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Methods and approaches used by FDA to evaluate the safety of food packaging materials

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In the Federal Register of July 17 1995 (60 FR 36582), the US Food and Drug Administration (FDA) established a 'threshold of regulation' process. This process was established for determining when the extent of migration to food is so trivial that safety concerns would be negligible. The process exempts materials in food-contact articles whose use results in dietary concentrations at or below 0·5 ppb (µg/kg) from the food additive listing regulation requirement. Carcinogens or substances that may be carcinogens are excluded from this regulation. This paper explores some of the ramifications of the threshold of regulation policy with respect to traditional migration testing. It examines the use of the threshold approach and migration modelling to estimate food additive exposures. These results indicate that modelling may be a reasonable alternative to traditional migration testing.

Keywords: migration modelling, food additive, threshold of regulation

Introduction

The Food and Drug Administration's (FDA) responsibility under the Federal Food Drug and Cosmetic Act is to ensure that the products it regulates are wholesome, safe and effective.

Premarket approval by FDA is currently required for food packaging materials used in the US that are not GRAS (Generally Recognized As Safe), prior sanctioned, or not reasonably expected to become a component of food. These components or food additives must be shown through the food additive petition process to be safe for their intended use. In some food packaging applications, the amount of migration could be considered so small as to be negligible and therefore present no public health or safety concern. In an effort to improve and speed the food additive petition process, FDA has adopted a threshold policy that defines this negligible exposure from migration.

This paper describes the development of the threshold of regulation policy and the use of migration modelling to calculate the exposures for this policy as well as the traditional additive review process.

Development of the Threshold of Regulation Policy

Toxicological data have shown that carcinogenic and non-carcinogenic toxic effects caused by the ingestion of chemical substances occur in predictable dietary concentration ranges. Thus, a specific level of dietary exposure or a 'threshold of regulation' that is well below the range of dietary concentrations that typically induce toxic effects can be established. As a result, those substances present in the daily diet at levels at or below the threshold would not require the extensive safety review and rule-making process that would normally be required to obtain an amendment to the food additive regulations.

The dietary concentration chosen as the threshold of regulation must be low enough to ensure that the public health is protected, even in the event that a substance exempted from regulation as a food additive is later found to be a carcinogen. Carcinogens and substances that may be carcinogens are excluded from the regulation (§170.39 (a)(1)) because the use of carcinogens as food additives is prohibited by the Delaney Clause of the US Federal Food, Drug and Cosmetic Act (section 409 (c)(3)(A)).

Because the likelihood of a substance posing a health hazard depends on its dietary concentration and on

its toxic potency, the agency considered both of these factors in establishing a threshold of regulation level. FDA reasoned that the degree of effort expended in its review of the safety of a substance should be related to the health risk and has infrequently required long-term toxicity testing for substances migrating into food at low levels. Thus in selecting a threshold of regulation level, FDA initially considered short-term toxicity data.

Although many of the substances that will be reviewed under the regulation will not have been subjected to toxicological oral feeding studies, the range of toxic potency for an unstudied compound can be predicted based on an analysis of the toxic potencies of a large number of representative compounds. Analysis of the data on 18 000 acute oral feeding studies in rats and mice showed that all of the acute toxic effects occurred above 1000 μg/kg (Rulis 1989). Because of the large number and wide variety of chemicals used in this analysis, it is representative of the substances used in the manufacture of food-contact articles. Therefore, this analysis was used to predict the upper-bound dietary concentration at which an unstudied chemical (i.e. one that has not been the subject of toxicological feeding studies) is likely to cause acute toxic effects.

The agency also considered the toxic effects that result from chronic exposure to chemical substances. The results of chronic oral feeding studies of 2 years on 220 compounds have shown that only 5 of the 220 chemicals exhibited toxic effects below 1 mg/kg. All five of the chemicals that were toxic at levels below 1 mg/kg were pesticides, compounds that would, based on their pesticidal activity, be expected to be more toxic than most substances (Frawley 1967). However, even among these five pesticides, none exhibited toxic effects at dietary concentrations below 0·1 mg/kg.

