et al.*, 1991).

615 ‡ threshold value corresponding to the migration of an authorized below the detection level through a functional barrier as described in article 10 of directive 2007/19/EC
616 (EC, 2007).

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Table III. List of inputs used to predict the migration from a polyolefin to a 50:50 v/v water-ethanol simulant.

PARAMETER	Migrant Homologous migrant [†] Polymer notation (unit)	Low molecular weight contaminants		Plastic additives		
		2-ITX not available LDPE ^{††}	DPM not available LDPE ^{††}	BHT not available HDPE ^{†††}	Irganox 1330 BHT (3) HDPE ^{†††}	Irganox 3114 BHT (3) HDPE ^{†††}
Thickness	l_P (μm)	50	50	200	200	200
Volume dilution ratio	$L_{F/P}$ (-)	360	360	50	50	50
Biot mass number	Bi (-)	10^3	10^3	10^3	10^3	10^3
Contact Time	t (days)	90	90	10	10	10
Temperature	($^{\circ}\text{C}$)	4	4	40	40	40
Likely initial concentration ^a	$\bar{C}_{i,P}^0$ ^a ($\text{mg}\cdot\text{kg}^{-1}$)	100 ± 10	100 ± 10	$10^3 \pm 100$	$10^3 \pm 100$	$10^3 \pm 100$
Conservative initial concentration ^b	$(C_{i,P}^0)^+$ ^b ($\text{mg}\cdot\text{kg}^{-1}$)	300	300	$3\cdot 10^3$	$3\cdot 10^3$	$3\cdot 10^3$
Likely diffusion coefficient ^c	$\bar{D}_{i,P}$ ^c ($\text{m}^2\cdot\text{s}^{-1}$)	$8.4\cdot 10^{-16}$ [$7.6\cdot 10^{-16}$ $9.2\cdot 10^{-16}$]	$7.3\cdot 10^{-14}$ [$6.7\cdot 10^{-14}$ $8.0\cdot 10^{-14}$]	$2.7\cdot 10^{-13}$ [$2.5\cdot 10^{-13}$ $2.9\cdot 10^{-13}$]	$1.6\cdot 10^{-15}$ [$1.5\cdot 10^{-15}$ $1.8\cdot 10^{-15}$]	$1.6\cdot 10^{-15}$ [$1.5\cdot 10^{-15}$ $1.8\cdot 10^{-15}$]
Conservative diffusion coefficient ^d	$D_{i,P}^+$ ^d ($\text{m}^2\cdot\text{s}^{-1}$)	$3.9\cdot 10^{-14}$	$1.1\cdot 10^{-13}$	$4.4\cdot 10^{-12}$	$3.6\cdot 10^{-14}$	$3.4\cdot 10^{-14}$
Likely partition coefficient ^e	$\bar{K}_{i,F/P}$ (-)	$1.4\cdot 10^{-9}$ [$3.7\cdot 10^{-10}$ $5.1\cdot 10^{-9}$]	$1.2\cdot 10^{-4}$ [$3.4\cdot 10^{-5}$ $4.6\cdot 10^{-4}$]	$2.1\cdot 10^{-4}$ [$5.7\cdot 10^{-5}$ $7.7\cdot 10^{-4}$]	2.9 [0.77 10]	0.013 [$3.5\cdot 10^{-3}$ 0.048]
Conservative partition coefficient	$K_{i,F/P}^+$ (-)	10^3	10^3	10^3	10^3	10^3

619 [†] molecule which gives a similar IR absorption spectrum with a molar ratio indicated between brackets.620 ^{††} density = 0.899, crystallinity = 30%; ^{†††} density = 0.959, crystallinity = 70%.621 ^a chosen to fit real concentrations for a similar packaging material.622 ^b three times the likely value (matched the maximal recommended values for Irganox 1330 and Irganox 3114).623 ^c robust estimate according from Vitrac *et al.* (2006) and available on the SAFE FOOD PACKAGING PORTAL (INRA, 2008), 95% confidence intervals in brackets include the overall uncertainty on $D_{i,P}$ and its activation energy for this class of substance.624 ^d from the overestimate model described in Beygley *et al.* (2005).625 ^e calculated from the generalize Flory-Huggins approach described by Gillet *et al.* (2009c) for water-ethanol mixtures, all inputs required from thermodynamical and
627 Molecular simulations are listed in Table 3. 95% confidence intervals based on a sensitivity analysis are indicated between brackets.

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630 **Table IV.** Combination of input values associated to each scenario. The index i in scenarios 1..8 corresponds to an identified substance, whereas
 631 the index h in scenarios 9..10 corresponds to an homologous molecule (BHT for antioxidants) with a similar mid-infrared vibrational spectrum
 632 (Gillet *et al.*, 2009a).

