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Risk Assessment on Food Contact Materials

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The CHALLENGE OF packaging MATERIALS

Emerging materials

- Active materials
- Intelligent materials
- Natural materials
- Bio-based mat.

Several Materials

- **PET** (bottles, trays, films)
- Polyolefins (HDPE, LDPE, PP…)
- Multilayers, adhesives,…
- Aluminium, varnishes,…
- Paper, printing inks…
- Wax
- Silicones
- Cork
- wood

Potential migrants

- Monomers and additives
- Contaminants from the first use
- Contaminants from the collection system (cross cont.)
- Degradation compounds from additives and polymer
- NIAS (oligomers and others)
- Metals/organometallic compounds……
- Pesticides
- Phytosterols…

SUSTAINABILITY

Mechanical recycling
Chemical recycling

Regulation 10/2011/EU on FCM&FCA
USP & EMA guidelines

FCM AND FOOD SAFETY
ARE THESE CONCEPTS COMPATIBLE?

- Leachables/migration lower than 0.15 ppb if the compounds are CMR
- Leachables/migration lower than 10 ppb for non authorized substances
- NIAS analyzed, declared and under control
- No toxic substances present
- All materials need to be evaluated

CRITICAL POINTS

- > 10.000 POTENCIAL MIGRANTS from FCM
- Identify all migrants
- Quantify all migrants
- Toxicity?
- Toxicity of mixtures?
- Identify the origin of migrants (safety-by-design)
- Responsibility of operator in the chain.

CONTROL iS ESSENTIAL!!

Substances of special concern from FCM

- Mineral oils: **MOAHs**
- Endocrine disruptors: (PFAS, PFOAS), surfactants, phthalates, bisphenol A, F, S… and derivatives,…
- Plasticisers
- PAHs (polyaromatic hidrocarbons)
- Oligomers.
- Microplastics and nanoplastics in food
- Nanomaterials/nanoparticles

Scientific evidences

- Migration of plasticisers (phthalates, ATBC, trimellitates, ESBO, …
- Migration of surfactants from adhesives used in multilayers (surfynol,…)
- Migration of oligomers (BADGE, …polyamide oligomers, …)
- Migration of Bisphenols (BPA, BPS,…)
- Migration of primary aromatic amines (PAAs)
- Migration of biocides: triclosan, BIT, MIT,CMIT (methylisothiazolinone, benzyl…chloromethyl…)
- Migration of PFOAS/PFOAS
- Migration of MOAHs
- Migration of photoiniciators (printing inks)

- Endocrine disruptors
- Reprotoxicity/infertility
- Cancer
- Obesogens
- Allergies
- citotoxicity

The weak signals

- Materials should be used for the purpose they were designed and sold
- NO evidence of influence of Al on Alzheimer. But SML for Al is 1 mg/Kg
- NO evidence of health affection from WAX
- Toxicity always studied for individual compounds, but toxicity of mixtures is never studied
- Migration of metals: ions?, organometals?, pure metals?
- Bioavailability of migrants: How is their behaviour in our body?

NIAS from PU adhesives in multilayer

[PET//FoilAl//PA//CPP]$_{FCS}$

	rt exact mass	Adduct	Compound Molecular Formula	Ethanol (10%) µg/Kg	Acetic acid (3%) µg/Kg	Ethanol (95%) µg/Kg
1	2.73_ 114.0922	$[MNa]^+$	Caprolactam $C_6H_{11}NO$	882±44	1040±170	1300±127
2	3.05 257.0999	$[MNa]^+$	**AA-DEG + H_2O (lineal ester)** $C_{10}H_{16}O_5 + H_20$	nd	51.2±10.1	nd
3	3.55 239.0905	$[MNa]^+$	**AA-DEG (cyclic ester)** $C_{10}H_{16}O_5$	366±38	57.9±11.9	759±72
4	4.93 237.1108	$[MNa]^+$	AA-NPG (cyclic ester) $C_{11}H_{18}O_4$	1.98±0.70	nd	1.50±0.30
5	5.23 281.1380	$[MNa]^+$	AA-dHAE (C_7) (cyclic ester) $C_{13}H_{22}O_5$	344±13	40.2±10.0	687±55
6	5.50 445.1492	$[MNa]^+$	PA-EG-AA-EG (cyclic ester) $C_{18}H_{20}O_8$	34.8±0.9	7.99±1.36	45.5±4.8
7	5.63 453.2098	$[MNa]^+$	AA-DEG-AA-NPG (cyclic ester) $C_{21}H_{34}O_9$	25.7±0.8	nd	25.1±2.6
8	5.96 473.1801	$[MNa]^+$	PA-DEG-AA-NPG (cyclic ester) $C_{23}H_{30}O_9$	38.8±1.6	7.84±1.52	60.1±6.1

AA: adipic acid; PA: phthalic acid; DEG: diethylene glicol; NPG: neopentilglycol; EG: ethyleneglycol; dHAE: dihydroxyalkyl ether; nd: non detected

