Annex 3. Case study: incident

In this document three (fictive) incidents are elaborated, namely, a high migration of ESBO from a PVC-lined metal lid of a glass jars into a food product, the migration of di-2-ethylhexyl adipate (DEHA) from a plastic film and the migration of 4,4'-methylene dianiline from kitchen utensils.

3.1. <u>ESBO (450 mg/kg) in a olive-in-oil sample</u>

As a first example, the risk of the high ESBO value in an olives-in-oil-sample (450 mg/kg) observed in one of the elaborated case studies is characterized (see **annex 1, table 1**).

3.1.1. <u>Hazard characterization & identification</u>

See **annex 1**, **1.1.** and **1.2.** A toxicological threshold value, namely a TDI of 1 mg/kg bw/day is available.

3.1.2. <u>Exposure assessment & risk characterization</u>

In the most conservative, worst-case scenario, where a consumption of 16.7 g packed food/kg bw (1 kg packed food for a person weighing 60 kg) is assumed (as is legally defined), an exposure of 7.5 mg/kg bw is obtained, which is well above the TDI.

As a 'more' refined first screening approach, it is supposed that all relevant foods have each the maximum measured concentration and are packed in jars with twist-off closure. Considering the P95 consumption value of 'consumers only', this results in an exposure of 1.04 mg/kg bw per day, which narrowly exceeds the TDI (**table 1**).

Table 1. Exposure of adults to ESBO (mg/kg bw per day) through in glass jars packed food (worst-case scenario based on max. ESBO levels of the FASFC control data (2008-2009-2010-2011-2012) and the P95 consumption level taken from the BFCS (Devriese *et al.*, 2005))

	[ESBO] max (mg/kg)	**exposure** (mg/kg bw/day) **population**	**consumers only**
Sauces	49.0	0.078	0.090
Vegetables-in-oil	450.0	0.576	0.860
Cheese-in-oil	36.1	0.000	0.030
Fish-in-oil	50.8	0.029	0.058
SUM		**0.682**	**1.037**

Remark that the consumption values were extracted from the consumption database (BFCS) based on the criterion "canned, salted, marinated and vacuum packed". Consequently, the actual exposure will be lower. Since it is highly unrealistic a person consumes 'high' quantities (P95 consumption) of the considered food products which all contain a high level of ESBO, a first refinement is to consider the P90 ESBO concentration data for the sauces, the cheese-in-oil and the fish-in-oil food categories, and different percentages of foods that are packed in jars with twist-off closure. As such, exposure values of 0.95, 0.76 and 0.48 mg/kg bw per day are estimated for consumers only (0.63, 0.51 and 0.32 mg/kg bw per day for the whole population) when assuming that 100%, 80% and 50% of foods are packed.
These values are below the TDI of 1 mg/kg. Notice that a TDI is generally considered as a toxicological reference dose for daily or chronic exposure, whereas the high ESBO level observed in the olives-in-oil sample can be assumed to be an incidental or punctual contamination.

3.1.3. <u>Conclusion</u>

Based on a more realistic, but still worst-case scenario in which it is assumed that all food are packed in jars with twist-off closure and contain a high ESBO level (P90), the presence of 450 mg/kg ESBO in the olives-in-oil sample does not immediately pose a health concern for adults.

3.2. Migration of adipate from a plastic film

DEHA (di(2-ethylhexyl)adipate, CAS n° 103-23-1) is widely used as a plasticiser for flexible poly(vinyl chloride) (PVC) products, notably food films, as well as in other plastics and in a number of other minor applications, such as lubricants and cosmetics. Food films used to wrap foods or for over-wrap of supermarket trays are in the range typically 8 to 25 micrometers thick and the total plasticiser content, including DEHA, would be in the range 10 to 30% by mass. Because of its relatively low molecular weight (MW = 370 g/mol) DEHA readily migrates into foods, especially into fatty foods, such as cheese and meat. In the past, DEHA was the sole or the dominant plasticiser used in such films but nowadays it is normally used at lower levels and in combination with other plasticisers (EFSA, 2005a).