On the basis of the results of these analyses, FDA concluded that the non-carcinogenic toxic effects caused by the majority of unstudied compounds would be unlikely to occur below 1 mg/kg. To provide an adequate safety margin, however, the dietary concentration chosen as a level that presents no regulatory concern should be well below 1 mg/kg. Therefore, FDA established a dietary concentration of 0·5 μg/kg (0·5 ppb) as the threshold of regulation for substances used in food contact articles. A 0·5 μg/kg threshold is 2000 times lower than the dietary concentration at which the vast majority of studied compounds are likely to cause non-carcinogenic toxic effects and 200 times lower than the chronic exposure level at which potent pesticides induce toxic effects. FDA believes that these safety margins, which are larger than the 100 fold safety factor that is typically used in applying animal experimentation data to humans (21 CFR 170.22), support a conclusion that substances consumed in a dietary concentration at or below 0·5 μg/kg are not of concern.

An additional consideration in establishing a threshold of regulation is that a substance that has not been tested for carcinogenicity may later be found to be a carcinogen. FDA used potency data on a large number of known carcinogens to estimate the risk of this possibility. These data were obtained from a carcinogenic potency database (Gold *et al.* 1984, 1986, 1987) that included data on more than 3500 long term chronic animal studies of 975 chemicals. FDA restricted its analysis to 477 animal carcinogens that were the subject of oral feeding studies showing a statistically significant increase in the incidence of animals with specific neoplasms ($p < 0·01$) (Rulis 1992). In those cases where multiple studies had been carried out on a specific chemical, the carcinogenic potency chosen represented the most sensitive species/sex/organ combination. Finally, in assessing the appropriate dietary concentration level to use as the threshold of regulation level, FDA has assumed that the distribution of carcinogenic potencies of the 477 chemicals studied is representative of all known and unknown carcinogens, and that it is very unlikely that an unstudied compound would both be a carcinogen and have an intrinsic carcinogenic potency greater than observed for the studied compounds. On the basis of the range of potencies exhibited by these 477 animal carcinogens, FDA has determined that most known carcinogens pose less than one in a million lifetime risk if present in the diet at 0·5 μg/kg (Rulis 1992). Therefore, a 0·5 μg/kg dietary concentration would take into consideration the event that a substance that is exempt from regulation as a food additive were later shown to be a carcinogen.

FDA also concludes that establishing a 0·5 μg/kg dietary concentration as the threshold of regulation is appropriate because it corresponds to a migration level that is above the measurement limit for many of the analytical methods used to quantify migrants from food-contact materials. Thus, decisions will usually be made based on dietary concentrations that result from measurable migration into food or food-simulating solvents rather than on worst-case

estimates of dietary concentration based on the detection limits of the methods used in the analysis.

Estimating the exposure

An estimate of the exposure to an additive in the diet is determined by combining migration data with information on the uses of food packaging that may contain the additive, such information includes food type distribution factors (f_T), and the fraction of the daily diet expected to contact specific packaging materials i.e. consumption factors (**CF**). Consumption factors are obtained by using information on US food packaging markets to estimate the fraction of the diet likely to contact broad categories of food packaging (i.e. glass, metal, plastic, paper) as well as specific types of food-contact polymers. The default CFs and f_T values used by FDA are listed in 'Recommendations For Chemistry Data For Indirect Food Additive Petitions', June 1995. These values are used by FDA unless there is justification for the use of other more appropriate values. To account for the variable nature of food contacting each packaging material, food type distribution factors (f_T), are calculated for each material to reflect the fraction of all food that is aqueous, acidic, alcoholic and fatty. The concentration of the additive in each type of food which it contacts is obtained by multiplying the individual f_T value by the amount of migration measured or calculated using a food simulant appropriate for that food type. By summing over the four broad food types (aqueous, acidic, alcoholic and fatty), a weighted average of migration is obtained. Multiplying this value by the CF gives the concentration of the migrant in the total diet. The total dietary concentration is calculated as follows:

$$\text{Dietary Concentration} = CF \times \sum_{i=1}^{4} (M_i \times f_i) \quad (1)$$

where M_i is the concentration of the migrant in the ith food-simulating solvent.

