# Examples of EFSA's safety evaluation of oligomers

L. Castle, CEF Panel, Chair of the FCM SWG
E. Barthélémy, EFSA Scientific Officer for FCM

*3rd FIP FCM Network meeting on 24-26 May 2016, Parma*

efsa
European Food Safety Authority

# CONTENT

- 8 examples are presented
- Monomer (x3), crosslinker (x2), polymeric additive (x3)
- Analysis in polymer (x2), in simulant (x6)
- With specific toxicological data provided (x1) and without inc. read across (x7)
- From no restriction to specific migration on oligomers

*It is not meant to be exhaustive*

# OLIGOMERS - CASE 1

**Analysis of the Low Molecular Weight Fraction (LMWF) in the polymer**: **monomer** perfluoromethyl perfluorovinylether used in the polymerisation process of fluoropolymers

*(EFSA Journal 2015;13(7):4171)*

- using **gel permeation chromatography (GPC)** analysis
- No **oligomers below 1 500 Da** were detected in uncured fluoro-and perfluoropolymers

# OLIGOMERS – CASE 2

**Analysis of the LMWF in the polymer and migration modeling**: **polymeric additive** (ethyl acrylate, methyl methacrylate) copolymer composed from evaluated and authorised monomers *(EFSA Journal 2011;9(12):2464)*

- LMWF below 1000 Da up to 1.3% using **size exclusion chromatography (SEC)**
- Migration modeling from PET and PLA (using PET parameters) expected **below 50 µg/kg food** => tier 1 (genotoxicity)

# OLIGOMERS – CASE 2 (CONTINUED)

- **Read across from monomers** that are non-genotoxic and the oligomers expected to be less reactive than their mnomers

  Oligomeric fraction is **not of safety concern for migration below 50 µg/kg food**

- **Restriction on the intended use** of the substance: in rigid PVC at ≤ 2% w/w and in PLA and PET at ≤ 5% w/w is not of safety concern for the consumer => **restricts the migration of oligomers below 50 ppb**

# OLIGOMERS - CASE 3

## Analysis in simulant(s): **crosslinker**

adipic acid dihydrazide for inner coating of plastics laminates

*(EFSA Journal 2015;13(1):3961)*

- To verify that no oligomers or other reaction products have penetrated the LDPE layer and migrated into food, **LC-MS** analysis **(+ and – mode)** was performed **on iso-octane and 95% ethanol** migration solutions
- No additional oligomers **compared to the blank LDPE** were detected

# OLIGOMERS - CASE 4

## Analysis in simulants: crosslinking co-monomer

1,7-octadiene to be used in all kinds of polyolefin *(EFSA Journal 2015;13(1):3979)*

- To explore the influence of the substance on the formation of oligomers and reaction products from the polymerization and manufacturing process, a **comparative migration test between LDPE made with- and without the crosslinker** was performed using 95 % ethanol

# OLIGOMERS - CASE 4 (CONTINUED)

- **GC/MS fingerprints** of the migration solutions were obtained; each consisting of a complex pattern of peaks and peak groups which were classified into different chemical classes and semi-quantified by use of an alkane standard
- **No indication of qualitatively** new substances formed and then migrating from the crosslinked LDPE sample

# OLIGOMERS - CASE 4 (CONTINUED)

- However, peaks and peak groups allocated to non-cyclic substances were considerably reduced for the crosslinked sample by factors of 2 – 4, whereas other peaks and peak groups assigned to cyclic substances increased by a factor of 25
- The potential migration of group of cyclic substances was estimated to be up to around **1 mg/kg food**

# OLIGOMERS - CASE 4 (CONTINUED)

- In the case of this crosslinking substance under evaluation, the functional olefinic groups are consumed by formation of new covalent bonds into the polymer network
- Oligomers or reaction products formed do not contain the substance latently, incorporation is irreversible
- Due to the complexity of the obtained GC/MS fingerprints with largely chromatographically unresolved substances it appears to be **virtually impossible to identify and quantitate each and every substance**.

# OLIGOMERS - CASE 4 (CONTINUED)

- This **compositional complexity will change** with polymerization process and from polyolefin to polyolefin and the present application is just one specific example
- polyolefin oligomers and other reaction products are likely to vary strongly in composition, depending on the polymerization and manufacturing processes used they were not evaluated by the Panel. **The evaluation of these oligomers and reaction products should be conducted case by case by the business operator**

# OLIGOMERS - CASE 5

## Analysis in simulant(s): **monomer**

1,10-decanediamine

*(EFSA Journal 2011; 9(2):2002)*

- **OM** (30 min/reflux/3 % AA) was < 1 mg/kg
- **GPC, FTIR, HPLC-UV/MS, GC/MS and HPLC/corona charged aerosol detector (CAD)** for identification and quantification.
- 5 largest peaks were oligomers containing the substance: highest migration was 21 ppb (MW= 548 Da) - four others and a few minor unidentified were estimated to migrate at or less than 10 ppb

# OLIGOMERS - CASE 5 (CONTINUED)

**Oligomers below 1000 Da containing the substance moiety migrate below 50 µg/kg**
=> tier 1 (genotoxicity)

- **Read across from monomers**
- Monomer is non-genotoxic *in vivo*
- Other co-monomers are authorised aliphatic diamines and carboxylic acids
- Low migration of the oligomers with a molecular weight below 1000 Da **does not raise a safety concern**