Commission Regulation (EU) n° 10/2011 states that to ensure compliance, SML values need to be expressed in mg/kg applying the real surface to volume ratio in actual or foreseen use. By derogation, for (i) containers and other articles, containing or intended to contain, less than 500 ml or grams or more than 10 l, (ii) materials and articles for which, due to their form it is impracticable to estimate the relationship between the surface area of such materials or articles and the quantity of food in contact therewith, (iii) sheets and films that are not yet in contact with food, and (iv) sheets and films containing less than 500 ml or grams or more than 10 l, the value of migration must be expressed in mg/kg applying a surface to volume ratio of 6 dm^2 per kg of food. For DEHA the Regulation sets a specific migration limit (SML) of 18 mg/kg food or food stimulant, corresponding thus to a limit of 3 mg/dm^2 for ''non-container'' packaging such as packaging films (i.e. based on the surface to volume ratio of 6 dm^2 per kg food given in the current EU legislation).

3.2.1. Hazard characterization & identification

The acute toxicity of DEHA is low by oral, inhalation or dermal exposure. The International Agency for Research on Cancer (IARC, 2000) reported that there is inadequate evidence in humans (Group 3, “not classifiable as to its carcinogenicity to humans”) and limited evidence in experimental animals for the carcinogenicity of DEHA.
The U.S. EPA (2008) lists a chronic oral Reference Dose (RfD, verified in 1992) of 0.6 mg/kg-day for DEHA based on fetal variations and reduced litter size and weight. A TDI of 0.3 mg/kg bw has been established for DEHA by the Scientific Committee on Food (SCF) (EFSA, 2005a).

3.2.2. Exposure assessment & risk characterization

The current, conservative procedure for estimating consumer exposure to substances migrating from FCM into food assumes a person consumes 1 kg of packaged food daily. However, in the case of fat, it has been demonstrated that the total daily fat consumption by European adults does not exceed 200 g. To take account of this, migration values into fatty foods are corrected by a Fat (Consumption) Reduction Factor (FRF), variable from 1 to 5, according to the formula FRF = (g fat in food/kg of food)/200 = (% fat × 5)/100. Additionally, to take the higher extractive power of the fat simulant D, olive oil, compared with fatty food into account, migrant values obtained using olive oil are corrected by applying a reduction factor, known as the DRF, variable from 1 to 5. A Total Reduction Factor (TRF) is obtained by multiplying the DRF by the FRF and with the restriction that its value should not be higher than 5 (Commission Regulation (EU) n° 10/2011; EFSA, 2005a).

There is a large body of literature describing laboratory studies of DEHA migration from plasticised films and several surveys of packaged foods have been reported (McCombie *et al.*, 2012; Goulas *et al.*, 2008; Goulas *et al.*, 2007; Holmes *et al.*, 2005; Petersen & Breindahl, 2000; Petersen & Breindahl, 1998; Petersen & Naamansen, 1998). Considering as an example the equilibrium migration value of 117.6 mg/kg detected by Goulas *et al.* (2008) after a certain storage period in fish fillets weighing averagely 135 g, packed in PVC-cling film (11 µm thickness, containing 8.9% (W/W) DEHA). Based on a total film/fillet contact area of ca. 170 cm^2 and taking the fat content of 8% of the fillet into account, this migration value corresponds to 3.74 mg DEHA/dm^2 (and a loss of 23.9% DEHA from the PVC film), which is above the SML for DEHA, and thus the film would be not conforming. Based on the default value of 6 dm^2/kg food/person per day, this value of 3.74 mg DEHA per dm^2 cling film corresponds to 22.44 mg/kg food, or to an exposure of 0.374 mg/kg bw/day respectively (consumption of 1 kg packed food, 60 kg bw), which is above the SCF TDI of 0.3 mg/kg bw. Moreover, considering the FCM usage or consumption values for children reported by Foster *et al.* (2010), the TDI is even exceeded up to 10 times (**table 2**). However, these FCM usage values are for packed food in general, whereas only a (small) percentage of food is wrapped in cling film. The exposure of children though, still remains close to the TDI when assuming that cling film contributes for 10% to FCM usage (**table 2**). On the other hand, migration of DEHA depends on fat and moisture content of the food, and not all packed or wrapped food will have e.g. a similar fat content as fish.