We calculated the maximum migration values that will produce a dietary concentration of 0·5 μg/kg (where kg is on a total diet basis) for the different food packaging polymers using Equation 1 and polymer densities (Table 1). The first column of numbers in Table 1 refer to thresholds for the maximum residual contamination in the package, assuming 100% of this residual amount migrates to all foods contacting the material and each 1 cm² of package material is in contact with 1·55 g of food. The second column in Table 1 represents the maximum amount of migration that could occur from a package into a food and still yield a dietary exposure ≤ 0·5 μg/kg. For example, in polystyrene (PS), the maximum additive/contaminant concentration in the polymer, assuming 100% migration, is 180 μg/kg. This amount will restrict the dietary exposure to 0·5 μg/kg or below. The amount of tolerable migration from PS to foods based on the threshold policy is 6 μg/kg, i.e. if a PS package construction restricts the amount of migration to 6 μg/kg or less, irrespective of what the total amount of the additive/contaminant is in the polymer, use of the package could be considered to constitute a minimal health risk.

Table 1. Threshold values for maximum residual additives/contamination and migration amounts which result in a 0·5 ppb (μg/kg) dietary Exposure to a contaminant.

	Concentration in polymer before migration[a]	Concentration in food after migration[b]
Polyethylene Terephthalate (PET)	215 ppb	10 ppb
Polystyrene (PS)	180 ppb	6 ppb
Polyvinyl Chloride (PVC)	90 ppb	5 ppb
High density Polyethylene (HDPE)	123 ppb	4 ppb
Polypropylene (PP)	778 ppb	25 ppb
Low Density Polyethylene (LDPE)	92 ppb	3 ppb
Polycarbonate (PC)	256 ppb	10 ppb

[a] Assumes the base package thickness is 508 μm (20 mil) and that 100% of the chemical migrates into the food and each cm² of packaging material is in contact with 1·55 g of food. Densities of the polymers are taken into consideration.
[b] The maximum tolerable migration from the polymer into food that results in a 0·5 ppb dietary exposure. This assumes total migration into all food types and uses FDA default consumption factors.

Using the threshold policy to evaluate the food package safety often requires the amount of migration to be determined. Traditionally, migration tests are performed by using food-simulating liquids such as water, edible oils, ethanol/water solutions and sometimes food. These tests are time consuming in two ways; generally the accelerated tests run for at least 10 days, and the analysis of the migrants at low concentrations in the simulants or food is generally difficult. These analyses are also expensive and generate hazardous laboratory waste. In an effort to overcome the inherent difficulties associated with migration testing and possibly simplify the process by which FDA evaluates migration from food packaging, predictive migration modelling offers advantages. Other researchers have also suggested the use of predictive migration modelling to estimate exposures for compliance with US and European Union (EU) food regulations (Baner *et al.* 1994, 1996). Before predictive migration modelling is adopted as a standard practice, one fundamental question needs to be addressed. Could migration testing be replaced by migration modelling and still ensure food safety?

