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Risk assessment of food contact materials: past experience and future challenges

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3 **Risk assessment of food contact materials:**
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For Peer Review Only

Abstract

The tiered approaches used in the European Union (EU) and the United States of America (USA) for the risk assessment of substances in food contact materials are based on the principle that the amounts of data required to establish safety-in-use depend on the extent of dietary exposure. Tiered approaches are increasingly recognised as sound approaches for chemical risk assessment, which not only offer consumers reasonable certainty of no harm but also avoid unnecessary toxicological testing and focus scarce risk assessment resources on substances of potential concern. Although the EU and USA approaches were developed separately, their tiered testing recommendations are similar. This paper indicates the savings they have brought in the use of animals and suggests areas where testing recommendations for higher dietary exposures might be further refined. It also discusses some of the future challenges in risk assessment of food contact materials.

Keywords :- Risk assessment, food contact materials, food packaging, European Union, tiered testing

Introduction

The first EU framework legislation on food contact materials, Council Directive 76/893/EEC, was introduced over 30 years ago (CEC, 1976). At the same time, the European Commission's Scientific Committee for Food (SCF) began the work of evaluating the many thousands of monomers, other starting substances, and additives that are used in the manufacture of food contact materials, a task that has been continued since 2003 by the European Food Safety Authority (EFSA). The SCF initially concentrated on evaluation of substances commonly used in plastics for which there was suspicion of toxicity, such as vinyl chloride, acrylonitrile, vinylidene chloride and styrene monomers (SCF, 1975, 1982), and the plasticisers, di-2-ethylhexylphthalate and di-2-ethylhexyladipate (SCF, 1984). The Committee also evaluated substances used in regenerated cellulose films (SCF, 1978). In 1986 the Committee published its first consolidated report on monomers and other starting substances used in plastics (SCF, 1986).

In 1989 the first framework Directive of 1976 was repealed and replaced by Council Directive 89/109/EEC (CEC, 1989), which, in turn, has been replaced by Regulation (EC) 1935/2004 (CEC, 2004). This legislation made it obligatory for the Commission to consult the SCF and subsequently EFSA on public health aspects of substances used in food contact materials. Accordingly, many opinions on the safety-in-use of such substances were adopted between 1986 and 2003 by the SCF and since then by the relevant EFSA Scientific Panel. These opinions form the basis for the positive lists of authorised substances incorporated into EU legislation. The main focus over the last three decades has been on substances used in plastics, with occasional opinions on other substances of potential concern, such as lead and cadmium (SCF, 1992a, 1992b), and the printing-ink component, 2-isopropyl-thioxanthone (ITX) (EFSA, 2005).

This paper is written from a European perspective, with reference to the similar safety assessment approach used in the United States of America (USA), and considers what has been learned from the past 30 years experience on the risk assessment of food contact materials and the nature of future challenges.

Use of tiered approaches for the safety assessment of food contact materials

The first EU guidelines on the toxicological evaluation of substances used in food contact materials were published by the SCF in 1977, followed by periodic updates (SCF, 1977, 1992c, 2001). The original guidelines were not prescriptive as to what toxicological tests should be conducted, but outlined the tests that might be required in certain cases as including acute toxicity, 90-day oral, long-term, reproduction, teratogenicity, and mutagenicity studies. The necessary tests depended on the physicochemical properties, the chemical structure, the toxicity of related compounds and the quantities migrating into food (SCF, 1977). Thus, there was early adoption of the idea of a tiered approach to toxicity testing, in which the amount of toxicity data required should increase as the known or anticipated human exposure increases.

Tiered approaches to toxicity testing are based on the founding principle of toxicology, first articulated by Paracelsus in the 16th century, which can be paraphrased as 'the dose makes the poison'. Tiered approaches are now widely recognised as sound, not only from a public health perspective, but also because of the need to focus scarce toxicology resources on the testing and evaluation of substances to which there may be greater human exposure and therefore a greater likelihood of causing toxicity. Tiered approaches to toxicity testing also help to reduce the unnecessary use of animals. Such approaches are used not only in the field of food contact materials, but also in other chemical sectors, including the new EU REACH legislation covering industrial chemicals (ECHA, 2008), and the testing requirements for food additives in the USA (FDA, 2006). The EU has maintained a tiered approach for testing and evaluation of substances used in food contact materials in subsequent revisions and updates to the 1977 guidelines and these more recent guidelines set out clear requirements for the toxicity tests that are needed, depending on which of three tiers of estimated human exposure a substance may fall into (SCF, 1992c, 2001).