Scenario	$C_{i,P}^0$ value	$K_{i,FI/P}$ value	$D_{i,P}$ value
1	$\bar{C}_{i,P}^0$	$\bar{K}_{i,FI/P}$	$\bar{D}_{i,P}$
2	$(C_{i,P}^0)^+$	$\bar{K}_{i,FI/P}$	$\bar{D}_{i,P}$
3	$\bar{C}_{i,P}^0$	$K_{i,FI/P}^+$	$\bar{D}_{i,P}$
4	$\bar{C}_{i,P}^0$	$\bar{K}_{i,FI/P}$	$D_{i,P}^+$
5	$(C_{i,P}^0)^+$	$K_{i,FI/P}^+$	$\bar{D}_{i,P}$
6	$(C_{i,P}^0)^+$	$\bar{K}_{i,FI/P}$	$D_{i,P}^+$
7	$\bar{C}_{i,P}^0$	$K_{i,FI/P}^+$	$D_{i,P}^+$
8	$(C_{i,P}^0)^+$	$K_{i,FI/P}^+$	$D_{i,P}^+$
9	$\bar{C}_{h,P}^0 \dagger$	$\bar{K}_{h,FI/P}$	$\bar{D}_{h,P}$
10	$(C_{h,P}^0)^+ \ddagger$	$\bar{K}_{h,FI/P}$	$\bar{D}_{h,P}$

633 \dagger 852 mg·kg⁻¹ in BHT to match an equivalent concentration in BHT patterns included in Irganox 1330 and Irganox 3114. \ddagger 3000 mg·kg⁻¹.

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3 635 **Figure 1:** Decision diagram to demonstrate the compliance of plastic materials according to
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5 636 article 8 of directive 2002/72/EC. Current and modified transition probabilities of acceptance are
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7 637 gathered in table 1. Additional improvements via iterative modeling appeared as dotted lines.
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12 639 **Figure 2.** Influence diagram relating all ten scenarios involved in the assessment of compliance
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14 640 when migration modeling and deformation experiments are combined together.
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20 642 **Figure 3.** Estimated concentrations in HDPE, $C_{i,P}^0$, of three additives against the number of
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22 643 extraction steps. All concentrations were normalized according the value after 4 extractions and
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24 644 denoted $C_{i,P}^0$.
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30 646 **Figure 4.** Dimensionless migration kinetics of BHT, Irganox 1330 and Irganox 3114
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32 647 corresponding to likely input values in Table III: a) kinetics on a log-log scale, b) kinetics
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34 648 against the square root of time. Dimensionless contact time, Fo_{10} , corresponding for each migrant
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36 649 to contact times of 10 days are depicted by dashed lines.
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42 651 **Figure 5.** Isocontours of $10^3 \cdot C_{i,F}^{(Fo)} / C_{i,P}^0$ against Fo and $K_{i,F/P}$ for a,c,e) $L_{F/P}=50$) and b,d,f) $L_{F/P}=83$:
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44 652 a-b) BHT, c-d) Irganox 3114, e-f) Irganox 1330. Scenarios 1..8 are also represented as α
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46 653 (scenarios 1 and 2), β (scenarios 3 and 5), γ (scenarios 4 and 6), δ (scenarios 7 and 8).
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52 655 **Figure 6.** Sensitivity diagram of $C_{i,F}^{(Fo)}$ against all unknowns: a) i =BHT, b) i =Irganox 3114, c)
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54 656 i =Irganox 1330, d) i =2-ITX, e) i =DPM. Error bars represent 95% confidence intervals on
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657 estimates. The limit of concern appears as a dashed line. Scenarios including $\bar{C}_{i,P}^0$ and $(C_{i,P}^0)^+$ are
 658 plotted as circles and squares respectively.

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 660 **Figure 7.** Decision diagrams expressed as ordered *MIC* values for scenarios 1..8: a) *i*=BHT, b)
 661 *i*=Irganox 3114, c) *i*=Irganox 1330, d) *i*=2-ITX, e) *i*=DPM.

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 663 **Figure 8.** Decision diagram when Irganox 1330 or Irganox 3114 is replaced by a similar
 664 concentration in BHT patterns, $\hat{C}_{BHT,F}^{F_{010}}$, with the properties of BHT (see Table 2). Scenarios 9 and
 665 10 are calculated with $\bar{D}_{BHT,P}$ and $\bar{K}_{BHT,F/P}$ whereas scenarios 9' and 10' are equivalent scenarios
 666 calculated with $D_{BHT,P}^+$ and $K_{BHT,F/P}^+$. The decision is taken by comparing $\hat{C}_{BHT,F}^{F_{010}} / SML_{BHT}$ with one.
 667 The corresponding limit for the real additives is also depicted.

668
 669 **Figure 9.** Decision diagrams expressed as minimum path lengths in the influence diagram
 670 depicted in Figure 1 (the decision process is started with scenario 10): a) *i*=BHT, b) *i*=Irganox
 671 3114, c) *i*=Irganox 1330, d) *i*=2-ITX, e) *i*=DPM.