Evaluating Migration

During the 1970s K. Figge (Figge 1972, 1980) studied the migration of antioxidants from HDPE, PVC and PS into food oils and fat simulants. These studies showed that the migration to the oils and fat simulants was predictable. The migration of the antioxidant butylated hydroxy toluene (BHT) and two hydrocarbons ($C_{18}H_{38}$ and $C_{28}H_{58}$) from polyolefins (LDPE, HDPE, PP, and polyethylene with 5% and 13% vinyl acetate copolymer (EVA)) into heptane, water, ethanol/water solutions, *n*-octanol, *n*-octadecane, corn oil, HB307, tributyrin, and trioctanoin at temperatures from 24 to 60°C was studied (Chang *et al.* 1982). They concluded from these studies that migration of antioxidants is predictable. The amount of migration is controlled by diffusion through the polymer according to Fick's 2nd Law and diffusion follows Arrhenius type behaviour. In another extensive study (A. D. Little 1983) the migration of BHT, Irganox 1010, styrene, an organo-tin stabilizer and the plasticizer dioctyl adipate were measured from HDPE, LDPE, PS, impact PS, PVC and EVA into many food simulating liquids and foods. From this study it can be concluded that migration is predictable and the amount migrating to food will always be less than to the food simulant, especially food oil.

In 1989 a very detailed migration study on the migration of BHT and Irganox 1010 from HDPE and LDPE by Candek *et al.* showed migration could be accurately predicted if all the migration controlling parameters are known. This study used measured values for the diffusion coefficient (D_p) of the additive in the polymer, the mass transfer coefficient (k_m) (mixing coefficient), partition coefficient (K) of the additive between the polymer and the food, and the reaction rate constant (k_r) for the degradation of the additive in the food (which affects the partition coefficient) to demonstrate that migration is predictable. A portion of the data from this study is illustrated in figure 1 which shows the migration of BHT from LDPE into water at 60°C. This figure clearly shows that migration of BHT is highly predictable if all parameters are known.

Most of the detailed migration studies performed before 1990 were at low temperatures, i.e. less than 60°C. In 1990 migration of antioxidants from polyolefins to food simulants and food was studied at high temperatures (Goydan *et al.* 1990). This work expanded the temperature range of known migration data for polyolefins to 135°C. This study showed, as did the other studies, that migration was predictable and migration to food was less than the migration to food simulants.

In a general sense, all of the detailed migration studies mentioned above have shown that migration is controlled by diffusion through the polymer according to Fick's 2nd Law and diffusion follows Arrhenius behaviour with temperature. These studies showed migration will generally follow the behaviour illustrated in figure 2, i.e. the amount of migration is linearly related to the square root of time and/or migration is solubility-limited as illustrated by the curve with a partition coefficient of 0·01. When exposure estimates to additives or contaminants migrating from food packaging are needed, assuming linear behaviour to predict migration as shown in figure 2 ensures a conservative exposure estimate. This is mathematically expressed by equation (2), for the case where migration is diffusion-controlled (Crank 1975):