The key aim of the evaluation of substances used in food contact materials is to establish their safety-in-use, albeit recognising that this can never be a guarantee of absolute safety. In this regard an important concept was elaborated by the US Food and Drug Administration (FDA), referring to food

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3 additives and ingredients, including food contact substances, and is set out in the Code of Federal
4 Regulations (21 *CFR* 170.3(i)), in which 'safety' was described as

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8 "a reasonable certainty in the minds of competent scientists that a substance is not harmful
9 under the intended conditions of use" (Sotomayor et al., 2007)

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12 A comparison of the tiered approaches to data requirements in the USA and the EU is shown in Table
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15 1. The approaches were developed separately and are not identical, the USA essentially having 4
16 tiers and the EU 3 tiers. Nevertheless, the recommendations for testing are similar for similar dietary
17 exposures.
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21 <<Insert Table 1 here>>
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25 Table 2 shows the approximate number of substances evaluated in the USA and the EU over recent
26 years and the distribution of those substances between the various tiers. The dietary exposure levels
27 referred to in Table 2 are essentially 'worst case' estimates, derived either from measurements of the
28 migration of the substance under evaluation into food or food simulants, or, in cases where migration
29 data have not been provided, from assuming that all of the substance present in a food contact
30 material does migrate into food.
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37 <<Insert Table 2 here>>
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41 In the US FDA evaluations between 2000 and 2006, the estimates of dietary exposure were below 50
42 $\mu\text{g}/\text{kg}$ diet for 85% of substances and for these either US tier 1 (no data) or US tier 2 (in vitro
43 genotoxicity tests only) would have been the data recommendations (Sotomayor et al., 2007). In the
44 EU evaluations between 2000 and 2007, the corresponding figure for substances with estimates of
45 dietary exposure below 50 $\mu\text{g}/\text{kg}$ diet was 60%, and for these EU tier 1 (in vitro genotoxicity tests
46 only) would have been the data recommendations. Only 15% of substances evaluated in the USA fell
47 into US tier 3 or US tier 4 categories for data recommendations, while 40% of substances evaluated
48 in the EU fell into EU tier 2 or EU tier 3 categories for data, with only a few of these falling into the tier
49 3 category, in which a considerable increase in the amount of testing is recommended. Thus these
50 tiered approaches make a substantial contribution to reducing the need for extensive testing in
51 animals. For example, at EU tier 3, and likely also at US tier 4, testing requirements would involve the
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3 use of at least 3800 animals, whereas this number reduces to 80 animals at EU tier 2 and 200
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5 animals at US tier 3, while EU tier 1, US tier 1 and US tier 2 require no live animal testing. These
6
7 tiered approaches appear to have served public health adequately, insofar as the occurrence of
8
9 identifiable health problems in humans has been avoided.

11 **Possible refinements and improvements to the current safety assessment approaches**

14 ***Genotoxicity testing***

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18 Genotoxicity data form the core of the majority of food contact material data submissions and are
19
20 normally required for all substances by the EU. In the USA, genotoxicity data are not required below
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22 the Threshold of Regulation value of 0.5 $\mu\text{g}/\text{kg}$ diet, corresponding to an intake of 1.5 $\mu\text{g}/\text{person}$ per
23
24 day, though if such data exist they should be submitted (FDA, 1995). The scientific basis for the
25
26 waiving of a requirement for genotoxicity data in the USA comes from examination of numerous
27
28 datasets on substances that are known to be carcinogenic, by mathematical modelling of their
29
30 observed dose-response curves and extrapolation down to much lower exposures in humans. Such
31
32 investigations have show that for carcinogen exposures below 1.5 $\mu\text{g}/\text{person}$ per day the estimated
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34 lifetime risk of cancer would be very low (less than 1 in a million) (Rulis, 1989; Cheeseman et al.,
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36 1999).

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38 This same value of 1.5 $\mu\text{g}/\text{person}$ per day has been used in the development of the decision tree for
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40 evaluation of substances for which there are few or no toxicity data, based on the concept of
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42 Thresholds for Toxicological Concern (TTC). In the TTC decision tree, 1.5 $\mu\text{g}/\text{person}$ per day is the
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44 human exposure threshold value below which the risk of cancer is considered to be very low (Kroes et
45
46 al., 2004; Munro et al., 2008). If this TTC value were to be utilised in EU evaluations of substances
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48 used in food contact materials, it would likely make a small contribution to reduction of testing, since
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50 the FDA has estimated that human exposure falls below this threshold in about 15% of all petitions on
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52 food contact materials (Sotomayor et al., 2007).