Table 2. Exposure to DEHA (117.6 mg/kg) based on general FCM usage values

		Exposure (mg/kg bw)	
age	**FCM usage** (dm^2/kg bw)	**100% cling film**	**10% cling film**
< 1 year	0.65 [a]	2.43	0.24
1-4 years	0.81 [a]	3.03	0.30
4-6 years	0.66 [a]	2.47	0.25
adults	0.1 [b]	0.37	0.04

[a]: Foster *et al.* (2010); [b]: Commission Regulation (EU) n° 10/2011

The dietary exposure to DEHA in the United Kingdom (MAFF reporting) has been estimated to be up to 8.2 mg/day (0.12 mg/kg bw/day for a 70 kg person), which is below the TDI of 0.3 mg/kg bw/day. Studies in humans indicate that this exposure value may be an upper limit given the fact that a median exposure of 2.7 mg/person/day was determined based on a limited 24-hr urine sampling (OECD, 2000; Loftus *et al*., 1994).
The EC SCF evaluated a biomarker study of the European Plasticised PVC Film Manufacturers' Association (EPFMA), resulting in estimated median DEHA intakes of only 1.04 mg/day in France, of 0.80 mg/day in Germany and of 0.86 mg/day in The Netherlands. The SCF concluded that, despite severe limitations of the surveys, the data are nevertheless reassuring and that on average, DEHA intakes are below the TDI established by the SCF (SCF, 2000).

3.2.3. Discussion & Conclusion

It is highly unlikely, but theoretically possible that if someone ate fatty foods such as fish or cheese wrapped in commercial cling film, each and every day of their lives, they could consume high levels of DEHA (Goulas *et al.*, 2008). In addition, the food may be repackaged one or several times by consumers at home. For instance, it was shown that when applying realistic practices from buying meat to the final food preparation, the concentration of DEHA increased from 20 to 100 mg/kg after repeated repackaging (Petersen & Naamansen, 1998). Additionally, temperature will affect migration as well (e.g. microwave cooking of foods can enhance migration). The extent to which high temperature enhances migration of DEHA into foods is dependent on the area in contact and the fat content of the food (OECD, 2000).

3.3. Migration of 4,4'-methylene dianiline (4,4'-MDA)

The migration of 4,4'-methylene dianiline (4,4'-diaminodiphenylmethane, 4,4'-MDA, CAS n°101-77-9) from polyamide/nylon cooking kitchen utensils is taken as a third example. This example is based on a control result, showing a migration level between 0.096 mg/kg and 0.563 mg/kg for the same lot of kitchen utensils (ladles), which is above the general standard for the migration of primary aromatic amines of 0.01 mg/kg or of 0.00166 mg/dm² (Commission Regulation (EU) n° 10/2011).

3.3.1. Hazard characterization & identification

4,4'-MDA is a primary aromatic amine, and is synthesized by reaction of formaldehyde and aniline in the presence of hydrochloric acid. 4,4'-MDA is primarily used to produce 4,4'-methylenedianline diisocyanate and other polymeric isocyanates (ECB, 2001; EPA, 2000). The origin of 4,4'-MDA in cooking utensils is unknown, but may possibly be linked to colorants, such as aniline, or to its use as a chemical intermediate or hardener/curing agent in manufacture of the polyamide/nylon (VKM, 2006).