All lactones (cyclic esters) are CLASS III of toxicity according to CRAMER list

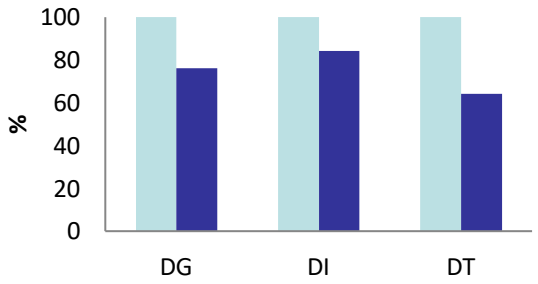
Lactones /NIAS should be [x] < 10 µg/Kg

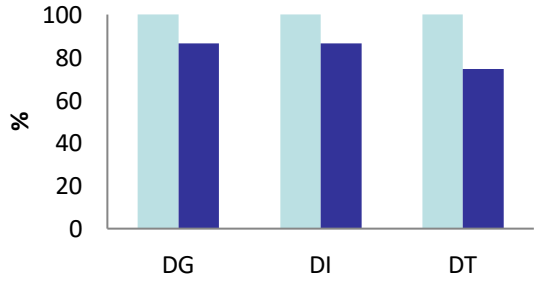
What happens with oligomers in our body?

- Behaviour of chemicals under similar conditions as those happening in the body (oral intake)
  - Gastric simulation
  - Intestinal simulation

Performance in Digestion

GASTRIC simulation:
HCl **0,07 M (pH ~1**) , 37ºC, 1-4 h





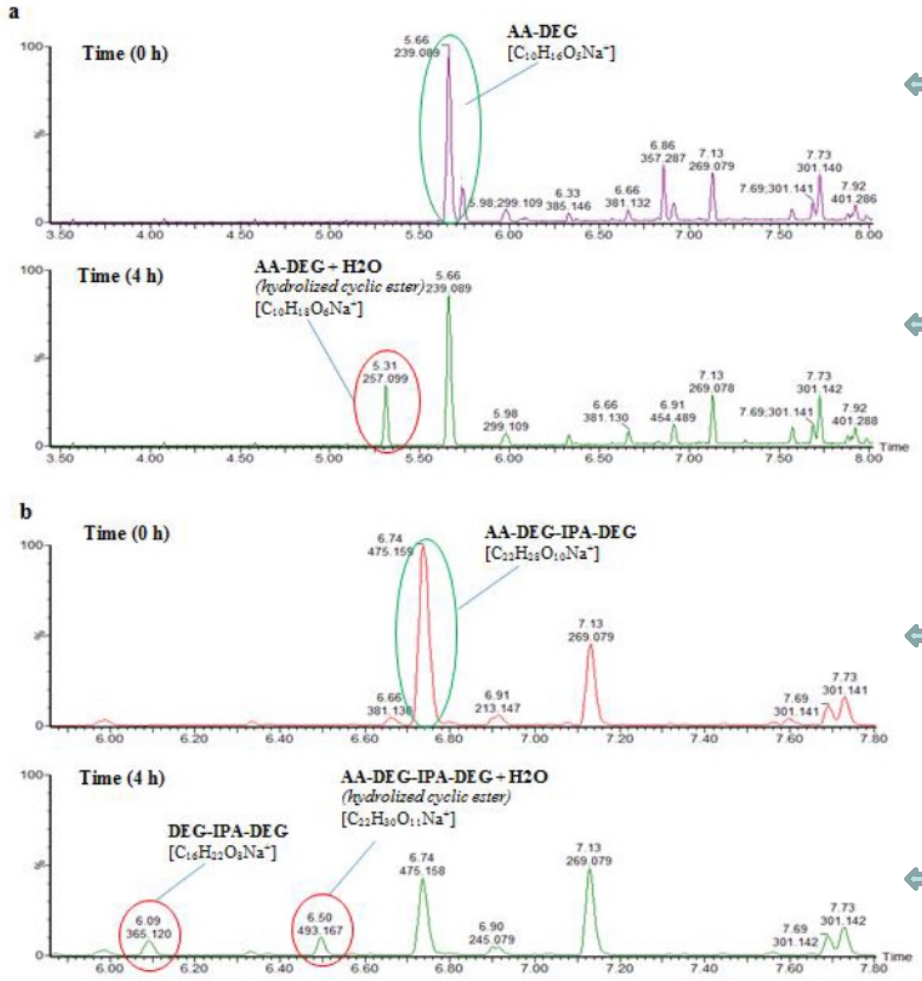
INTESTINAL Simulation:
Pancreatic extract
(KH2PO4, Taurocholate sodium , NaOH)
(pH a 7,5±0,1), 37ºC, 1-4 h

- **AA-DEG:**
  - Gastric Digestion : 24 % de disminución
  - Intestinal Digestion: 16 % de disminución
  - Total DIgestion: 36 % de disminución

- **AA-DEG-IP-DEG**
  - Gastric digestion:: 14 % de disminución
  - Intestinal DIgestion: 14 % de disminución
  - Total Digestion: 25% de disminución