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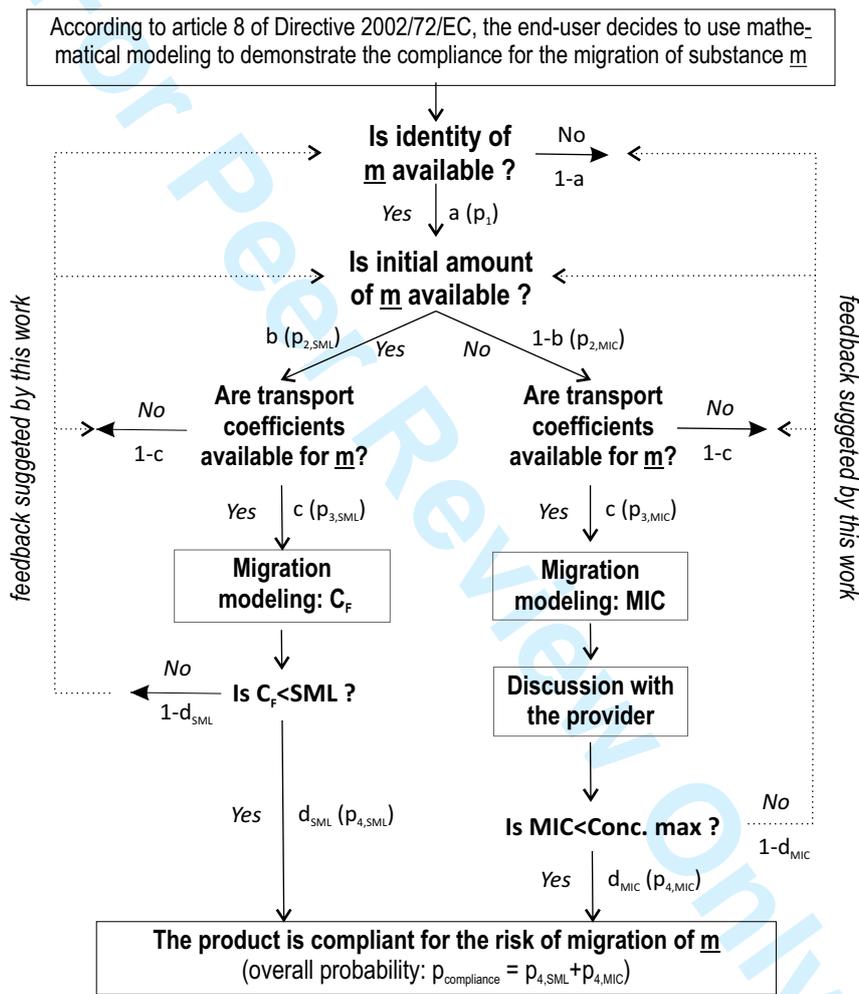


Fig. 1
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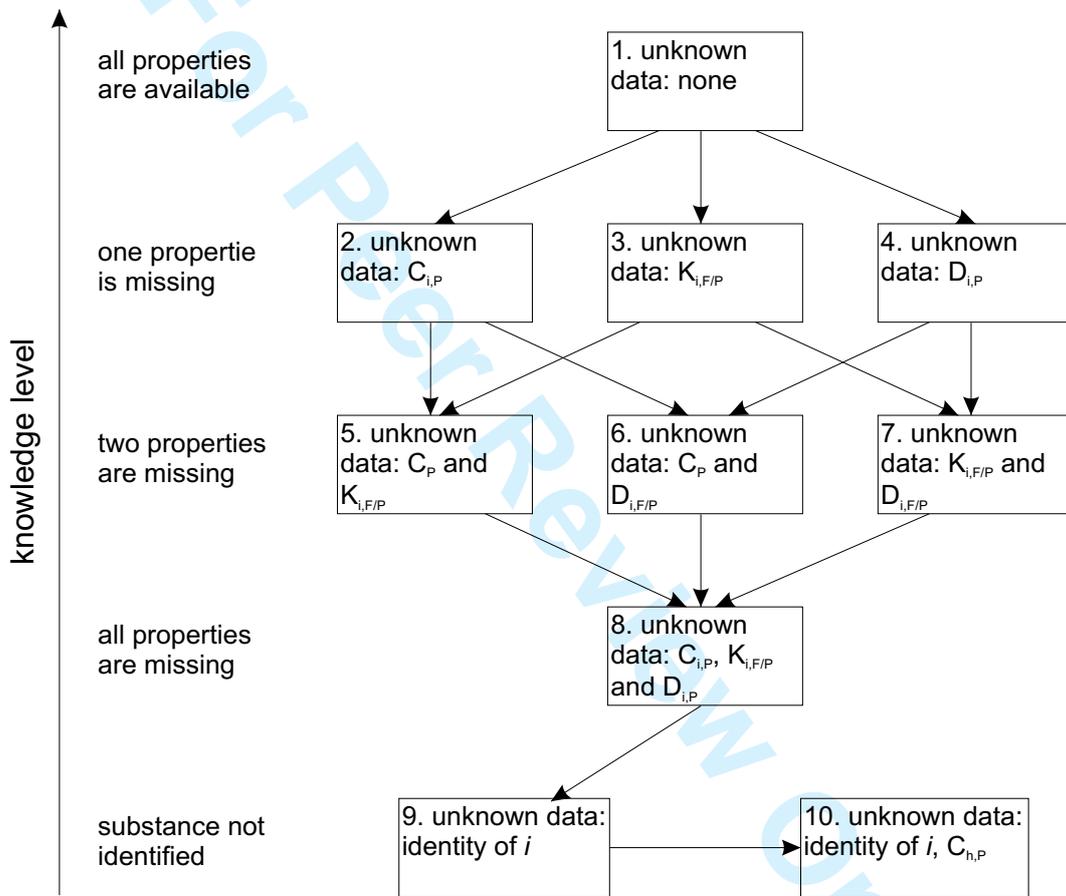


