FOOD STANDARDS
Australia New Zealand
Te Mana Kounga Kai – Ahitereiria me Aotearoa

Supporting document 3

Risk profile – Proposal P1034

Chemical Migration from Packaging into Food

Executive summary

Food packaging is manufactured from a range of materials including glass, paper/ paperboard, a variety of plastics, and metals such as aluminium and steel. The bulk packaging material is often modified due to the use of adhesives, protective coatings and printing inks, for example. Several thousand chemicals are used in the manufacture of food packaging and other materials that come into contact with food during its production and processing.

In order to gain an understanding of the risk posed by chemical migration from packaging into food, FSANZ has been investigating information on the hazard characteristics of chemicals used in the production of food packaging, and estimated dietary exposure to these chemicals due to migration into food. Use of the threshold of toxicological concern (TTC) concept has been particularly valuable for this work.

The toxicological properties of packaging chemicals span a continuum ranging from innocuous ("non-toxic") to concerning (e.g. carcinogenic or toxic to reproduction/ development). For example, the EU plastics regulation contains specific permissions for the use of water and vegetable oils in the production of food contact materials, while the same regulation also lists over 30 substances that may be used in food contact materials but, because of their adverse toxicological profiles, must not be detectable in food.

The TTC approach is a screening tool, based on risk assessment principles, that categorises chemicals into various levels of safe expected exposure depending on chemical structure features. Estimated dietary exposure that is below the applicable TTC indicates no safety concern, while exposure above the threshold indicates that appropriate toxicity data on the chemical, or a close structural relative, is required to perform a safety assessment.

A TTC analysis, conducted on a USFDA database of over 1300 food contact substances, showed that for 86% of the substances, estimated dietary exposure is less than the lowest TTC value for non-genotoxic substances (0.0015 mg/kg bw/day). For many of the chemicals with estimated dietary exposures exceeding their respective TTC thresholds, specific toxicity data were located in various databases and the published literature that support the safety of those chemicals. For some packaging chemicals, supporting toxicity data may not be publically available, or toxicity data on structurally related substances was used for safety assessment.

A conclusion of low risk resulting from the above analysis is consistent with the findings of analytical surveys investigating the presence of specific packaging chemicals in Australian foods.

However, FSANZ has identified two chemicals for which additional food concentration data are required in order to determine if dietary exposure to these chemicals poses a health risk. These two chemicals, diethylhexyl phthalate (DEHP) and diisononyl phthalate (DINP), belong to the phthalate family of compounds, some members of which migrate efficiently into foods. FSANZ is currently conducting a study to acquire data on DEHP and DINP levels in a wider range of foods.

The potential risk from the migration into food of chemicals in recycled paperboard, particularly mineral oils, is not yet well characterised and research is ongoing internationally. However, a recent Australian survey, carried out by FSANZ, did not find widespread migration of mineral oils into food products or identify any specific public health and safety concerns.

Table of contents

1   Introduction

Food packaging is manufactured from a range of materials including glass, paper/ paperboard, a variety of plastics, and metals such as aluminium and steel. The bulk packaging material is often modified due to the use of adhesives, protective coatings and printing inks, for example. Several thousand chemicals are used in the manufacture of food packaging and other materials that come into contact with food during its production and processing. For example, more than 3200 food contact substances are listed in the US Code of Federal Regulations[1]. Chemicals used in the production of food contact materials include solvents, monomers, cross-linking agents, catalysts, plasticisers, and antioxidants/ stabilisers.

Internationally, there are extensive regulations that aim to provide assurance that the migration levels of these substances into food do not present an unacceptable risk to human health. In order to gain an understanding of the risk posed by chemical migration from packaging into food (CMPF), FSANZ has been investigating information on the hazard characteristics of chemicals used in the production of food packaging, and estimated dietary exposure to these chemicals due to migration into food. A wide range of information sources have been used for this work, in particular United States Food and Drug Administration (USFDA) and European Food Safety Authority (EFSA) databases and publications, information in the published scientific literature, and information from analytical surveys of foods, including Australian data. Information from a New Zealand analytical survey of packaging chemicals in food will be published later in 2016.

Regarding migration levels and estimated dietary exposure to food packaging chemicals, this document emphasises recent data because of its greater relevance to current dietary exposure. It is important to note that dietary exposure to specific packaging chemicals can vary markedly with time as industry continually seeks to replace/reduce the use of chemicals of potential concern with chemicals that have more favourable hazard profiles and/or exhibit lower migration levels into food (C&EN 2015; Rice 2015).

2   Risk assessment of food packaging chemicals

The scientific principles that apply to the risk assessment of other chemicals in food, such as food additives, contaminants and processing aids, also apply to food packaging chemicals. An overview of these risk assessment principles is presented in the FSANZ document *Risk Analysis in Food Regulation* (FSANZ 2013), while detailed information is provided in FAO/WHO (2009). The core principle in food chemical risk assessment is that risk is a function of both the intrinsic hazard characteristics of the chemical (i.e. its toxicological properties) and dietary exposure to the chemical from consuming food and beverages.

3   Hazard characteristics

The toxicological properties of packaging chemicals span a continuum ranging from innocuous ("non-toxic") to concerning (e.g. carcinogenic or toxic to reproduction/ development). For example, the EU plastics regulation contains specific permissions for the use of water and vegetable oils in the production of food contact materials, while the same regulation also lists over 30 substances that may be used in food contact materials but, because of their adverse toxicological profiles, must not be detectable in food[2] (EC 2011).

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[1] USFDA database of food contact substances regulated in the Code of Federal Regulations:
http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/IndirectAdditives/ucm115333.htm
[2] A detection limit of 0.01 mg/kg is applicable unless specified differently for an individual substance.