None of them were 100% degraded during digestion

Results of Gastric Digestion
Time 0 and after 4 hours



Lactone G (AA-DEG)
$[C_{10}H_{16}O_5Na^+]$

Class III

Lactone G + H2O (lactone hidrolized)
$[C_{10}H_{18}O_6Na^+]$

Class I

Lactone AA-DEG-IPA-DEG
$[C_{22}H_{28}O_{10}Na^+]$

Class III

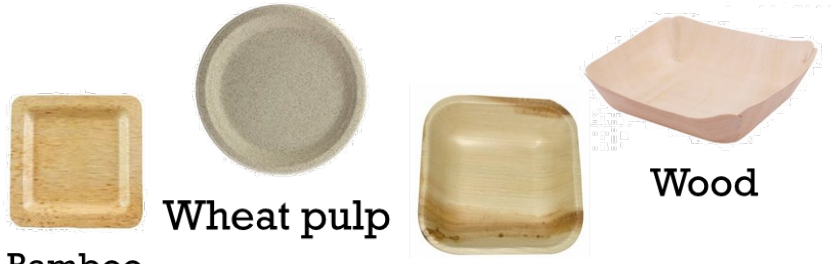
Lactone AA-DEG-IPA-DEG
$[C_{22}H_{30}O_{11}Na^+]$ hydrolized
$[C_{16}H_{22}O_8Na^+]$

Class I

Sara Ubeda, Margarita Aznar, Anna Kjerstine Rosenmai, Anne Marie Vinggaard, Cristina Nerín. Migration studies and toxicity evaluation of cyclic polyesters oligomers from food packaging adhesives. *Food Chemistry.* ***2020****, 311, 125918. DOI:10.1016/j.foodchem.2019.125918*

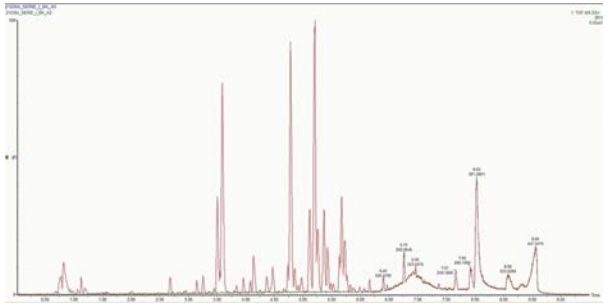
Emergent polymers

- **Wheat pulp and wood dishes are safe** for single-use purposes
- These materials **contained common additives found in plastic** materials
- Most of the migrants **detected from the bamboo utensils were melamine** and its derivatives
- Bamboo-based utensils tested **do not comply** with the EU legislation