Fig. 2

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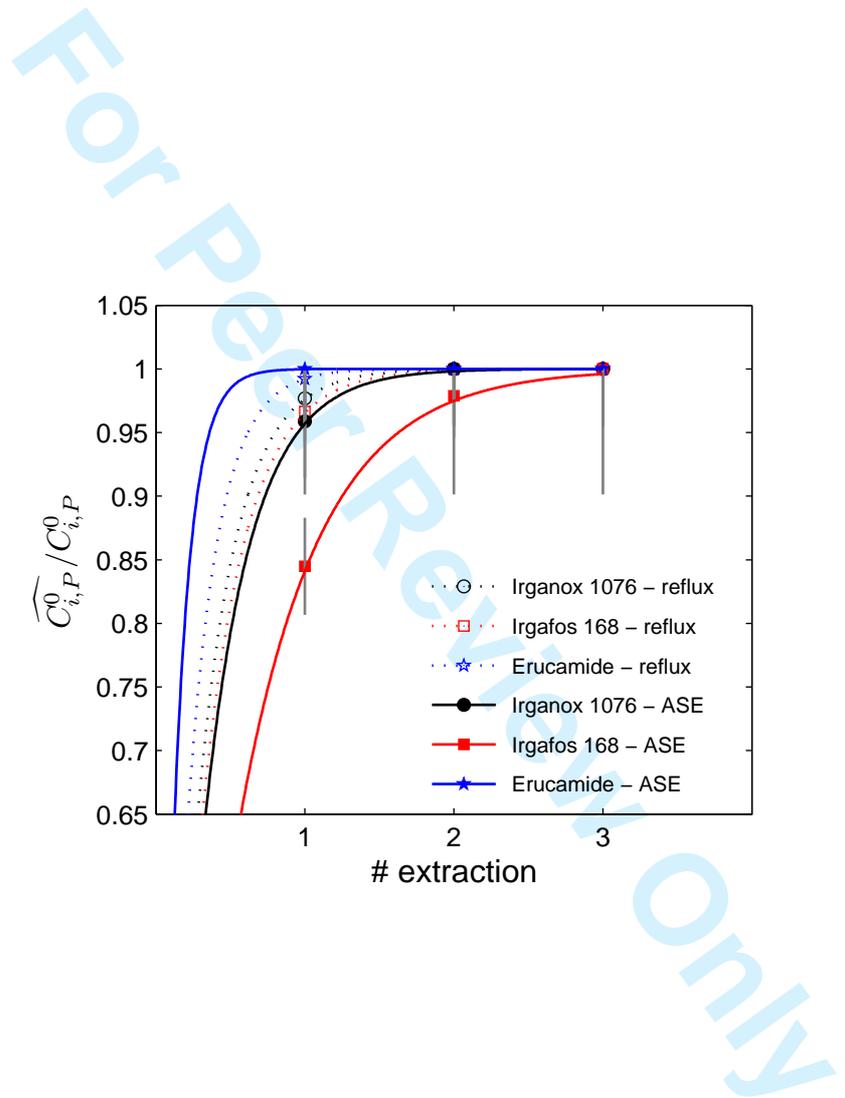