In contrast, the toxicological properties of some packaging chemicals are not well defined and published studies have cited potential health concerns in such cases (e.g. for certain printing ink chemicals; Jung et al. 2013). However, if migration levels are sufficiently low, extensive toxicological characterisation of a substance is not necessarily required by agencies that conduct risk assessments for regulatory purposes, as detailed in guidelines and published risk assessments (EFSA 2008; USFDA 2002). EFSA have recently re-affirmed that the amount of toxicity data needed should be related to the expected human dietary exposure and that this applies to all migrating substances, i.e. substances that are both intentionally and non-intentionally used in the manufacture of food contact materials (non-intentionally added substances includes impurities, degradation/reaction products, and the low molecular weight oligomeric fraction of polymeric substances). Consistent with previous guidance, EFSA also stated that genotoxicity testing for substances used in food contact materials is always required even if their migration into food leads to a low exposure (EFSA 2016).

In some cases, toxicity data on a structurally related substance may have been deemed sufficient to support the safety of the proposed use of a chemical ("read-across" approach e.g. EFSA 2015a). Computational toxicology tools such as quantitative structure-activity relationship (QSAR) analysis are also used in the premarket assessment of food contact substances (Arvidson et al. 2010). Alternatively, for substances with no appropriate toxicity data, the threshold of toxicological concern (TTC) approach can be used for safety assessment (EFSA/WHO 2016). FSANZ has conducted a TTC analysis of a USFDA database of food contact substances, as described in Section 5 below.

4   Dietary exposure

Exposure to chemicals present in the diet is estimated by combining food consumption data with food chemical concentration data (FSANZ 2009). The complexity of methods used to calculate dietary exposure range from simple to refined, and the method chosen can depend on the specific question(s) to be addressed and the amount and type of data available on food chemical concentrations and food consumption. In some cases, a screening approach based on worst-case exposure scenarios can be appropriate for risk assessment purposes. For example, in a recent analytical survey of 30 packaging chemicals conducted by FSANZ, a screening approach based on the Budget method was used to calculate the Theoretical Maximum Daily Exposure (TMDE) for each detected chemical. The TMDE for each chemical was calculated using the maximum concentration found in the analysed food samples, assuming that 50% of foods and beverages consumed contained the chemical at that level. For all but two of the detected chemicals, the TMDE supported a conclusion of negligible to low health risk (FSANZ 2016; see Section 6 for further details of this study).

Refined estimates of dietary exposure are possible when there are data on migration levels in a wide range of foods. For example, in the past 10 years extensive migration data have become available for bisphenol A (BPA), allowing EFSA to calculate better estimates of dietary exposure (see Section 6 for details).

In order to gain insight into the range of estimated dietary exposures for a large fraction of the total number of food contact substances in use, FSANZ has analysed a USFDA database containing dietary exposure information on more than 1300 food contact substances (USFDA CEDI database[3]).

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[3] USFDA Cumulative Estimated Daily Intake (CEDI) Database for Food Contact Substances. This database includes dietary exposure contributions from food contact other than food packaging (e.g. conveyor belts, pipes, kitchen appliances, utensils and cookware).

The CEDI database is particularly valuable because the same methodology is used for each chemical to calculate estimated dietary exposure and the database currently contains information on over 1300 chemicals, which represents approximately 1/3rd of the total number of food contact substances regulated in the US.[4] Estimated dietary exposures are derived from the approved uses of the chemicals and data on migration levels into foods and/or food simulants.[5] Information on the fraction of the daily diet expected to contact specific packaging materials (the 'consumption factor'; CF) is included in the dietary exposure calculations. In addition, a 'food-type distribution factor' (f_T) is used for each packaging material to reflect the fraction of all food contacting each material that is aqueous, acidic, alcoholic or fatty. Total food intake (solids and liquids) is assumed to be 3 kg per person per day. Assessment of a proposed new use for a packaging chemical takes into account dietary exposure from the new use in addition to dietary exposure resulting from all existing approved uses (USFDA 2007).

The median estimated dietary exposure in the CEDI database is 0.00035 mg/kg bw/day and 59% of the substances lie in the range 0.0001–0.001 mg/kg bw/day. Dietary exposure to 82% of the food contact substances is less than 0.001 mg/kg bw/day and only 28 substances (2%) have estimated dietary exposures greater than 0.01 mg/kg bw/day (Table 1). However, there are some substances which migrate readily into food and are used in a wide range of packaging materials, and these factors contribute to higher dietary exposure to such chemicals because they are more likely to be present at higher concentrations in a wider range of regularly consumed foods. For example, a recent USFDA risk assessment included an estimate of total dietary exposure resulting from 24 approved uses of an antioxidant used in adhesives and a range of plastics commonly used in food packaging (Neal-Kluever et al. 2015; see also Section 6). Estimated dietary exposure to this widely used food packaging chemical (0.075 mg/kg bw/day) lies at the upper end of the range for food contact substances. For comparison, the CEDI database contains only 6 substances with estimated dietary exposures greater than 0.075 mg/kg bw/day.

Table 1: Dietary exposure to a subset of food contact substances (1302 substances in USFDA CEDI database[3])

Estimated Dietary Exposure (mg/kg bw/day)	Number of substances (percentage of total)
< 0.00001	116 (9%)
< 0.0001	304 (23%)
< 0.001	1069 (82%)
< 0.01	1272 (98%)

There is evidence to indicate that the overall low estimated dietary exposure to food packaging chemicals, as shown in the USFDA CEDI database, would be similarly low for Australia/New Zealand populations. First, results from FSANZ analytical surveys of packaging chemicals in foods are consistent with the low migration levels contained in the CEDI database.