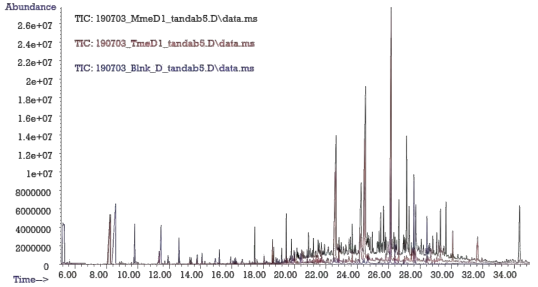


Migration studies
Directive (UE) 10/2011

Dry foods
Hydrophilic/acid foods
Lipophilic foods



Non-volatile compounds
UPLC–ESI-Q-TOF-MS



Volatile compounds
SPME-GC-MS

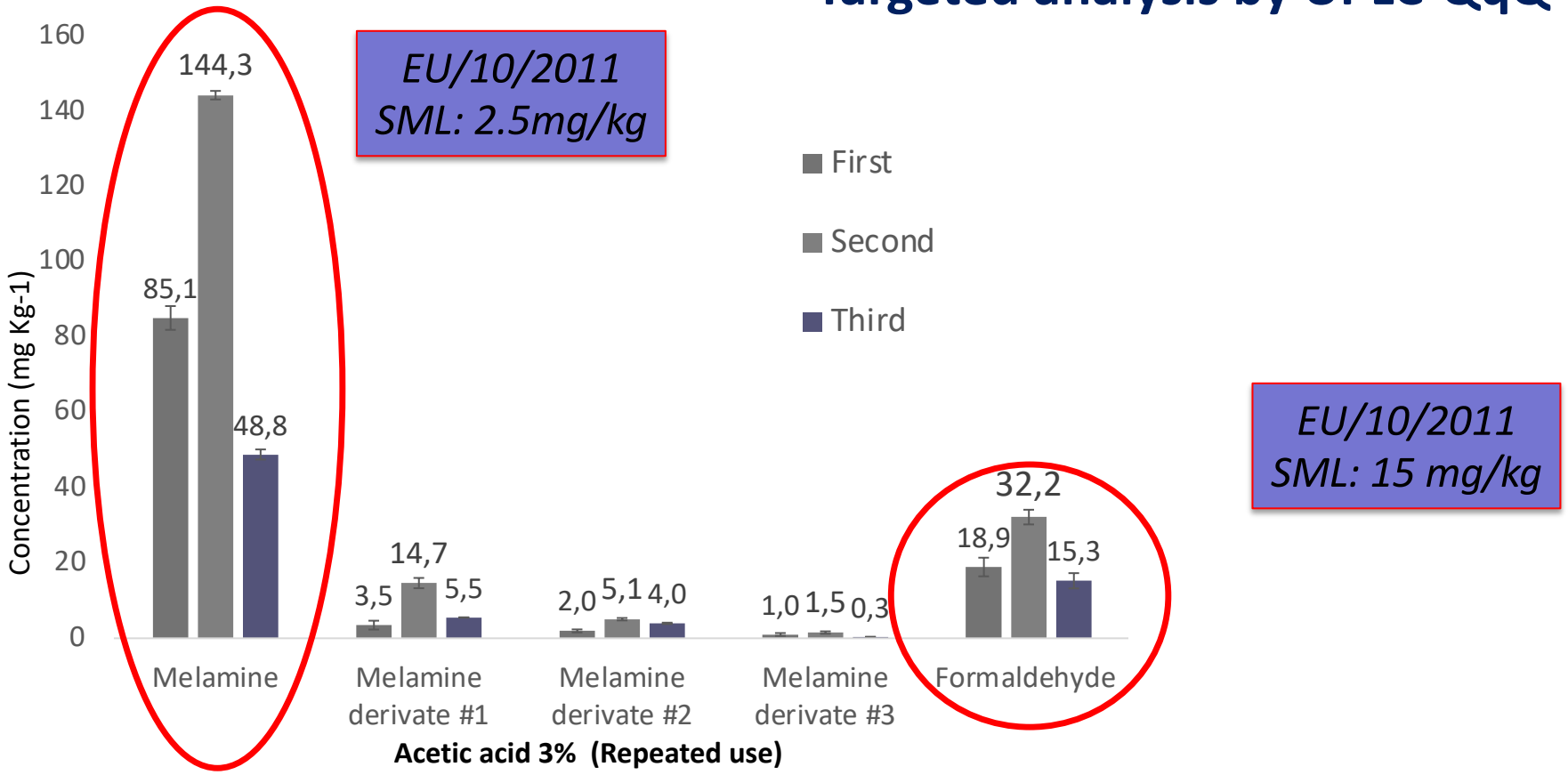
UPLC-MS-QTOF

“Bamboo” kitchenware/tableware

Bamboo powder was used as filler in melamine

Quantification: Melamine and formaldehyde (3 sequential migrations)

Targeted analysis by UPLC-QqQ



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Recycled materials

GUIA group

- > 450 compounds found in migration in mixed polyolefins, 39.2 % were food related and 24.1 % were found as saturated hydrocarbons, fatty acyls, or prenol lipids
- Some compounds exceeded their specific migration limits in polyolefins
- 265 substances were detected in migration in rHDPE milk bottles
- Washing the rHDPE twice and applying extra decontamination techniques reduced most chemicals detected, including two toxicity level V substances