$$M_t = 2C_0 l \sqrt{\frac{D_p t}{\pi}} \qquad (2)$$

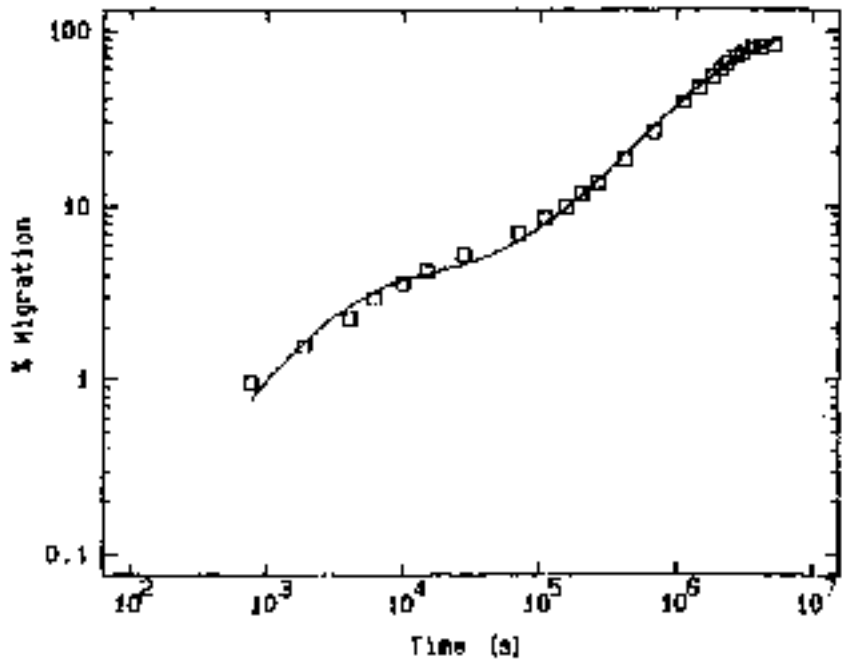

Figure 1. Migration of BHT from LDPE into water at 60°C. The solid line is the predicted amount of migration based on modelling taking into account diffusion in the polymer (D_p), resistance to mass transfer (k_m), partitioning of the additive between the polymer and the water (K), and reaction of the additive in the water (k_r). Open squares are the experimental data. Reprinted with permission from Gandek et al. (1989). Copyright 1989 American Chemical Society.

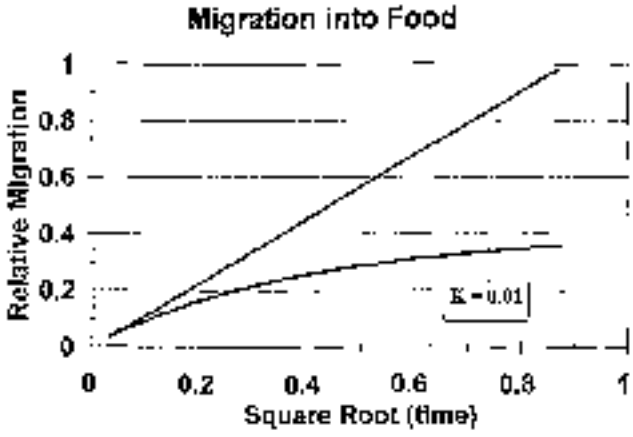

Figure 2. Illustration of the general migration behaviour to food. The amount of migration is generally linearly related to time or approaches the solubility limit of the food (indicated by the partition coefficient $K = 0.01$).

M_1 is the mass that migrates per unit surface area, C_0 is the concentration (w/w) of the compound (additive or contaminant) in the polymer, ρ is the polymer density (g/cm^3), D_p is the diffusion coefficient of the migrant in the polymer and t is the package life time in seconds (i.e. the length of time the food is in contact with the polymer). Equation (2) assumes there is no solubility-limited partitioning effect ($K = 1$) of the additives between the polymer and food, and that other external phase effects (such as mixing or reaction with food) are minimal. This assumption can lead to a significant overestimated migration. From a regulatory point of view, the failure of equation (2) to take into account external phase effects is not necessarily a major shortcoming. Typically, in the absence of migration data, 100% migration is assumed as a conservative approach for estimating exposure. These external phase effects, if need be, can and have been modelled (Gandek *et al.* 1989) but add significant complexity to predicting exposures from migration. The M_1 value calculated from equation (2) must be divided by 1.55 g_{food}/cm^2 surface area to convert the migration values from a mass/surface area basis to an M_1 value (mass/mass basis) so a dietary exposure can be estimated using equation (1).

The critical parameter that must be easily determined or estimated to increase the use of migration model-

ling for exposure estimates in regulatory work is the diffusion coefficient. This is because all parameters in equation (2) are generally known or easily measured except for the diffusion coefficient that is generally unknown and must be measured in some type of kinetic experiment (permeation, sorption, or desorption experiments). These kinetic experiments can be time-consuming and costly. Recently, an alternative approach for estimating diffusion coefficients from a number of different polymers was developed (Baner *et al.* 1994). An empirical correlation approach was used where known diffusion coefficients were fitted to an Arrhenius type equation, resulting in equation (3):

$$D_p = 10^{\left[A_p - a \times MW - b\left(\frac{1}{T}\right)\right]} \qquad (3)$$

where the coefficient A_p accounts for the effect of the polymer on diffusivity, MW is the additive/contaminant's molecular weight, T is the temperature in K, and a and b are correlation constants for molecular weight and temperature effects on diffusion with values of 0·010 and 10450 respectively. The A_p coefficients are 9 for LDPE, −3 for PET and 5 for HDPE and PP.