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[4] There are currently over 3200 substances listed in a USFDA database of food contact substances that are included in the Code of Federal Regulations (CFR) and over 1200 entries in the USFDA Food Contact Notification (FCN) database.
[5] In cases where the use level of the food contact substance is low, it may be possible to dispense with migration studies altogether by assuming 100% migration of the substance into food. Semi-empirical methods using diffusion calculations may also be used to estimate migration levels (USFDA 2007).

For example, in a 2011 survey, levels of phthalates, perfluorinated chemicals, semicarbazide, acrylonitrile and vinyl chloride were below the limit of quantification (LOQ) for the 65 packaged foods and beverages analysed (FSANZ 2011)[6].

Similarly, in a recent FSANZ study, 81 typically consumed foods and beverages were tested for 30 packaging chemicals. Most foods contained no detectable levels of the chemicals analysed. However, low levels (parts per million or parts per billion) of several chemicals were detected in a small proportion of foods. Concentrations of these chemicals were generally comparable to, or lower than, those reported in previous Australian and international studies (FSANZ 2016).

Another factor contributing to variability in dietary exposure to packaging chemicals relates to differences in the use of specific food packaging materials in various countries. However, any differences between the USA and Australia/New Zealand in the use of various food packaging materials would not be expected to markedly alter dietary exposure to the majority of food packaging chemicals. To support this, results of a published study indicate that the relative use of major food packaging materials is broadly similar in the US and in an EU country, the Republic of Ireland (Duffy et al. 2007). This study found, for example, that in an Irish population 'total plastics' had the highest consumption factor[7] (0.83) which is similar to the value of 0.79 used by the USFDA in dietary exposure calculations. There are also data supporting the concept that the relative use of major packaging materials may have changed to only a small degree in the US in the past 30 years. For example, it was reported that the consumption factor for polystyrene (based on US market data collected around 1980) was 0.1, whereas data collected 25 years later led to the calculation of a new consumption factor of 0.14 (Cassidy and Elyashiv-Barad 2007).

It is concluded that the overall low estimates of dietary exposure to food contact substances present in the USFDA CEDI database (e.g. 98% of substances with estimated dietary exposures below 0.01 mg/kg bw/day; Table 1) are reasonably anticipated to be similar for Australia/New Zealand.

5.   Threshold of Toxicological Concern analysis

The Threshold of Toxicological Concern (TTC) concept is a screening tool based on risk assessment principles. The TTC concept is used to assess low level chemical exposures and to distinguish those chemicals with no appreciable human health risk from those for which further data are required for risk assessment (Kroes et al. 2000; EFSA/WHO 2016).

The TTC concept categorises chemicals into various levels of safe exposure depending on chemical structure (Cramer et al. 1978). The thresholds were originally derived from toxicity data on over 600 chemicals with conservatism built into the approach to establish protective TTC values (Munro et al. 1996). A recent review of the TTC approach has confirmed its conservatism and that the threshold values derived by Munro et al. (1996) remain appropriate (EFSA/WHO 2016).

Chemicals categorised as structural class I, II or III are assigned respective TTC values of 0.03, 0.009 and 0.0015 mg/kg bw/day. The TTC threshold applicable to a specific chemical is compared to its estimated dietary exposure.

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[6] One chemical, epoxidised soybean oil (ESBO) was detected at above the LOQ in this study (in three foods); however ESBO is not present in the USFDA CEDI database. Based on the levels detected, dietary exposure to ESBO from these foods was concluded to pose no health and safety risk to consumers (FSANZ 2011).
[7] The consumption factor (CF) is used by the USFDA in dietary exposure calculations to describe the fraction of the daily diet expected to contact specific packaging materials (USFDA 2007).

Estimated dietary exposure that is below the TTC threshold indicates no safety concern, while exposure above the threshold indicates that appropriate toxicity data on the chemical, or a close structural relative, is required to perform a safety assessment. The TTC approach should not be used for certain substances including high potency carcinogens, inorganic chemicals, metals and organometallics, steroids, and chemicals that are known or predicted to bioaccumulate (EFSA 2012). In those cases, toxicity data on the substance, or a closely related substance, are required for safety assessment.

The most notable current use of the TTC concept is by JECFA, EFSA and FEMA[8] for the safety evaluation of the large number of flavouring agents that are used by the food industry. The TTC concept is also embodied in the US Threshold of Regulation (TOR) exemptions for food contact substances. To be eligible for a TOR exemption, a substance used in a food-contact article will be exempted from regulation if the use in question has been shown to result in, or may be expected to result in, dietary concentrations at or below 0.0005 mg/kg, corresponding to dietary exposure levels at or below 0.0015 mg/person/day (based on a diet of 3 kg food/beverages per day). Carcinogens or suspected carcinogens are excluded from this regulation (Begley 1997); however, the value of 0.0015 mg/person/day was derived from a large database of carcinogenic potencies, and was determined to be low enough to ensure that public health is protected even in the event that a substance exempted from regulation is later found to be a carcinogen (Munro et al. 2002).

FSANZ has compared TTC values to estimated dietary exposures for food contact substances that are contained in the USFDA CEDI database. Estimated dietary exposures for 86% of the substances (1119/1302) are below the lowest TTC value for non-genotoxic substances (structural class III: 0.0015 mg/kg bw/day) (Figure 1). Based on a recent re-evaluation of the Munro et al. (1996) TTC database, a higher threshold of 0.004 mg/kg bw/day was derived for structural class III substances when organophosphates and organohalogens were excluded from the analysis (Leeman et al. 2014). Estimated dietary exposures for 97% of the CEDI substances (1260/1302) are below 0.004 mg/kg bw/day.