Mixed polyolefins

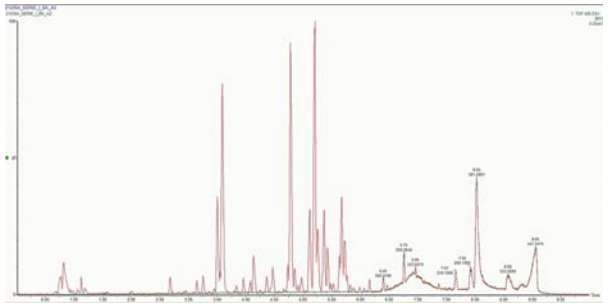
Flakes Pellets

Migration studies
Directive (UE) 10/2011

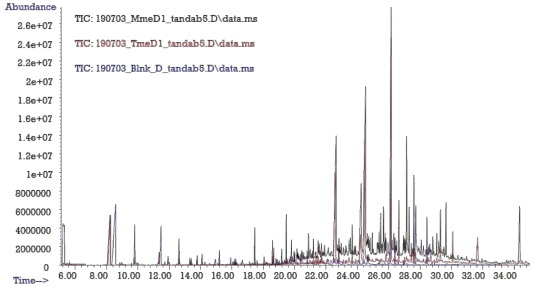
rHDPE milk bottles

Flakes Pellets

Dry foods
Hydrophilic/acid foods
Lipophilic foods



Non-volatile compounds
UPLC–ESI-Q-TOF-MS

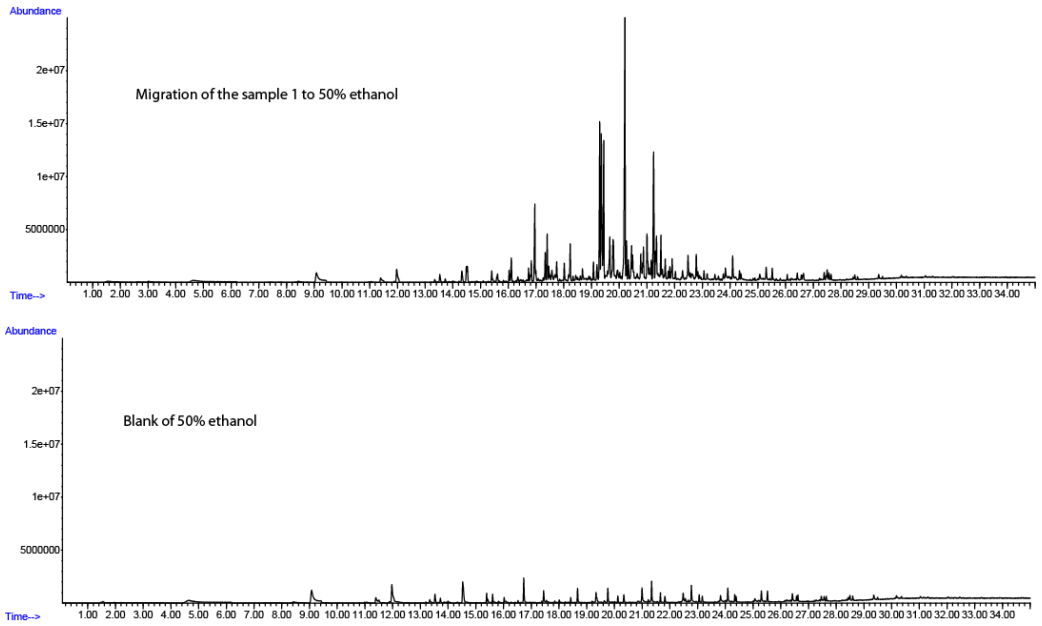


Volatile compounds
SPME-GC-MS

https://doi.org/10.1021/acs.analchem.2c05389

Su et al. Anal. Chem., 2023

Migration from rHDPE to milk

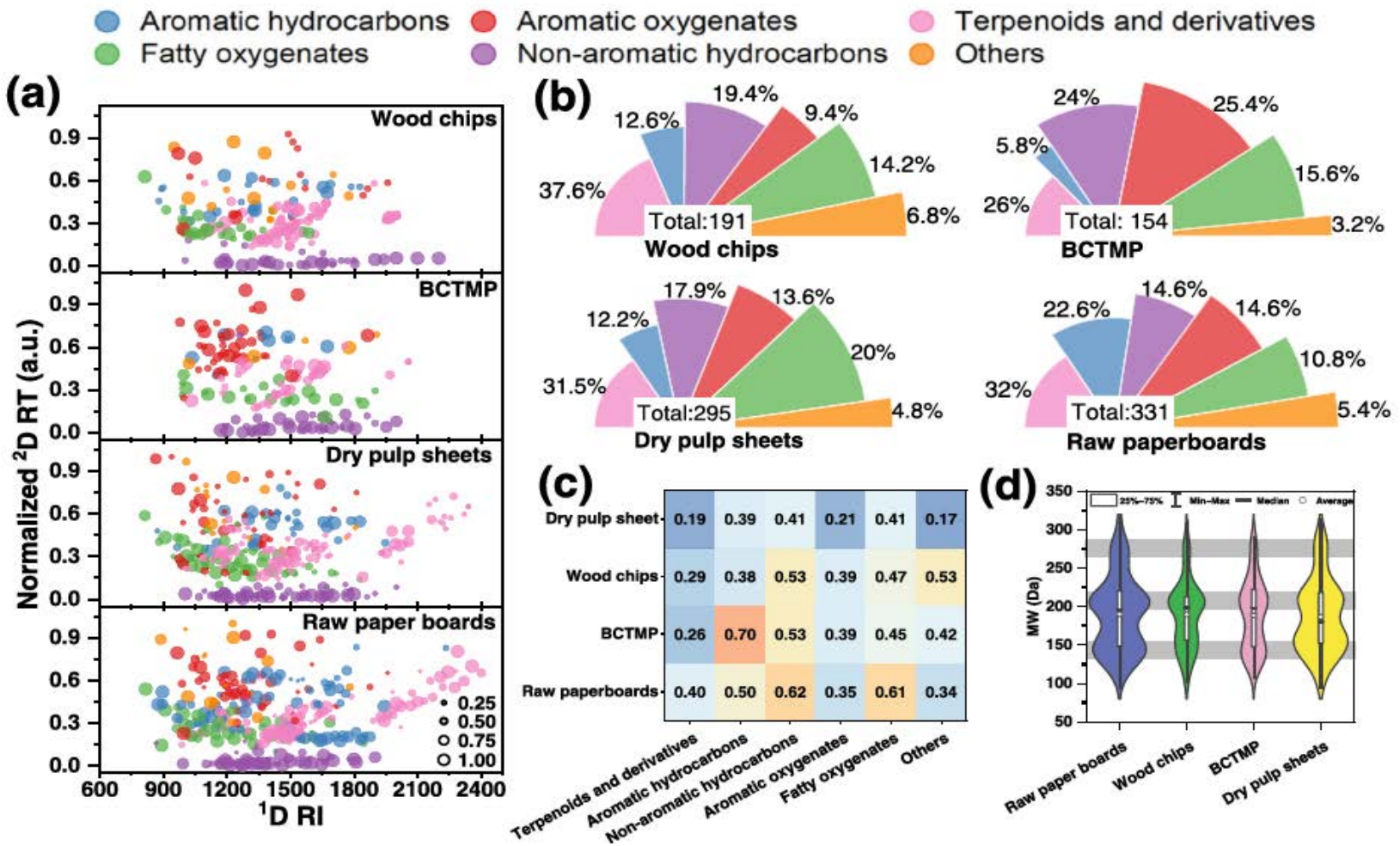


№	Compound	Migration to skimmed milk ng/g		Migration to soy milk ng/g		Migration to horchata ng/g		SML EU/10/2011 ng/g	Cramer toxicity
		Sample 1	Sample 2	Sample 1	Sample 2	Sample 1	Sample 2		
4	Diphenyl ether	0.18±0.02	0.16±0.04	0.12±0.01	0.58±0.15	0.20±0.03	0.07±0.01		III
6	Naphthalene, 2-methoxy-	<2.76	<2.76	<0.78	<0.78	<0.78	<0.78		III
7	2,5-Cyclohexadiene-1,4-dione, 2,6-bis(1,1-dimethylethyl)-	0.26±0.01	<0.24	<0.24	<0.24	<0.24	<0.24		II
9	Butylated Hydroxytoluene	0.26±0.02	0.26±0.02	<0.22	0.24±0.02	<0.22	<0.22	3000	