Another semi-empirical diffusion model has been developed (Limm and Hollifield 1996) which is based on the simplification of existing diffusion theories by Pace and Datyner (1979) and the generalized trend found by Berens and Hopfenberg (1982) for the diffusion of small molecules in polymers. From these studies it is possible to arrive at the following relationship,

$$\ln D_p(MW, T) = \ln A + \alpha(MW)^{1/2} - \frac{K(MW)^{1/2}}{T} \qquad (4)$$

where D_p is the diffusion coefficient of a contaminant/additive, MW is the molecular weight of the contaminant/additive, T is the temperature in K and A, α and K are constants determined from experimental data.

Results of migration modelling

For polyolefin food packaging, equations (2) and (3) have been used to calculate the amount of migration for 21 different chemicals from 1377 test samples including aqueous and fatty foods and simulants over a temperature range from −5 to 121 °C (Baner *et al.* 1996). This study found the ratio of experimental to the calculated values ranges from 1 to 0·001. For no case would the exposure to these chemicals have been underestimated by using these migration modelling calculations.

The use of modelling has also been used to determine the amount of di-(2-ethylhexyl) adipate (DEHA) plasticizer migration from PVC films into food (Mercea *et al.* 1990). This study relied on migration and diffusion parameters determined elsewhere (Till *et al.* 1982). Migration from plasticized PVC films can be difficult to model because of the number of additives in these films and the high plasticizer content which causes the diffusion coefficient to be concentration dependent. In almost all the 12 foods tested, the amount of migration predicted was greater than the amount measured. Therefore, the exposure to DEHA generally would not have been underestimated by modelling.

Similarly, the migration of acetyltributyl citrate (ATBC) from a PVC/PVDC film can be estimated by assuming ATBC has a similar diffusion coefficient to DEHA (Till *et al.* 1982). For example, after reheating pizza in the microwave oven for 5 min, 35 mg/kg ATBC was found to migrate to the food from a PVC/PVDC film containing 4·8% ATBC (Gilbert *et al.* 1988). Even though the pizza was microwaved for 3 min and the resulting temperature was not known, if it is assumed that the pizza reaches at least 100 °C for 1 min, and that all the migration is accounted for by the 1 min at 100 °C, then using the diffusion coefficient 2×10^{-8} cm^2/s (Till *et al.* 1982), the amount of migration calculated using equation (2) is 57 mg/kg. In this same study, the maximum amount of ATBC migrating to food was 47 mg/kg. The food was a biscuit that was microwaved for 4 min.

The microwave susceptor package provides a unique case for predicting the likelihood of migration of components of the adhesive used to affix the PET to the paperboard. When the microwave susceptor package is heated in the oven its temperature changes drastically, from 0 °C to 220 °C in 3–5 min. A typical susceptor package is a layered construction with a 12·5 μm PET film adhering to paperboard with about a 12·5 μm adhesive layer. In some commercial susceptor constructions, 6·2 mg/dm^2 or 49 mg/cm^3 of diethylene glycol dibenzoate plasticizers (DEGDB) were present in the 12·5 μm adhesive layer (Begley and Hollifield 1990). It has also been shown that these packages reached temperatures well over 200 °C for at

least 1 min, with a maximum temperature about 220°C (Begley and Hollifield 1990). If it is assumed the susceptor package reaches 220°C for 1 min and that all migration takes place in this time interval, then the diffusion coefficient for DEGDB (molecular weight = 316) in PET at 220°C can be calculated from equation (3) to be $1{\cdot}3 \times 10^{-8}$ cm^2/s. The amount of DEGDB migration across the PET layer can be estimated by integrating the concentration distance profile for the case where the diffusing material is initially confined to a defined space given in equation (4) (Crank 1975):