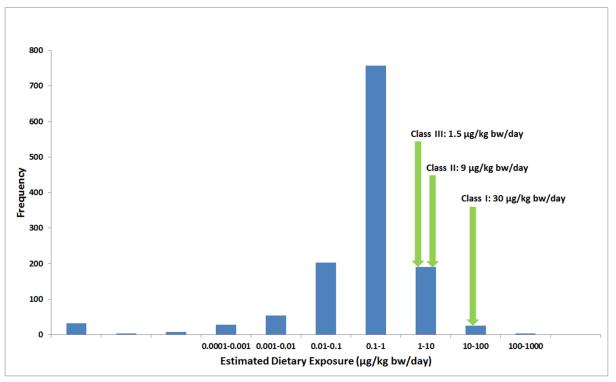[8] The Flavor and Extract Manufacturers Association of the United States

Figure 1: Histogram of estimated dietary exposure to food contact substances. Data were sourced from a USFDA database that currently contains information on 1302 substances. Estimated dietary exposures for 59% of the substances are in the range 0.1–1 µg/kg bw/day. The three TTC thresholds for non-genotoxic substances are indicated. 86% of the substances have estimated dietary exposures below the lowest threshold (class III: 1.5 µg/kg bw/day).

For many of the chemicals with estimated dietary exposure exceeding their respective TTC thresholds, specific toxicity data were located in various databases and the published literature that support the safety of those chemicals (Attachment 1 provides examples). For a substantial fraction of chemicals in the CEDI database it is expected that the supporting toxicity data are unpublished, while for some chemicals the USFDA would have used read-across and/or QSAR approaches for safety assessment (Bailey et al. 2005; Arvidson et al. 2010).

As indicated above, the CEDI database currently represents a substantial subset (approximately 1/3rd) of the total number of chemicals that are covered by US food contact regulations (~4000 substances). It is not expected that the distribution of estimated dietary exposures for the remaining food contact substances would differ substantially from the distribution in the current CEDI database, which has a large peak corresponding to an exposure range of 0.0001–0.001 mg/kg bw/day and only a small fraction (2%) with estimated dietary exposures above 0.01 mg/kg bw/day.

It is concluded from this analysis that estimated dietary exposures to the majority of food contact substances, when used in accordance with US regulations, are below the lowest threshold of toxicological concern for non-genotoxic substances. This implies that repeat-dose toxicity data would not be required for the majority of substances in order to support a conclusion of negligible risk for the specific food contact use(s).

6 Risk assessment of specific packaging chemicals

Included below are examples of recent risk assessments that have been conducted on several chemicals/chemical classes used in the production of food packaging. Also included is risk assessment information on the three food packaging chemicals for which maximum levels (MLs) are included in the Australia New Zealand Food Standards Code, namely acrylonitrile, tin and vinyl chloride.

FSANZ has recently published phase 2 of the 24th Australian Total Diet Study (ATDS) which investigated the presence of 30 packaging chemicals in a total of 81 typically consumed foods and beverages (FSANZ 2016). Findings and conclusions from this study are summarised below for bisphenol A (BPA), several phthalates, printing ink chemicals and perfluorinated chemicals. Results of a similar study conducted by NZ MPI will be available later in 2016.

In June 2015, it was reported that the USFDA is considering post-market evaluations of a range of food contact substances, including phthalates and phthalate alternatives; Irganox 1076; Irgafos 168, polyolefins, metallocenes, and alkyl tins (FoodChemNews 2015). As described below, the USFDA has recently published a re-evaluation of Irganox 1076 which is widely used as an antioxidant in plastic food packaging.

6.1 Bisphenol A

Background information on BPA, including information on a risk assessment published by EFSA in 2014, was provided in the Consultation Paper for the present Proposal (FSANZ 2014a). Subsequent relevant information on BPA is provided here.

In January 2015, EFSA published an updated risk assessment on BPA and lowered the Tolerable Daily Intake (TDI) from 0.05 mg/kg bw to 0.004 mg/kg bw (EFSA 2015b). The lower TDI, which was derived using new data and inter-species extrapolation of BPA dose metrics, is temporary pending the outcome of a long-term study in rats currently being undertaken in the US (Heindel et al. 2015). The study is designed to address some uncertainties regarding the potential effects of BPA.

EFSA also updated its dietary exposure assessment in 2015. In 2006, EFSA estimated adult dietary exposure to BPA as 0.0015 mg/kg bw/day for high consumers (95th percentile), however it was noted that urine biomonitoring studies indicated an upper level of total exposure (dietary and non-dietary) of 0.00016 mg/kg bw/day. EFSA noted that the discrepancy between these values was likely to be due to the conservative assumptions made in the dietary exposure assessment (EFSA 2006). The 2015 estimate, which required fewer assumptions, indicated that dietary exposure to BPA for adolescents, adults (including women of childbearing age) and elderly/very elderly ranged from 0.00012 to 0.00016 mg/kg bw/day (mean) and from 0.00034 to 0.00039 mg/kg bw/day for high exposure (95th percentile). The highest estimated dietary exposure, 0.00086 mg/kg bw/day (for toddlers), was only 21% of the temporary TDI. EFSA concluded that there is no health concern for any age group from dietary exposure to BPA (EFSA 2015b). In a Chinese total diet study, mean dietary exposure of adults to BPA was estimated to be only 1.1% of the EFSA temporary TDI (Niu et al. 2015).

In phase 2 of the 24th ATDS, BPA was detected in 8 of the 17 composite foods tested. The maximum observed concentration of 0.074 mg/kg was well below the EU specific migration limit (SML) of 0.6 mg/kg. Assuming that 50% of foods and beverages consumed contained BPA at the maximum detected level, the theoretical maximum daily exposure (TMDE) to BPA was calculated to be 5% of the EFSA temporary TDI. FSANZ concluded that the public health and safety risk from BPA migration into food is very low (FSANZ 2016).