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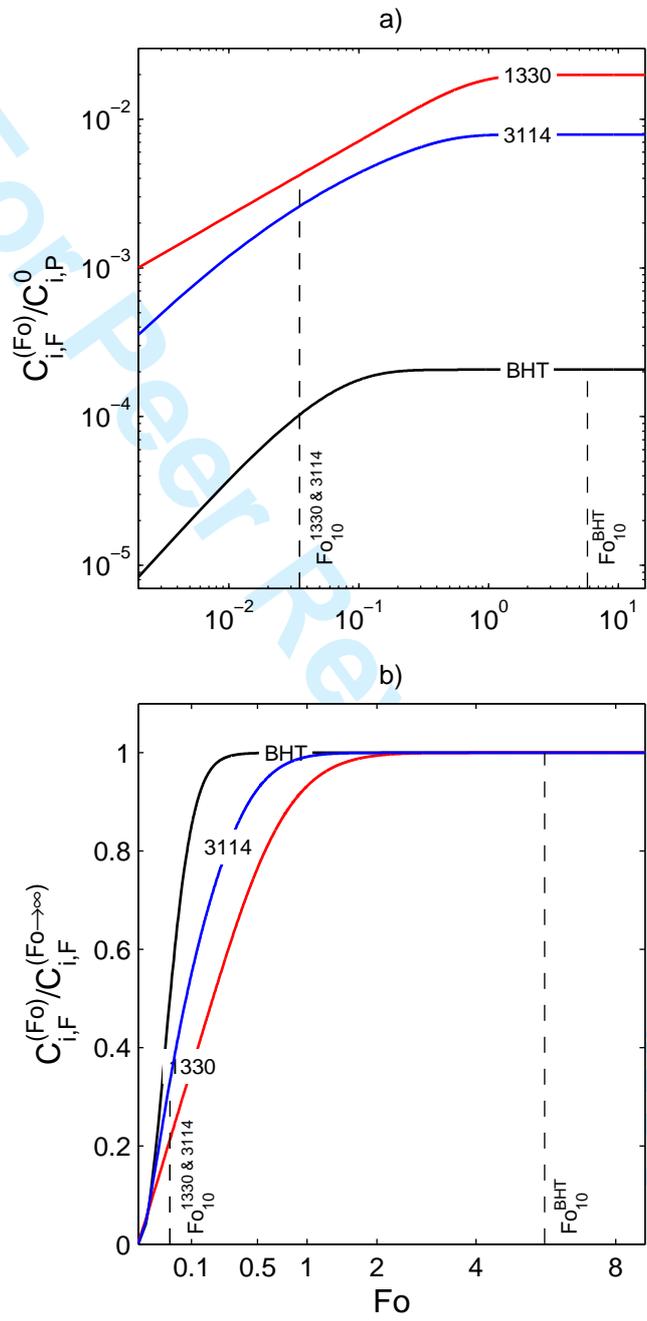


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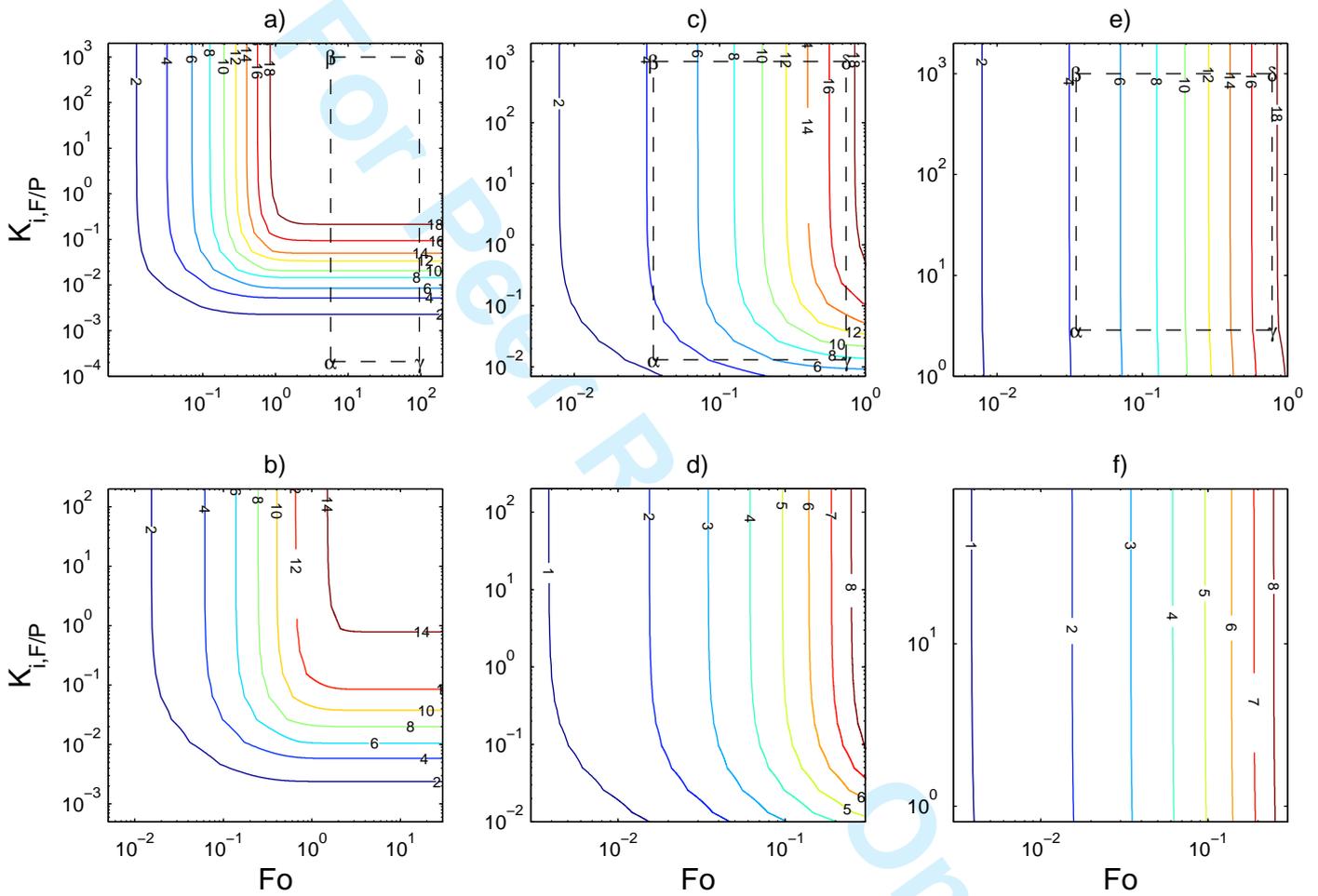