10	2,4-Di-tert-butylphenol	<0.25	0.35±0.04	<0.25	<0.25	<0.25	<0.25		I
18	Dodecanoic acid, ethyl ester	<0.65	<0.65	<0.65	1.72±0.21	<0.65	<0.65		I
27	n-Hexyl salicylate	<1.18	<1.18	5.36±0.32	18.8±2.0	<1.18	<1.18		I

migration to 50% ethanol analyzed by HS-SPME-GC-MS

Migration to skimmed milk, soy milk and horchata

Volatile compounds found from paper



BCTMP= Bleach chemi-thermo-mechanical pulp

Origin:

- Natural/raw materials
- Process
- processing aids
- Functional additives (IAS)
- Degradation compounds

Hanke et al, Food Packaging and Shelf Life 37 (2023) 101062

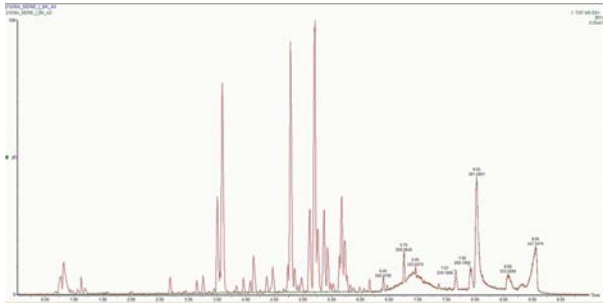
Bio-based polymers

- **21 volatile NIAS were determined** in a novel starch-base biopolymer
- **37 different compounds were detected** in PLA+PE biopolymer
- Intentionally added substances **(NIAS)**: lubricants, plasticizers, slip agents, and antioxidants.
- NIAS: **oligomers**
- A re-formulation of the starch-based material is needed for foods with lipophilic character
- **Most of them are not compostable/biodegradable in the environment**