Urine biomonitoring studies on BPA provide information on total exposure, noting that estimated exposure to BPA from non-dietary sources is minor compared to dietary exposure (EFSA 2015b). Recent urine biomonitoring studies provide evidence that total exposure to BPA is low relative to the EFSA temporary TDI. A study in Australian children aged 0–15 years reported mean BPA exposure of 70 nanograms/kg bw/day which is 1.8% of the EFSA temporary TDI (Heffernan et al. 2014). A urine biomonitoring study in the US reported median exposure to BPA for the population of 25 nanograms/kg bw/day, or 0.6% of the temporary TDI (LaKind & Naiman 2015).

6.2   Diethylhexyl phthalate (DEHP)

DEHP is widely used as a plasticiser, most notably to improve the flexibility and durability of materials made from polyvinyl chloride (PVC). Some phthalates have been the subject of concern in regard to their potential for adverse reproductive and developmental effects, as shown in laboratory animal studies. Based on laboratory animal studies showing adverse effects on the testes, EFSA established a TDI for DEHP of 0.05 mg/kg bw, derived from a no observed adverse effect level (NOAEL) of 5 mg/kg bw/day and application of an uncertainty factor of 100 (EFSA 2005a). EFSA used European data on DEHP concentrations in foods to provide estimates of dietary exposure in various population groups. The highest derived dietary exposure estimate of 0.026 mg/kg bw/day (in children aged 1–6 years) corresponded to 52% of the TDI. An SML for DEHP of 1.5 mg/kg was subsequently established by the European Commission in order to reduce the risk of exceedance of the TDI (Petersen and Jensen 2010).

Recent European studies have reported a large range of estimated dietary exposures to DEHP. For example, studies in Norway, Belgium, Germany and Ireland gave highest dietary exposure estimates that are 1%, 6%, 57% and 3% of the TDI, respectively (Sakhi et al. 2014; Fierens et al. 2014; Heinemeyer et al. 2013; FSAI 2016). A US study has reported that DEHP dietary exposure estimates were below the TDI for adolescents and women of reproductive age, however estimated dietary exposure was 180% of the TDI for infants aged 1–2 years consuming diets high in meat and dairy (Serrano et al. 2014).

For phase 2 of the 24th ATDS, 15 of 48 composite foods contained detectable levels of DEHP (FSANZ 2016). The European SML for DEHP of 1.5 mg/kg was exceeded in savoury breads (6.7 mg/kg) and takeaway hamburgers (4.2 mg/kg), and the TMDE[9] calculated for screening purposes exceeded the EFSA TDI by a factor of 4. In response to the outcome of the screen, FSANZ is currently conducting a follow-up analytical survey of a wider range of foods in order to allow an estimate of dietary exposure to DEHP that can be used for risk characterisation.

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[9] In phase 2 of the 24th ATDS, the theoretical maximum daily exposure (TMDE) was calculated by assuming that 50% of foods and beverages consumed contained the chemical at the maximum detected level (FSANZ 2016). This is a worst case exposure scenario used for screening purposes only.

6.3   Diisononyl phthalate (DINP)

DINP may be used as a replacement for DEHP and other lower molecular weight phthalates (ECHA 2010). DINP has a more favourable hazard profile than DEHP and the TDI for DINP established by EFSA (0.15 mg/kg bw) is 3-times the DEHP TDI. The DINP TDI was derived from a NOAEL of 15 mg/kg bw/day in a two-year rat study and application of an uncertainty factor of 100 (EFSA 2005b). Adverse liver and kidney effects were observed at the next higher dose (152 mg/kg bw/day).

In phase 2 of the 24th ATDS, DINP was detected in the same number of composite foods as DEHP (15 out of 48; FSANZ 2016). The TMDE that was estimated exceeded the EFSA TDI by 9-fold. However, as for DEHP, FSANZ is conducting a follow-up analytical survey of a wider range of foods to allow a better estimate of dietary exposure to DINP.

6.4   Other phthalates

The 24th ATDS included the analysis of 12 additional phthalates in the same 48 composite foods that were analysed for DEHP and DINP. Based on the low levels of detection in only a small number of foods, no public health and safety concerns were identified for these phthalates. However, it was noted that three of the detected phthalates are not on EU or US lists of approved food contact substances (FSANZ 2016). Based on the low levels of detection, the risk was assessed to be negligible (using conservative dietary modelling). These phthalates may have been intentionally used in the food packaging, or in other food contact applications, as replacements for phthalates of potential concern, such as DEHP and DINP (C&EN 2015).

6.5   Printing ink chemicals

Printing inks typically contain a number of components such as pigments, solvents, binding agents, plasticisers and photoinitiators (chemicals that facilitate UV curing of inks). It was recently reported that more than 100 incidents of contamination of packaged food with photoinitiator chemicals have been notified by the EU Rapid Alert System for Food and Feed (RASFF) (Lago et al. 2015). The potential migration into food of printing ink chemicals has been investigated in several recent analytical surveys, including phase 2 of the 24th ATDS.

A 2011 study by the UK Food Standards Agency (UK FSA) investigated the presence of 20 printing ink chemicals in 350 foods packaged in printed paperboard. All samples were stated to be heavily printed. The analysed chemicals were selected on the basis of previous knowledge of their potential to migrate from packaging into food. The majority of the selected substances were photoinitiators but some were plasticisers and binders. The report noted that there is limited toxicological data available for many of the substances included in the survey. Toxicological data on related substances were used in the absence of data on specific substances. Eighty four of the 350 food samples tested contained detectable levels of one or more of the ink chemicals. Based on a risk assessment, the UK FSA concluded that the findings did not indicate any safety concerns (UK FSA 2011; Bradley et al. 2013).