Fig. 5

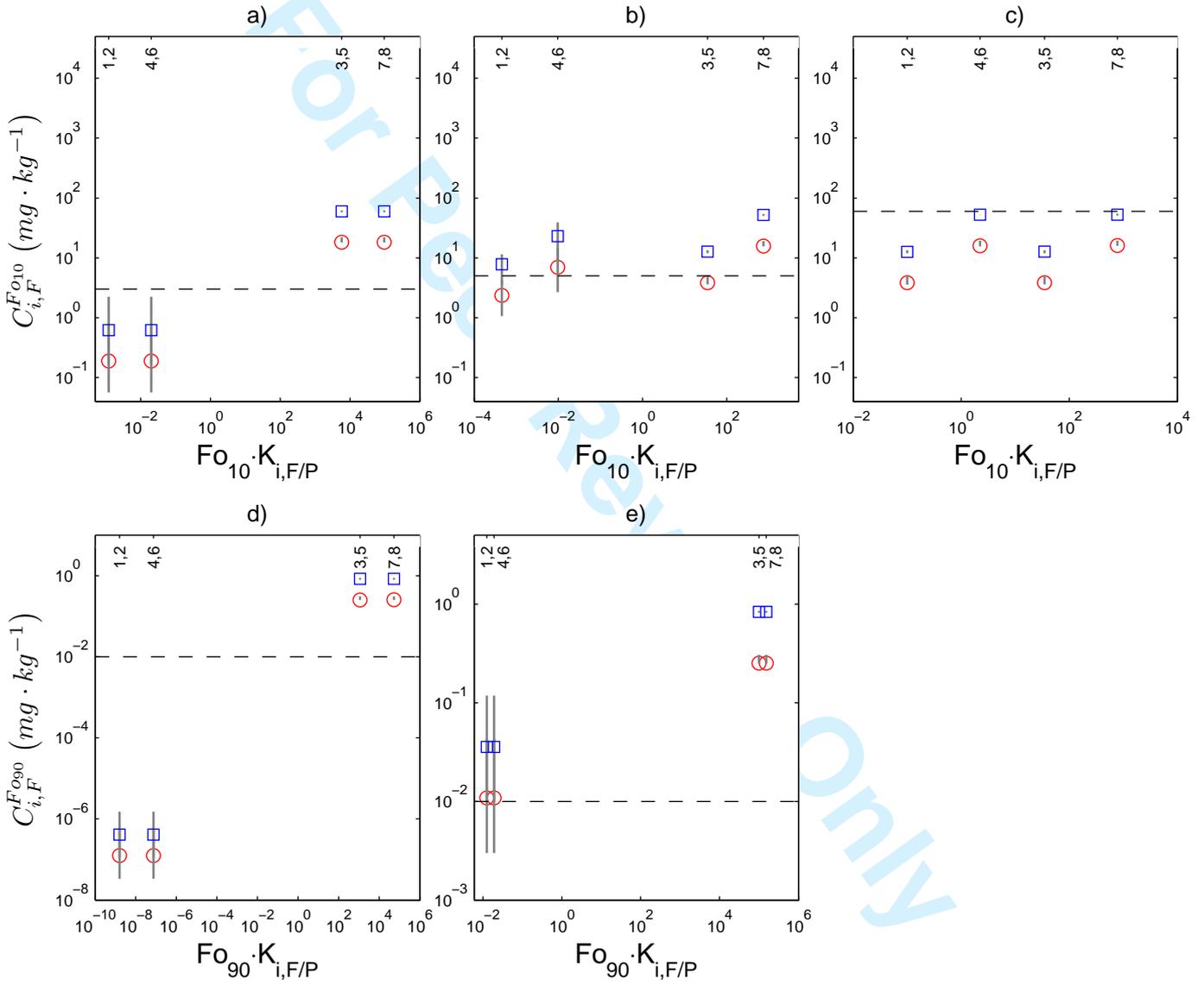


Fig. 6

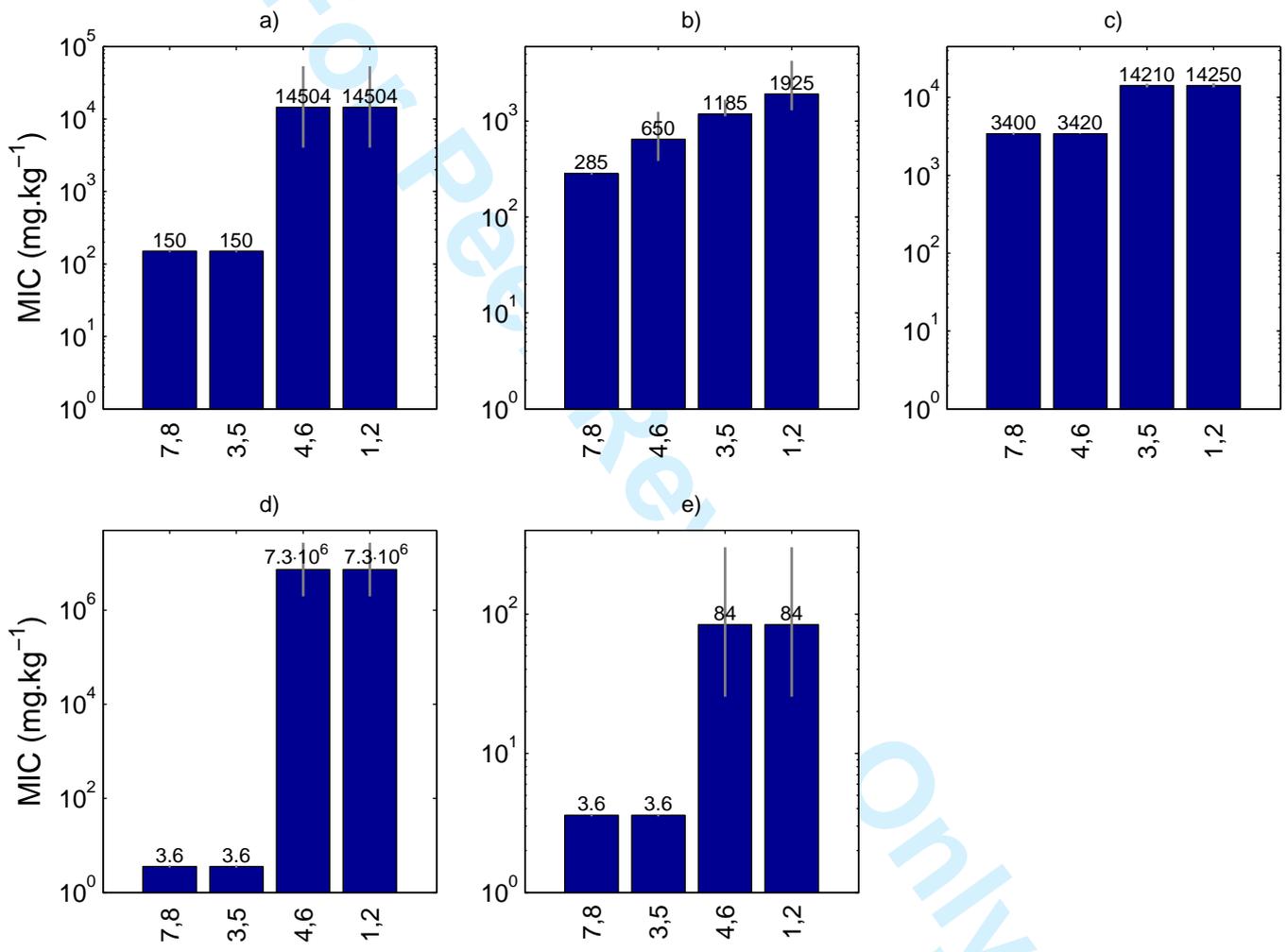