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54 In considering the likely protection that is offered by the TTC value of 1.5 $\mu\text{g}/\text{person}$ per day, it is
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56 interesting to note that under EU legislation, a number of substances known to be both genotoxic and
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58 carcinogenic are allowed to be used in food contact materials, including some that are classified by
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60 the International Agency for Research on Cancer as either carcinogenic to humans (vinyl chloride,

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3 ethylene oxide), probably carcinogenic to humans (butadiene, epichlorohydrin), or possibly
4 carcinogenic to humans (acrylonitrile, propylene oxide) (IARC, 1987). These well-known substances
5 have been used in food contact materials worldwide for many years and are authorised for use under
6 EU legislation on condition that they do not migrate into food in amounts that are detectable by an
7 agreed sensitive method. In practice, this means that concentrations in food should be below 10 µg/kg
8 of diet, which, interestingly, is 20 times higher than the TTC threshold of 1.5 µg/person per day, which
9 equates to 0.5 µg/kg of diet (though it is appreciated that the genotoxic and carcinogenic substances
10 mentioned above are actually likely to be present in food at concentrations that are far lower than 10
11 µg/kg of diet). Thus if the TTC value of 1.5 µg/person per day were to be used in the EU to waive the
12 requirement for genotoxicity testing, it should not imply any reduction in the current levels of
13 protection.
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25 26 **Possibilities for flexibility on other data recommendations**

27 28 ***Scientific arguments in support of reductions in testing***

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31 It is clearly a shared responsibility between petitioners, as data providers, and risk assessors, as data
32 evaluators, to approach the needs for risk assessment with a view to reducing the number animals
33 used to the minimum necessary to reach a sound conclusion about the safety-in-use of a substance.
34 This requires application, on a case-by-case basis, of what have become known as 'intelligent' or
35 'integrated' testing strategies and risk assessment strategies. It recognises that guidelines are only for
36 guidance and not a list of mandatory studies.
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47 In that context, EU risk assessors consider scientific arguments that may reduce the amount of testing
48 needed to reach a sound conclusion on the safety-in-use of a particular substance. For example:-
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52 • If the chemical structure of a substance is considered to be innocuous, or the substance
53 breaks down to innocuous substances in the gut, the EU tier 2/3 data may not be needed,
54 even if migration is estimated to be above the tier 2 threshold of 50 µg/kg of diet.
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58 • If a substance is closely structurally related to another substance, or substances, for which
59 there are already toxicity data, then based on these similarities, it may be possible to make
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3 inferences about the toxicological properties of the substance under evaluation ('read
4 across').

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- 8 • If there are chronic toxicity/carcinogenicity studies, then a 90-day study in a second species
9 may not be required at EU tier 3.
 - 10 • If evidence of absence of bioaccumulation has been provided at EU tier 2, then a study of
11 absorption, distribution, metabolism and excretion (ADME) may not be required at EU tier 3.
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18 The above scenarios have been all encountered from time to time in EU evaluations and the
19 flexibilities indicated above have often been applied by the risk assessors.
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22 23 24 25 ***Substitution of 90-day oral studies by 28-day oral studies*** 26

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28 For some substances falling into EU tier 2 data recommendations, there may be circumstances where
29 it could be considered whether a well-conducted 28-day oral study might obviate the need for a 90-
30 day oral study. The OECD Test Guideline 407 for a 28-day oral study is now a more powerful
31 indicator of toxicity than it was when first issued in the 1980s. In 1995 it was updated to include
32 additional parameters that are better indicators of neurotoxicity and immunotoxicity and it has recently
33 been further updated to include additional parameters for detection of endocrine effects (OECD,
34 2008a). For many newer industrial chemicals, depending on the tonnage marketed, a 28-day, but not
35 a 90-day oral study may be available to fulfil requirements under the Notification of New Substances
36 Regulations, now superseded by the REACH legislation. There is a continuing debate among
37 toxicologists about the circumstances in which a 28-day study might be an adequate substitute for a
38 90-day study. In the case of substances used in food contact materials, it could be considered
39 whether an adequately designed 28-day oral study, say in combination with an ADME study to
40 exclude the possibility of accumulation with repeated dosing, would be sufficient for conclusion of a
41 safety evaluation at EU tier 2. Judgement of the sufficiency of such an approach might also depend
42 on other factors, such as the absence of structural alerts for toxicity, or knowledge of the toxicity of
43 related substances.
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Evolving strategies for reproductive and developmental toxicity testing