In a German study, 99 foods predominately packaged in paperboard were analysed for 11 printing ink chemicals. One or more ink chemicals were detected in 33 foods, however the potential risk due to the levels of these substances was not addressed in the paper (Jung et al. 2013).

The 24th ATDS included the analysis of 11 printing ink chemicals in 60 composite food samples. Based on the low levels of detection in only a small number of foods, the screening method identified no public health and safety concerns for these chemicals (FSANZ 2016).

6.6   Antioxidants used in packaging

Antioxidants are widely used to enhance the stability of food contact materials (e.g. to delay the degradation of plastics). The USFDA recently published a post-market re-evaluation of an antioxidant compound with 24 approved food contact uses in the US (Neal-Kluever et al. 2015). The compound, commonly known as Irganox 1076, is approved for use in adhesives and in a range of plastics widely used in food packaging including polyethylene, polypropylene and polystyrene. The re-evaluation was conducted to ensure that current dietary exposures from the use of Irganox 1076 in food contact articles are accurately captured and that all relevant toxicological information available since the time of premarket approval was considered.

Estimated dietary exposure to Irganox 1076, taking into account all approved uses, was calculated to be 0.075 mg/kg bw/day[10]. The toxicological database included repeat-dose studies of various durations in three animal species. A NOAEL of 64 mg/kg bw/day from a chronic rat study was considered to be appropriate for use in risk characterisation. This NOAEL is ~850 times the estimated dietary exposure (i.e. the margin of exposure (MOE) is 8.5-times the conventional 100-fold safety factor), leading the USFDA to conclude that current dietary exposure to Irganox 1076 does not present a human health concern.

6.7   Perfluorinated chemicals

Since the 1960s, various perfluorinated chemicals (PFCs) have been approved in the US for use in grease-proof coatings on food packaging including paper wrappers and paperboard containers (USFDA 2015). Some perfluorinated compounds have been shown to bioaccumulate in animals and in humans and to also exhibit adverse effects in laboratory animal studies, including reproductive and developmental toxicity. In general, substances with perfluorinated alkyl chains greater than or equal to eight carbons in length (C8 PFCs) bioaccumulate, while those less than eight carbons in length do not (Rice 2015). Following a review of C8 PFCs, the USFDA worked with several manufacturers to remove grease-proofing agents containing C8 PFCs from the marketplace. As a result of this initiative, in 2011 these manufacturers volunteered to stop distributing products containing C8 PFCs for food-contact purposes (USFDA 2015).

In January 2016, the USFDA withdrew the authorisation of three C8 PFCs used as oil and water repellent coatings on paper and paperboard in contact with food.
The three PFCs are as follows:

1. Diethanolamine salts of mono- and bis (1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range C8–C18;
2. Pentanoic acid, 4,4-bis [(*gamma-omega*-perfluoro-C8-20-alkyl)thio] derivatives, compounds with diethanolamine; and
3. Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([*gamma*], [*omega*]-perfluoro C4-20 alkylthio) methyl]-1,3-propanediol, polyphosphoric acid and ammonium hydroxide.

It was noted that there were deficiencies in the available information used to determine migration levels of these substances into food, and for this reason a reliable estimate of dietary exposure to the substances could not be calculated. The USFDA concluded there is no longer a reasonable certainty of no harm from food contact use of the three substances (US FR 2016).

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[10] This level of dietary exposure is at the upper end for a food contact substance. For comparison, the USFDA CEDI database of ~1300 food contact substances contains only 6 substances with estimated dietary exposures greater than 0.075 mg/kg bw/day. Additional information on this database is provided in Sections 4 and 5.

The 24th ATDS included the analysis of two other C8 PFCs in 50 composite food samples. PFOS was detected at low levels (0.001 mg/kg) in two out of the 50 foods; however the TMDE was low in comparison to the TDI indicating a negligible public health and safety risk. PFOA was not detected in any foods (FSANZ 2016).

6.8 Food packaging chemicals in the *Australia New Zealand Food Standards Code*

6.8.1 Acrylonitrile

Acrylonitrile is a starting substance for the production of certain resins and plastics. Substances derived from acrylonitrile may contain residual amounts of the monomer which can potentially migrate into food. An assessment by the then Australia New Zealand Food Authority (ANZFA) concluded that acrylonitrile is carcinogenic in rats when administered via the oral route (ANZFA 1999a), consistent with an earlier JECFA evaluation (WHO 1984). ANZFA further concluded that there was no evidence of adverse health effects resulting from low level exposure via food, however the potential for carcinogenicity requires that exposure should be kept as low as possible. It was therefore proposed to retain the existing ML for all food which was set at the limit of detection (LOD) of 0.02 mg/kg (ANZFA 1999a).

In a FSANZ analytical survey, a range of foods packaged in plastic were tested for acrylonitrile. The foods tested included full fat milk, minced beef, yogurt, tomato sauce, pre-prepared meals, orange juice and still water. The analytical method had a limit of quantification (LOQ) ranging from 0.001 to 0.01 mg/kg depending on the food matrix. There were no detections of acrylonitrile in any food (FSANZ 2011). Reports from the 1980s indicated parts-per-billion (ppb = μg/kg) levels of acrylonitrile in some foods. An absence of detectable acrylonitrile in foods analysed in the above FSANZ study is consistent with the reported large improvements in the formulation and production of food packaging materials that use acrylonitrile as a starting substance (ATSDR 1990; NICNAS 2000).