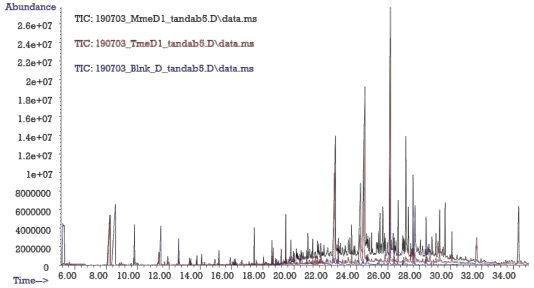
Polylactic acid (PLA)+polyester film

Migration studies
Directive (UE) 10/2011

Dry foods
Hydrophilic/acid foods
Lipophilic foods



Non-volatile compounds
UPLC–ESI-Q-TOF-MS



Volatile compounds
SPME-GC-MS

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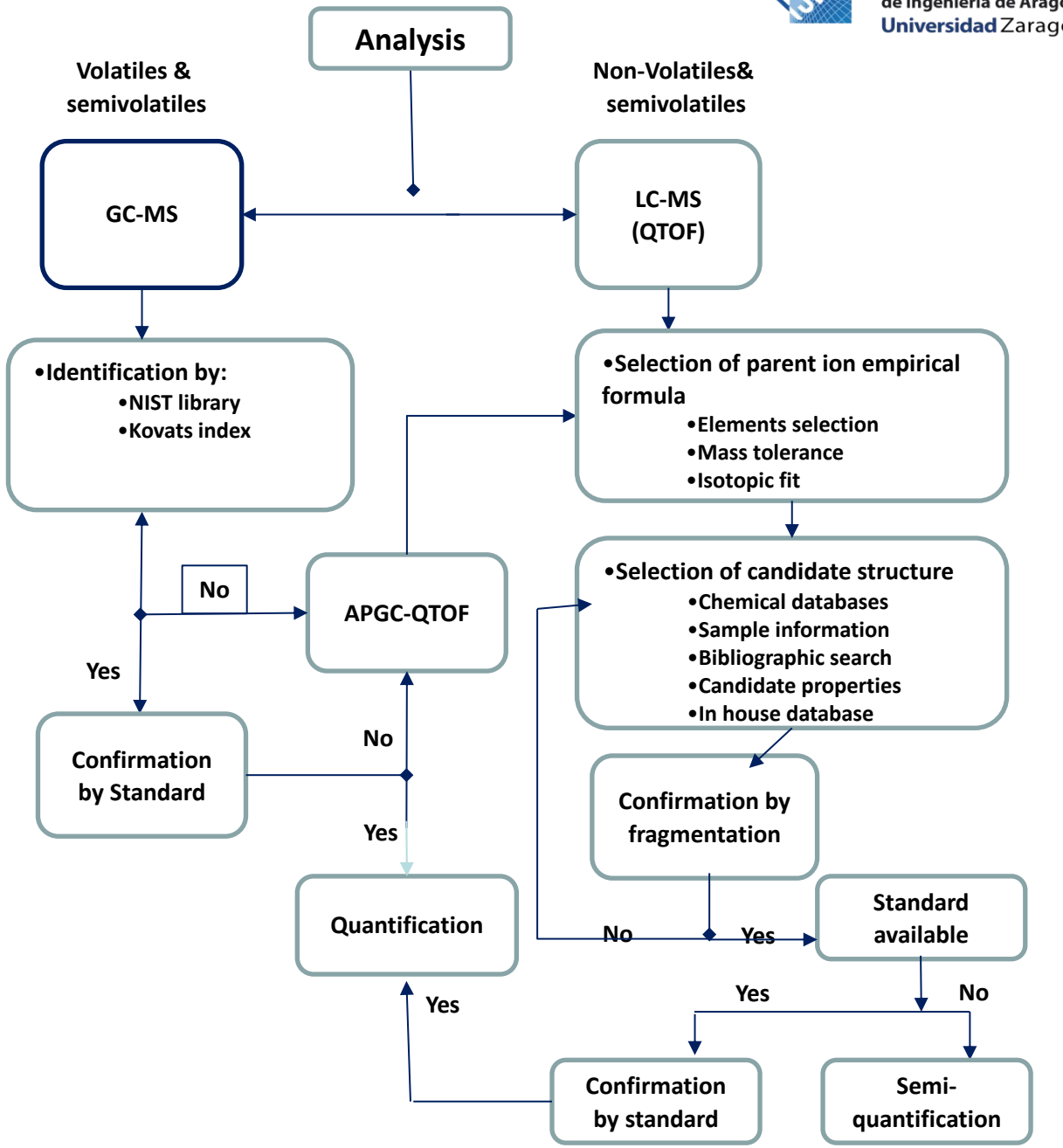
Decision tree for the analytical procedure in NIAS identification

Sample preparation

Screening Analysis



C. Nerin*, P. Alfaro, M. Aznar, C. Domeño
Anal. Chim. Acta. Volume 775, 2 May 2013, Pages 14–24
DOI:10.1016/j.aca.2013.02.028. 2013

C Nerin et al. Food Additives & Contaminants: Part A
DOI: 10.1080/19440049.2021.2012599

Limitations of screening

- **Many compounds aren't detected in the screening**
  - Mineral oils (MOHs, MOAHs)
  - Primary Aromatic Amines
  - Formaldehyde, acetaldehyde,…
  - Bisphenol A
  - Organotin compounds
  - BADGE-HCl and BADGE-diols
- **Absence of standards to confirm the identification & quantification**
- **Detection limits are not enough. 1-10 ppb is required for all migrants!**
- **Confidence limit of identification**

Identification using LIBRARIES

In-House library (UNIZAR) in UPLC-IMS-QTOF

Using certified/pure standards in our lab. Experimental CCS values

+

Prediction models for Retention time and CCS (developed in UNIZAR)

Mol file + **RT** + **CCS**

CPPdb (chemicals associated to plastic packaging) from Groh et al. DOI: 10.1016/j.scitotenv.2018.10.015

FCCdb (food contact chemicals database) from Groh et al. https://doi.org/10.5281/zenodo.3240108.

> 10,000 compounds with CCS and RT in the library

Song et al. J. Agric. Food Chem. 2022, 70, 9499−9508

In-House library (UNIZAR) in UPLC-QTOF-MS

In-house MS/MS library and *mspcompiler* R package which contains 449 and 172 food packaging associated chemicals in positive and negative mode has been built. It Will be in public domain and available in https://zenodo.org/record/4454648

Su et al. Anal. Chem, 2023

RISK ASSESSMENT OF NIAS

EUROPEAN LEGISLATION
(EU/10/2011)

NATIONAL
LEGISLATION

TOXICITY REPORTS

NO TOXICITY DATA

Threshold of Toxicological Concern (TTC) approach
(not suitable for carcinogenic, mutagenic or reprotoxic compounds)