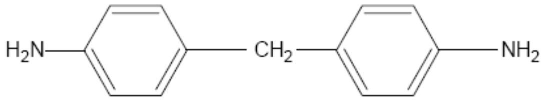

Figure 1. Structure of 4,4'-methylene dianiline (4,4'-MDA, CAS n°101-77-9)

According to the EU classification, 4,4'-MDA is a category 2 carcinogen ("may cause cancer"), and a category 3 mutagen ("possible risks of irreversible effects") (ECB, 2001). The IARC classifies 4,4'-MDA in group 2B ("possible carcinogenic to humans"), based on sufficient evidence for carcinogenicity in rats and mice (ECB, 2001; EPA, 2000). The U.S. Environmental Protection Agency (EPA) has not classified MDA for carcinogenicity (EPA, 2000).

The *in silico* toxicology software package Tox Tree ('Toxic Hazard Estimation by decision tree approach'), places 4,4'-DMA in Cramer Class III, which corresponds to a threshold of 90 µg/person/day or 1.5 µg/kg bw/day. However, for substances with a structural alert for genotoxicity a threshold of 0.0025 µg/kg bw/day (0.15 µg/person/day) has been set (EFSA, 2012a).
On the other hand, some toxicological studies are available, and since 4,4'-MDA is to be considered a genotoxic and thus non-threshold carcinogen, a Benchmark Dose Lower Limit (BMDL)[1] is proposed (EFSA, 2005). The Norwegian Scientific Committee for Food Safety modeled a $BMDL_{10}$ value of 1.7 mg/kg bw/day for 4,4'-MDA, based on two-year animal studies showing that the oral treatment of rats and mice with 4,4'-MDA is associated with tumors of the thyroid and the liver in rats and mice (considering the incidence of neoplastic hepatic nodules as the most sensitive end point) (VKM, 2006).

3.3.2. Exposure assessment & risk characterization

Assuming the default worst-case consumption value of 1 kg packed food (or 1 kg or liter of food being into contact with the ladle)[2], a migration of 4,4'-MDA between 0.096 mg/kg and 0.563 mg/kg corresponds to an exposure between 1.6 and 9.4 µg/kg bw/day for a person of 60 kg and to 1.4 and 8.0 µg/kg bw/day for a person of 70 kg (TTC values are based on a body weight of 60 kg, whereas a body weight of 70 kg has been assigned as the default body weight for the European adult population; EFSA, 2012b). These values are above the Cramer Class III threshold of 1.5 µg/kg bw/day and far above the threshold of 0.0025 µg/kg bw/day for substances with a structural alert for genotoxicity. Compared to the $BMDL_{10}$ value of 1.7 mg/kg bw/day, these exposure values result in an MOE ('margin of exposure' = $BMDL_{10}$ / exposure) between 1240 and 181, indicating a major concern (EFSA, 2005b). When a more realistic scenario is assumed, where e.g. 300 ml of soup is prepared with the ladle of concern is consumed, MOE values between 604 and 4132 are obtained for a person weighing 60 to 70 kg. These values are still much lower than 10,000, which the EFSA Scientific Committee view as a low priority for risk management (EFSA, 2005b).

3.3.3. Conclusion

MOE values indicate a major concern. Remark that the MOEs were calculated for an adult consumer whereas for children MOE values would be much lower. Moreover, intake of 4,4'-MDA from other potential sources than cooking utensils was not considered in this risk assessment due to lack of data.

[1] A BMDL corresponds to the lower limit of a one-sided 95% confidence limit interval on the Benchmark dose (BMD) corresponding to a 10% tumor incidence above the control.
[2] The Norwegian Scientific estimated the intake of 4,4'-MDA migrating from cooking utensils by assuming a surface area of the utensil of maximum 1 dm^2 used in a pot with a volume of 1 litre for 30 min., and that the whole food content cooked in this pot is consumed per day by one person with a body weight of 70 kg (VKM, 2006).

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