Fig. 7

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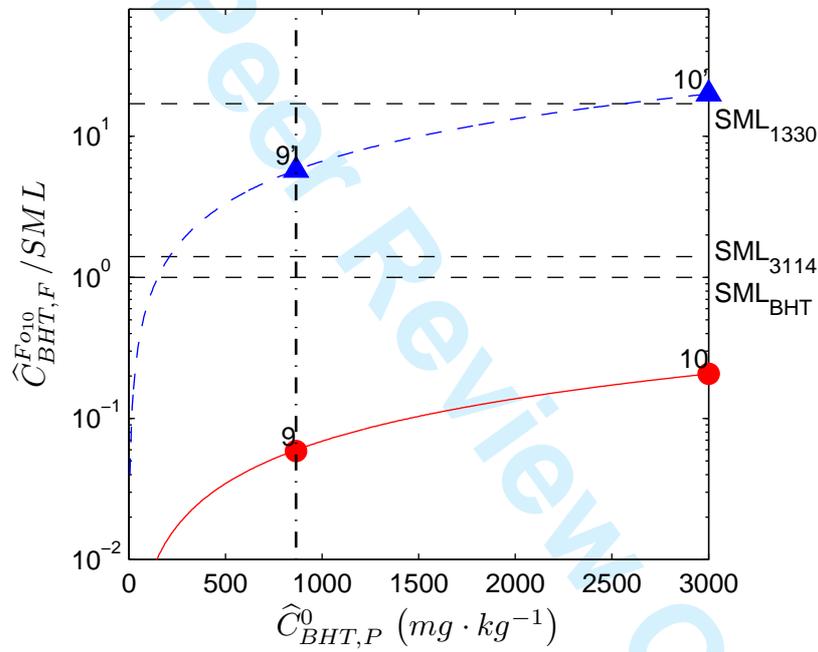


Fig. 8