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3 Strategies for reproductive and developmental toxicity testing have received a lot of attention in the
4 last 5 years or so. Among repeated-dose tests, multi-generation studies such as the two-generation
5 study, consume the largest numbers of animals. The Agricultural Chemical Safety Assessment
6 Technical Committee of the ILSI Health and Environmental Sciences Institute (HESI) has proposed
7 replacing the two-generation study with an extended one-generation study, which would reduce the
8 number of animals used from around 2600 to 1400 (Cooper et al., 2006). The proposal has been
9 designed to ensure that endocrine disruptors acting primarily during prenatal development or in early
10 postnatal life would be detected. Although originally developed in the context of agricultural
11 chemicals, the ILSI HESI proposal could be applied equally well to other types of chemical and the
12 OECD has taken up the extended one-generation study as a draft guideline on which there has
13 already been a public consultation (OECD, 2008b).
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28 In the area of developmental toxicity testing, the Veterinary International Conference on
29 Harmonisation (VICH), ILSI HESI, and others, have proposed strategies that may obviate the need in
30 certain cases for testing in a second species (Hurt et al., 2003; Cooper et al., 2006; Janer et al.,
31 2008). It seems likely that these strategy proposals will eventually also impact on testing
32 recommendations for reproductive and developmental toxicity testing of substances used in food
33 contact materials.
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44 **Future challenges**

45 ***Areas requiring new guidelines***

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47 Looking ahead to future challenges in risk assessment of substances used in food contact materials,
48 there are a number of obvious and immediate challenges, such as what will be the data needs for
49 active and intelligent packaging, or for food contact materials containing substances that are present
50 in nanoscale form, or for recycled plastics. For recycled plastics, EFSA has now issued guidelines
51 (EFSA, 2008) and the challenge will be to establish whether, over time, the data requirements in
52 these guidelines adequately cover potential problems that may be anticipated with the presence of
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3 contaminants in recycled plastics. The impact of the increasing use of functional barriers in food
4 contact materials also needs to be considered in relation to data needs for substances present in
5 materials that are behind the barrier, which may include recycled plastics (Dole et al., 2006). EFSA
6 has also developed draft guidelines for the assessment of substances used in active and intelligent
7 packaging, which were published for public consultation in 2009 (EFSA, 2009a). In these draft
8 guidelines it is proposed to follow the same tiered approach for toxicity testing requirements as is
9 used for conventional food contact materials (SCF, 2001).
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21 In the rapidly expanding area of the application of nanoscience and nanotechnology to food and feed
22 products, EFSA is in the process of developing advice on the potential risks from substances present
23 in nanoscale form in food and feed and how they may be assessed for safety prior to marketing. In
24 the food sector, it is apparent that food contact material applications of nanoscience represent the
25 largest innovatory sector. The initial guidance from EFSA's Scientific Committee addressed generic
26 issues in the risk assessment of chemicals present in food in nanoscale form (EFSA, 2009b). It can
27 be anticipated that further guidance specific to the various applications in food, including food contact
28 materials, will need to be developed. The several challenges here are not only ones for risk
29 assessors, such as detection of unanticipated toxicities from nanomaterials, but also ones for
30 petitioners generating the data needed for safety assessments, since some of the biggest challenges
31 lie in the need to develop methodologies for the detection and quantitation of engineered
32 nanomaterials in food.
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48 ***Evaluation of substances hitherto unregulated***

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51 While all food contact materials should conform to general EU food law, in that they should not
52 endanger human health, several sectors do not have EU specific regulations and hence no positive
53 lists of authorised substances; these include paper and board, rubber and other natural materials,
54 coatings, printing inks, adhesives, solvents, ceramics and metals. To date, these types of materials
55 have received very little regulatory attention. Systematic evaluation of substances used in these types
56 of food contact materials would challenge the resources available for testing and risk assessment, as
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3 has the evaluation of plastics, which has consumed a major part of EU risk assessment resources for
4 the last 20 years. If these other types of food contact material were to come under regulatory scrutiny,
5 it would make sense, at least from the public health viewpoint, to focus risk assessment efforts first on
6 those substances which might be more likely to give rise to health risks. Prioritisation for early
7 evaluation might include aspects such as migration above 5 mg/kg diet, fatty food contact, use in
8 packaging for foods specifically made for infants and young children, and suspect chemical
9 structures.
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18 ***Making use of newer developments in risk assessment***