$$C_x = \tfrac{1}{2}C_0\left[\mathrm{erf}\left(\frac{h-x}{2\sqrt{(D_p t)}}\right) + \mathrm{erf}\left(\frac{h+x}{2\sqrt{(D_p t)}}\right)\right] \quad (5)$$

where C_x is the concentration of the chemical resulting from diffusion of the chemical various distances x from the centre of the adhesive, h is the thickness of the adhesive. Integrating equation (4) at distances greater than the sum of the adhesive layer and the PET film thickness will give an estimate of the amount of migration expected. The amount of predicted DEGDB migration by using the parameters given above and assuming 80 g/dm^2 food contact is 18 mg/kg. The experimentally measured amounts were 11 mg/kg to French fries in 4 min heating and 18 mg/kg to Miglyol® for 3 min heating (Begley and Hollifield 1990). Similar migration values would also be predicted by using equations developed by Laoubi and Vergnaud (1995) for migration through a layer. The amount of migration predicted agrees with the experimental values, but more importantly, the calculated values show the amount of migration would be significantly above all the maximum migration amounts listed in table 1 that would typically permit exclusion from regulation using the threshold of regulation approach. Migration amounts of this magnitude would rarely qualify for an exemption from regulation because they require extremely small consumption factors (see equation (1)) to obtain a 0·5 µg/kg dietary concentration. Typically, general PET food packages have a CF = 0·05. However, because of the very small fraction of food in the daily diet that would come in contact with, susceptor packaging (current market volume data show less than 0·1% (CF = 0·001) of foods in the daily diet will come in contact with susceptor packages), the resulting dietary concentrations of DEGDB are insignificant. A similar conclusion can be determined for the epoxy monomer, bisphenol A diglycidyl ether, which has been reported to migrate from microwave susceptor packaging into food and Miglyol® (Begley *et al.* 1991, Sharman *et al.* 1995).

Evaluating recycled plastics for food packaging is one area where we have to use a migration modelling approach coupled with surrogate testing to ensure their safe use (Kuznesof and Vanderveer 1995). This is because the chemical history of recycled plastics will always be unknown, and only a minuscule fraction of this material could ever be tested for contamination. Therefore, the ability to model the worst case migration is important in determining if the threshold of regulation dietary concentration is exceeded (Begley and Hollifield 1995).

Although there are many instances where modelling will give good estimates of migration, there are some instances where migration modelling will fail. For example, the food may plasticize the polymer. This increases the diffusion coefficient of the solute (additive) in the polymer, therefore increasing the amount of migration. Generally, good manufacturing practices should minimize this by ensuring the food is not highly interacting with the polymer. Modelling would also fail in the case where a solute exceeds its solubility in the polymer. In this case, a large fraction of the solute will be on the surface of the polymer and just dissolve into the food or food-simulating liquid. This case is easily checked by washing the polymer surface with a food-simulating solvent and comparing the amount found in the wash to the amount predicted for a diffusion controlled situation. Therefore, migration modelling may be used as a check on migration experiments. If a model predicts a significant amount of migration, but analytical work with a suitably low detection limit does not detect migration, it suggests that something may be amiss. For example, the additive may be reacting either in the polymer or in the food simulant to produce a species that is not detected by the analysis. The reactions of monomers and additives with the food simulating liquids have been demonstrated (Gandek *et al.* 1989, Philo *et al.* 1994).

Conclusion

For many packaging components, the amount of migration data available today and the ability to predict the diffusion coefficient of an additive/contaminant in the polymer make it possible to estimate

the amounts of chemicals migrating from food packaging without the need for additional migration testing. Using approaches for conservatively estimating diffusion coefficients and migration amounts, will ensure that migration amounts are not underestimated. The use of modelling will provide adequately conservative but more realistic estimates of migration and exposure for additive evaluations than has been the case where 100% migration has been assumed because of a lack of actual migration data. In the event a health concern or a regulatory action arises, there is no substitute for the actual analysis of the food to accurately determine the extent of migration.

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