6.8.2 Tin

The main source of dietary exposure to tin is via ingestion of inorganic tin from canned foods. Inorganic tin is found in food in both the +2 and +4 oxidation states; it may occur in cationic form (stannous and stannic compounds) or as anions (stannites and stannic compounds) (WHO 2006). Steel cans used in the food industry are coated in a thin layer of tin and/or a lacquer. The tin and lacquer acts to prevent corrosion of the steel. Although tin is corrosion resistant, acidic food like fruits and vegetables can cause corrosion of the tin layer of unlacquered cans resulting in transfer of inorganic tin into the food. Dietary exposure to inorganic tin is greatly reduced when cans are lacquered (Biégo et al. 1999).

In 1989, JECFA established a PTWI for inorganic tin of 14 mg/kg bw (WHO 1989). The most recent JECFA evaluation of inorganic tin stated that the basis for the previously established PTWI was unclear and may have been derived from intakes associated with acute effects (WHO 2006). In assessment published in 1999 by ANZFA considered the various MLs for tin in force at the time and concluded that there are limited concerns to public health and safety other than acute gastric disturbances when levels of tin in food exceed 250 mg/kg (ANZFA 1999b).

6.8.3 Vinyl chloride

Vinyl chloride is a starting substance for the production of polyvinylchloride (PVC) plastics used in the manufacture of food packaging materials, and small amounts may remain in such materials. An assessment by ANZFA concluded that vinyl chloride is carcinogenic in rats when administered via the oral route (ANZFA 1999a), consistent with an earlier JECFA evaluation (WHO 1984).

ANZFA further concluded that there was no evidence of adverse health effects resulting from the low level of exposure to vinyl chloride via food, however the potential for carcinogenicity requires that exposure should be kept as low as possible. An ML of 0.01 mg/kg (set at the LOD) applicable to all food was established in 1999 (ANZFA 1999a) but was amended in 2013 to reflect achievability of detection in packaged water (FSANZ 2012). Vinyl chloride is considered by the International Agency for Research on Cancer to be a human carcinogen based on epidemiological data from occupational exposure (IARC 2008).

No studies have been located reporting the analysis of infant formula for vinyl chloride and there are limited data on vinyl chloride levels in other foods. In a FSANZ analytical survey, a range of foods packaged in plastic were tested for vinyl chloride. The foods tested included full fat milk, minced beef, yogurt, tomato sauce, pre-prepared meals, orange juice and still water. The analytical method had a limit of quantification (LOQ) ranging from 0.001 to 0.01 mg/kg depending on the food matrix. There were no detections of vinyl chloride in any food (FSANZ 2011).

Reports from the 1970s indicated parts-per-million levels of vinyl chloride in some foods (e.g. up to 98 mg/L in vinegar, 1.8 mg/L in edible oils, and 8.4 mg/L in alcoholic beverages) when these foods were packaged and stored in PVC containers (ATSDR 2006). An absence of detectable vinyl chloride in foods analysed in the above FSANZ study is consistent with the reported large improvements in the formulation and production of PVC packaging materials (ATSDR 2006).

7   Food packaging made from recycled materials

Concerns have been raised about the potential public health and safety risks from the use of recycled materials in the production of food packaging. There have been particular concerns regarding the migration of uncharacterised substances from packaging into food, for example from packaging manufactured using recycled materials which may not be adequately controlled with respect to chemical contamination, or for which the recycling process results in the formation of novel chemical species (Nerin et al. 2013). There is potentially more uncertainty around the identity and levels of "non-packaging" chemicals in recycled packaging (i.e. chemicals that are not used to produce the original packaging) – and this is taken into consideration in EFSA and USFDA pre-market assessments of specific recycling processes. These processes almost exclusively relate to the use of post-consumer plastics to produce packaging materials.

The potential risk from the migration into food of chemicals in recycled paperboard, particularly mineral oils, is not yet well characterised and research is ongoing internationally. FSANZ has recently conducted an analytical survey of mineral oils in packaging materials and packaged food purchased in Australia. The survey did not find widespread migration of mineral oils into food products or identify any specific public health and safety concerns.

It does not appear that EFSA or the USFDA have assessed any specific processes to mitigate the levels of mineral oils in recycled paperboard. Use of an appropriate barrier material (e.g. an internal plastic lining or coating) has been proposed to reduce migration of mineral oils (Biedermann and Grob 2013).

8   Conclusions

Based on the available data, the overall human health risk posed by chemical migration from packaging into food is considered to be low. This is predominantly due to the low dietary exposure expected for the majority of chemicals used in the production of food packaging.

For example, estimated dietary exposure for 98% of food contact substances in a USFDA database is less than 0.01 mg/kg bw/day, while for 86% of the substances estimated dietary exposure is less than the lowest threshold of toxicological concern for non-genotoxic substances (0.0015 mg/kg bw/day).

This general conclusion of low risk based on TTC considerations is consistent with the findings of analytical surveys investigating the presence of specific packaging chemicals in Australian foods. However, using the screening methodology of the ATDS, FSANZ has identified two chemicals for which additional chemical concentration data for a targeted number of foods are required in order to determine if dietary exposure to these chemicals may pose a health risk. These two chemicals, DEHP and DINP, belong to the phthalate family of compounds, some members of which migrate efficiently into foods, in particular those with a high fat content. FSANZ is currently conducting a study to acquire data on DEHP and DINP levels in a targeted range of foods.

The potential risk from the migration into food of chemicals in recycled paperboard, particularly mineral oils, is not yet well characterised and research is ongoing internationally. However, a recent Australian survey, carried out by FSANZ, did not find widespread migration of mineral oils into food products or identify any specific public health and safety concerns.