# OLIGOMERS - CASE 5 (CONTINUED)

**Restriction** "There is no safety concern if the substance is only used as a co-monomer for manufacturing polyamide articles for repeated uses in contact in aqueous, acidic and dairy foodstuffs at room temperature or for short term contact up to 150°C and its migration does not exceed 0.05 mg/kg food"

- **Restricted uses** such as repeated uses, t/T and food are expected to limit the migration of oligomers below 50 ppb

# OLIGOMERS – CASE 6

## Analysis in simulant(s): **monomer**

furan-2,5-dicarboxylic acid for manufacturing polyethylene furanoate (PEF)

*(EFSA Journal 2014;12(10):3866)*

- migration tests on PEF with 3 % AA, E10, E20, E50, E95 and isooctane
- Using **HS-GC/MS, FID; SPME, DCM -GC/MS**
- For E20 (20 % ethanol) most representative and still conservative) **60 ppb** (tier 1 genotoxicity)

# OLIGOMERS – CASE 6 (CONTINUED)

- **Read across from monomers**: absence of genotoxicity of the starting monomers, **no concern on genotoxicity for the oligomeric species identified**
- May be anticipated that the oligomers could be hydrolysed *in vivo* back to their starting substances. However, no data were available to demonstrate this.
- **Restriction** "migration of the oligomers less than 1000 Da does not exceed 50 µg/kg food"

# OLIGOMERS – CASE 7

**Analysis of the LMWF in simulant(s)**: **polymeric additive** ethylene-vinyl acetate copolymer wax *(EFSA Journal 2014;12(2):3555)*

- Specific migration of LMWF was estimated for LDPE containing the copolymer in simulants such as 95 % ethanol and olive oil
- Analysis by **GC/FID and by GPC**, along with migration modelling, migration of the LMWF was conservatively estimated to be up to ca. 5.8 mg/kg (tier 2: 90-d tox study, etc.)

# OLIGOMERS – CASE 7 (CONTINUED)

- **Read across** from related polymeric additive: oral 120-d rat study with NOAEL of 80 mg/kg bw/ day: sufficiently large MoS (approx 1000) compared to max 5 mg/kg food - In line with supportive data from subchronic studies on oxidised polyethylene waxes
- No data on potential accumulation but taking into account likely hydrolysis to an ethylene-vinyl alcohol copolymer chain, the Panel considered as supporting evidence results from the studies on oxidised polyethylene waxes => accumulation in man not anticipated

# OLIGOMERS – CASE 7 (CONTINUED)

- Restriction: "…does not raise a safety concern if the substance is used **up to 2 % w/w** in only polyolefin materials and articles and the **migration of LMWF <1000 Da does not exceed 5 mg/kg food**."
- Restriction in use **+** migration limit on oligomers

# OLIGOMERS – CASE 8

**Analysis in simulant(s): polymeric additive** methacrylic acid, 2,3-epoxypropyl ester, copolymer with acrylic and/ or methacrylic acid alkyl (C1-C4) esters for use in PVC coatings for food cans *(EFSA Journal 2012;10(5):2744)*

- Migration of LMWF <1000 Da into simulants was determined by GPC
- Migration of LMW oligomers, containing GMA or hydrolysed GMA unit, into 10 % and 50 % ethanol by **GC/MS (GMA, EMA), LC/MS/MS (GMA.$H_2O$) analysis**

# OLIGOMERS – CASE 8 (CONTINUED)

- Migration was up to 16 µg/ 6 dm² => tier 1 (genotoxicity), chlorinated oligomeric species were not detected at LOD of 0.5 µg/6 dm²
- **Oligomers <1000 Da** and corresponding chlorinated oligomers **were tested**
  - In *in vitro* and *in vivo* genotoxicity tests
  - In a 90-day oral rat study => NOAEL for o-EMA-GMA considered to be 150 mg/kg bw/day (why a 90-d if 16 ppb migration?)
- **Restriction on use**, substance "is not of safety concern if used in PVC coatings up to 25 %", restricts the migration of oligomers

# CONCLUSION: SOME PATHWAYS

**Analysis in POLYMER** ⟷ **AND/OR** ⟷ **Analysis in SIMULANTS/FOODS**

- Low Molecular Weight Fraction (LMWF)
- Size Exclusion Chromatography (SEC)

**Migration evaluation**

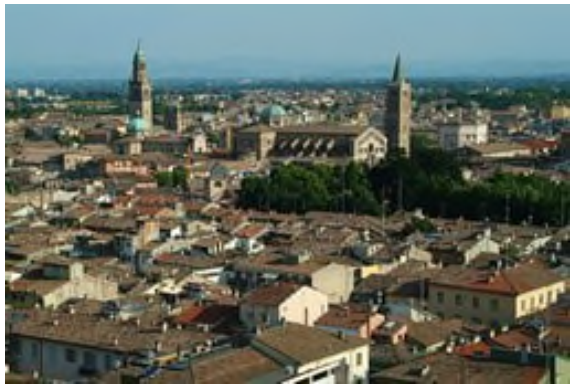
- Total mass transfer of LMWF
- Modelling of the distribution (EC, 2012)

- With or without comparison with polymer without the substance
- GPC, GC/MS, FID, LC/MS, UV, etc.

**Toxicological evaluation**

- Hydrolysis, loss of functional group
- Read across (e.g. with monomer, related substances)
- Toxicological tests (easier for polymeric additives)

# THANK YOU FOR YOUR ATTENTION



***Any comments, questions?***

***Let us contribute together to a safe food…***