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20 The TTC concept has already been mentioned above in the context of estimating risks from
21 carcinogens, but the TTC approach also encompasses evaluation of substances for the likelihood of
22 toxicity of any type. EFSA's Scientific Committee is currently considering the wider applicability of the
23 TTC concept to the work of all its Scientific Panels dealing with chemicals, including the Panel that
24 evaluates food contact materials. The dietary exposures corresponding to EU tier 2 data
25 recommendations in the EU scheme range from 50 µg/kg up to 5 mg/kg of diet. If the TTC concept
26 (Kroes et al., 2004; Munro et al., 2008) were to be applied within this EU tier 2 range, it could allow
27 substances with simple chemical structures, that are efficiently metabolised and of low potential
28 toxicity (TTC structural Class I, for which the human exposure threshold is 1800 µg/day) to be
29 evaluated in the absence of toxicity data, other than genotoxicity data, provided migration did not
30 exceed 600 µg/kg of diet. Similarly, substances with intermediate chemical structures, that are less
31 innocuous than simple structures but do not have a positive indication of toxicity (TTC structural Class
32 II, for which the human exposure threshold is 540 µg/day) could be evaluated in the absence of
33 toxicity data, other than genotoxicity data, provided migration did not exceed 180 µg/kg of diet.
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49 The TTC approach could also be used for initial screening of substances that are not intentionally
50 added to food contact materials but nevertheless may migrate into food. These include impurities,
51 breakdown products and transformation products originating from the use of an intentionally added
52 substance. Any such not-intentionally-added substance present in food at concentrations below the
53 relevant TTC value would not need to be further considered or at least considered as low priority for
54 further evaluation, while those present in concentrations exceeding the relevant TTC value could be
55 treated according to the existing EU tiered approach.
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3 Since genotoxicity data are the key information for the majority of evaluations in the area of food
4 contact materials, it would also be worthwhile to explore the value of evolving computational toxicity
5 methods that use chemical structure-activity relationships derived from test data to predict the
6 likelihood of genotoxicity in structurally-related but untested substances (see, for example, Cariello et
7 al., 2004; Kazius et al., 2005; Rothfuss et al., 2006; Mazzatorta et al., 2007).
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13 **Conclusions**

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16 In view of the very large number of substances used in food contact materials, risk assessment
17 approaches need to be both firmly science-based and resource efficient, in order to deliver adequate
18 and timely protection for public health. The tiered approaches to toxicity data needs for risk
19 assessment, used both in the EU and the USA, appear to have served public health needs well, while
20 at the same time allowing substances with large and complex databases, such as phthalates and
21 bisphenol A, to be singled out for more detailed assessment. However, the numbers of substances
22 coming forward for evaluation are unlikely to diminish. So continuing efforts will be needed to refine
23 data needs and to incorporate new, validated risk assessment methods that allow risk assessors to
24 focus on those substances that are more likely to pose a risk to human health.
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Table 1: Comparison of tiered approaches in the USA and the EU

Dietary exposure ($\mu\text{g}/\text{kg}$ of diet)	Tiered data approaches	
	USA	EU
≤ 0.5	Threshold of Regulation: no tests required (but provide any existing information on genotoxicity or carcinogenicity) ~ US tier 1	3 in vitro genotoxicity tests [As below] (in vivo tests only if positive in vitro) ~ EU tier 1
$>0.5 - 50$	2 in vitro genotoxicity tests to cover gene mutation and chromosome aberration [Ames, mouse lymphoma assay (MLA) preferred] ~ US tier 2	3 in vitro genotoxicity tests [Ames, gene mutation in mammalian cells (MLA preferred), chromosome aberration in mammalian cells] ~ EU tier 1
$>50 - 1000$	In vivo chromosome aberration study 90-day oral studies in 2 species Further studies may be required depending on results ~ US tier 3	3 in vitro genotoxicity tests 90-day oral study Evidence of absence of bioaccumulation ~ EU tier 2
>1000	Discuss requirements for further tests with FDA (e.g. as food additive petition) ~ US tier 4	As above ~ EU tier 2
>5000	As above	As above + ADME 90-day oral study in 2 nd species Reproduction in 1 species Developmental toxicity in 2 species Chronic toxicity/carcinogenicity in 2

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		species ~ EU tier 3
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Table 2: Numbers of substances evaluated at each tier in the USA and in the EU

USA	EU
<p>383 submissions evaluated 2000-2006</p> <ul style="list-style-type: none"> • 85% had exposure levels below 50µg/kg diet (genotoxicity tests only) ~ tier 1 or 2 • 15% had exposure levels above 50µg/kg diet ~ tier 3 or 4 	<p>193 submissions evaluated 2000-2007</p> <ul style="list-style-type: none"> • 60% had exposure levels below 50µg/kg diet (genotoxicity tests only) ~ tier 1 • 27% had exposure levels of 50 - 5000µg/kg diet ~ tier 2 • 13% had exposure levels above 5000µg/kg diet ~ tier 3