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Attachment 1 – Comparison of estimated dietary exposures and human no effect levels for certain food contact substances

The Table below lists food contact substances for which:

(i)   estimated dietary exposure, as listed in the USFDA CEDI database, exceeds the TTC class III threshold of 0.0015 mg/kg bw/day; and

(ii)   a human oral Derived No Effect Level (DNEL) is available from the European Chemicals Agency (ECHA) website.

As defined by ECHA, the DNEL is the level of exposure above which humans should not be exposed, and is typically derived by applying an uncertainty factor to a NOAEL identified in a suitable repeat-dose toxicity study (ECHA 2012).

The 34 substances resulting from this analysis are listed in order of decreasing estimated dietary exposure. No substances were identified with an estimated dietary exposure greater than 20% of the DNEL. For 25 substances, estimated dietary exposure was less than 1% of the DNEL.

Chemical name	CAS no.	Estimated Dietary Exposure (EDE)[†] (mg/kg bw/day)	Human oral Derived No Effect Level (DNEL)[‡] (mg/kg bw/day)	EDE as a percentage of the DNEL
Castor oil, hydrogenated	8001-78-3	0.72	24	3%
Pentaerythrityl tetrakis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate)	6683-19-8	0.12	1.4	8%
Tris(2,4-di-tert-butylphenyl) phosphite	31570-04-4	0.091	0.58	16%
Butyric acid, 3,3-bis(3-tert-butyl-4-hydroxyphenyl)ethylene ester	32509-66-3	0.047	13	0.4%
Triisopropanolamine	122-20-3	0.044	9.7	0.5%
Bis(2,4-di-tert-butyl-6-methyl phenyl) ethyl phosphite	145650-60-8	0.029	2.9	1%
N,N'-hexamethylenebis(3,5-di-tert-butyl- 4-hydroxyhydrocinnamamide)	23128-74-7	0.025	27	0.1%
Calcium bis(monoethyl(3,5-di-tert-butyl- 4-hydroxybenzyl)phosphonate)	65140-91-2	0.022	3.0	0.7%
Caprolactam	105-60-2	0.022	8.6	0.3%
4-((4,6-bis(octylthio)6-bis(octylthio)6-bis(octylthio)-s-triazin-2-yl)amino)-2,6-di-tert-butylphenol	991-84-4	0.018	3.9	0.4%
2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane, 3,9-bis[2,6-bis(1,1-dimethylethyl)-4-methylphenoxy]-	80693-00-1	0.016	4.5	0.4%
Trimellitic anhydride	552-30-7	0.013	2.5	0.5%
1,2-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamoyl)hydrazine	32687-78-8	0.011	3.1	0.4%
2,4,7,9-tetramethyl-5-decyne-4,7-diol ethylene oxide adduct	9014-85-1	0.011	0.25	4%
2-methyl-4,6-bis((octylthio)methyl)phenol	110553-27-0	0.010	0.36	3%
Trimethylolpropane	77-99-6	0.0072	1.7	0.4%
1,4-butylene glycol	110-63-4	0.0029	8.0	0.04%

Chemical name	CAS no.	Estimated Dietary Exposure (EDE)[†] (mg/kg bw/day)	Human oral Derived No Effect Level (DNEL)[‡] (mg/kg bw/day)	EDE as a percentage of the DNEL
2-(2'-hydroxy-5'-methylphenyl)benzotriazole	2440-22-4	0.0029	1.2	0.2%
2,4-di-tert-pentyl-6-(1-(3,5-di-tert-pentyl-2-hydroxyphenyl)ethyl)phenyl acrylate	123968-25-2	0.0028	55	0.005%
1,4-cyclohexanedimethanol	105-08-8	0.0027	3.6	0.08%
Acetone	67-64-1	0.0025	62	0.004%
Aluminium oxide	1344-28-1	0.0025	3.3	0.08%
Phosphorothioic acid, O,O,O-triphenyl esters, tert-butyl derivatives	192268-65-8	0.0025	0.080	3%
Tri(2(or 4)-C9-10-branched alkylphenyl) phosphorothioate	126019-82-7	0.0025	1.6	0.2%
Triphenylphosphorothioate, O,O,O-	597-82-0	0.0025	0.21	1%
Gum rosin	8050-09-7	0.0025	10	0.025%
Oleoyl sarcosine	110-25-8	0.0025	5.0	0.05%
Thioethylene glycol bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate)	41484-35-9	0.0025	0.69	0.4%
4-chloro-3-methylphenol	59-50-7	0.0025	0.89	0.3%
Phthalic anhydride	85-44-9	0.0024	5.0	0.05%
Benzenesulfonic acid, 2,2'-(1,2-ethenediyl)bis[5-[[4-bis(2-hydroxyethyl)amino]-6-[(4-sulfophenyl)amino]-1,3,5-triazin-2-yl]amino]-, tetrasodium salt	16470-24-9	0.0023	3.0	0.08%
1,3,5-triazine-2,4,6-triamine, N,N'''-1,2-ethanediylbis[N-[3-[[4,6-bis[butyl(1,2,2,6,6-pentamethyl-4-piperidinyl)amino]-1,3,5-triazin-2-yl]amino]propyl]-N',N''-dibutyl-N',N''-bis(1,2,2,6,6-pentamethyl-4-piperidinyl)-	106990-43-6	0.0023	0.025	9%
Octamethylcyclotetrasiloxane	541-02-6	0.0018	5.0	0.04%
2-hydroxy-2-methyl-1-phenyl-1-propanone	7473-98-5	0.0016	0.40	0.4%

[†] Estimated dietary exposures from USFDA CEDI database:
http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/CEDI/ucm2006857.htm
[‡] Human oral derived no effect levels (DNELs) from European Chemicals Agency (ECHA) database:
http://echa.europa.eu/