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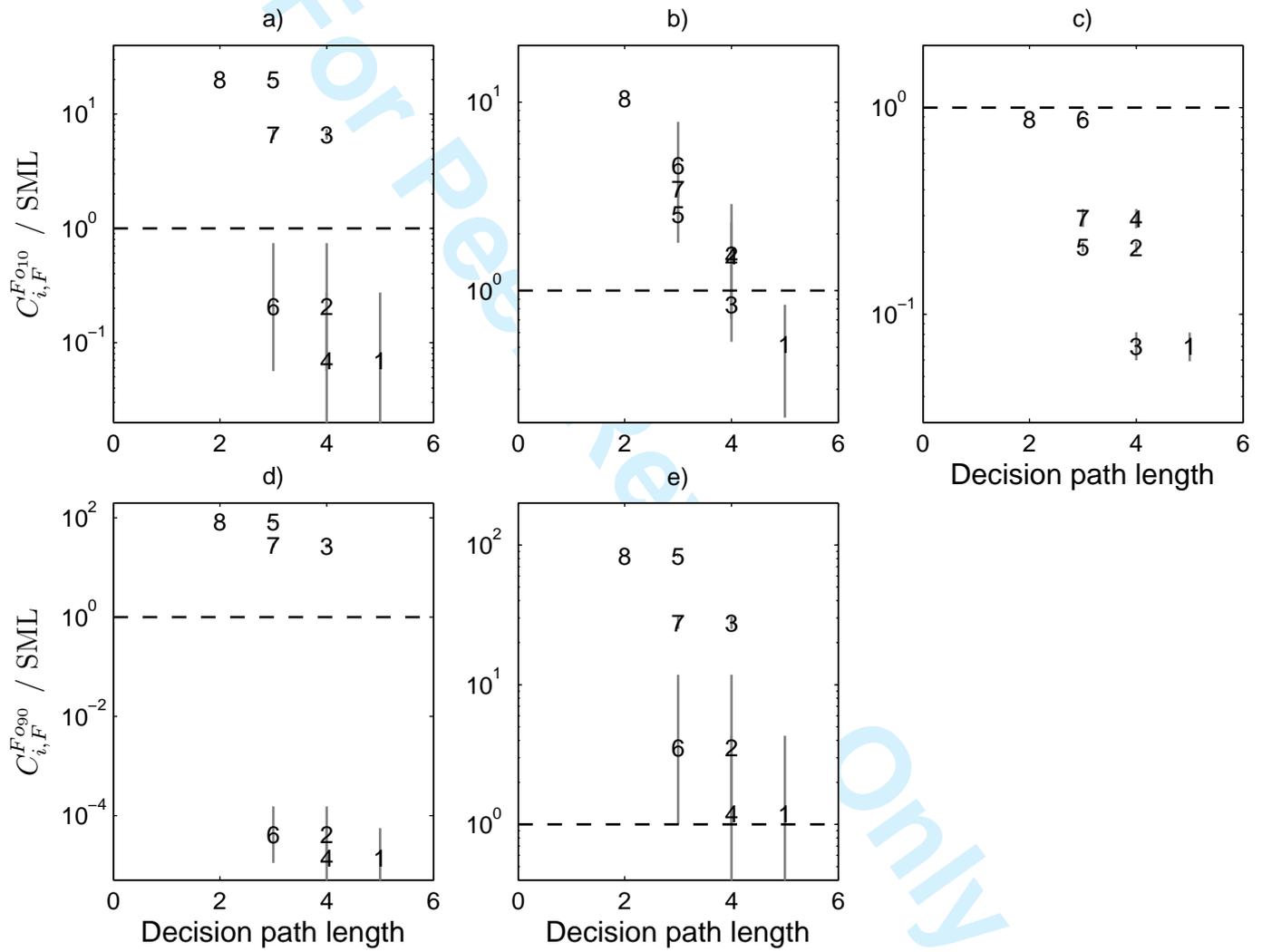


Fig. 9