Examples of EFSA’s safety evaluation of oligomers

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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*
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 monomers.

  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**
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.
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
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.
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.
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.
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.**
Analysis in simulant(s): monomer
1,10-decanediamine

- **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 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
Analysis in simulant(s): monomer

carboxylic 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)
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”
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.)
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
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
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.H2O) analysis
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)

Toxicological evaluation

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

- 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...