CRAMER RULES

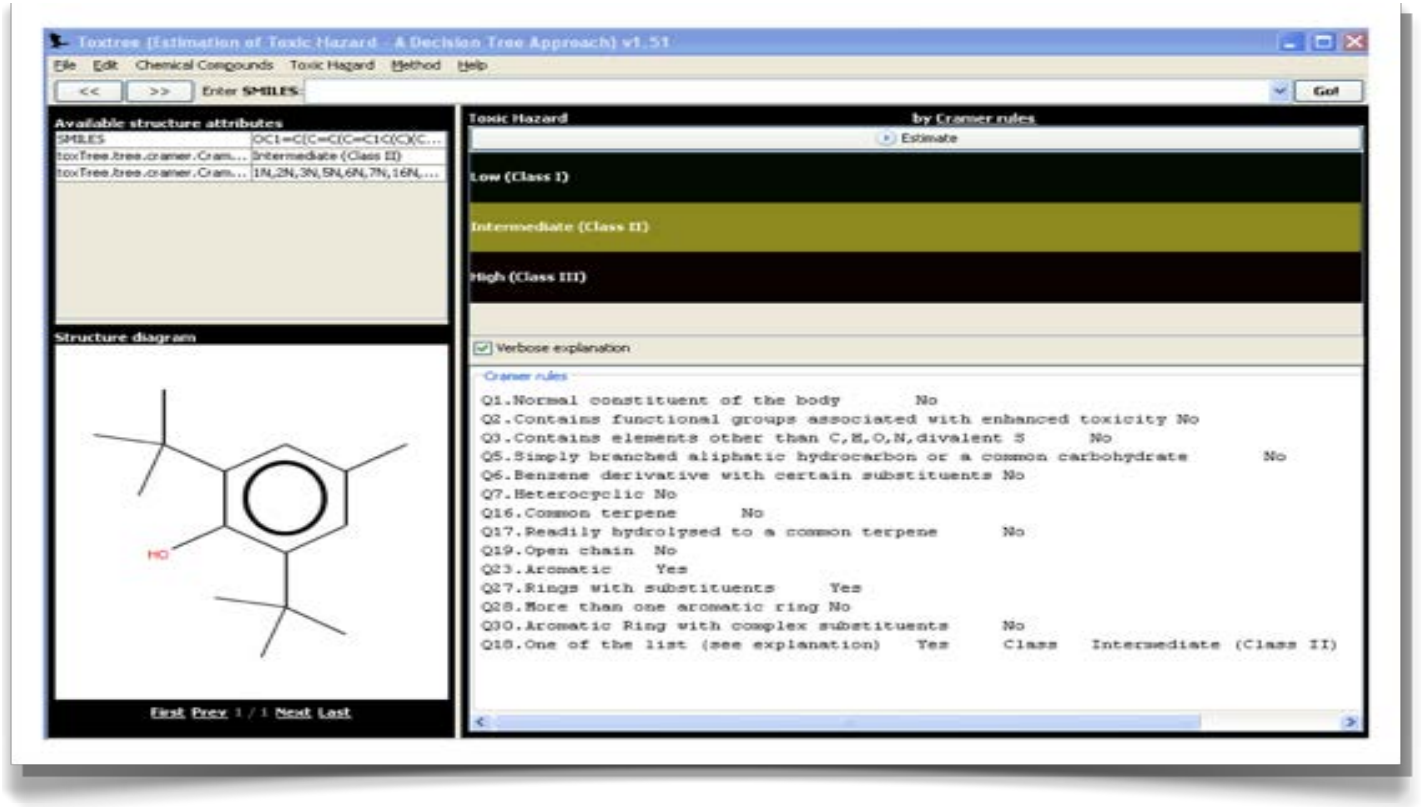
Threshold of Toxicological Concern

TOXICITY CLASIFICATION-Cramer rules (Toxtree v1.51)

Class I (Low)
<1.8 mg/person/day

Class II (Medium)
<0.54 mg/person/day

Class III (High)
0.09 mg/person/day



EDI (Estimated Dayly Intake) (mg/person/day)= Mig (mg/Kg) x 3 Kg /day/person x CF

Harmonization of Risk Assessment and Risk Management

Risk = Hazard x exposure

- Risk = 0 doesn’t exist
- What value could be accepted by legislators?
- What value could be accepted by consumers?
- What happens with the global food market?

Several considerations on Risk Assessment (in EU)

- The food (targets) is presumed to be **consumed daily by a 60 kg adult up to 1 kg, which is adjusted to 0.75 kg for children (5 kg body weight)**

- **Any unknown substance** (NIAS, residues) should be treated as potentially **genotoxic** (maximum exposure 0.0025 µg/kg body weight/day)

- **Exposure only covers ingestion** via contamination **by plastic packaging**; **other materials exist** (papers, cardboard, elastomers, varnishes), and **other exposure sources** are possible through skin absorption and ingestion

Conclusions

- The **number of migrants** from **packaging materials** can be very high.
- **Although Risk Assessment needs to be applied, clear definition of many details are missing.**
- **Exposure of all materials needs to be taken**
- **Identification of any migrant is required. Then, Databases and libraries as well as experience are extremmely important for identifying the chemicals.**
- **HARMONIZATION OF RISK ASSESSMENT WORLDWIDE SHOULD BE DONE.**

ILSI organizes a workshop 17th and 18th April 2024 in Brussels to discuss harmonization on RA&RM

Interesting References

- **An Overview** of Approaches for Analysing NIAS from different FCMs
https://ilsi.eu/publication/an-overview-of-approaches-for-analysing-nias-from- different-fcms/

- **Guidance** in selecting analytical techniques for identification and quantification of non-intentionally added substances (NIAS) in food contact materials (FCMS)

  Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2022 Mar;39(3):620-643. doi: 10.1080/19440049.2021.2012599. Epub 2022 Jan 26.

R+D+i Projects

(the latest ones)

- **NATURALPACK (INTERREG)**
- **MIGRESIVES Project (EU, VI FP, Collective Research Project)**
- **NAFISPACK Project (EU, VII FP)**
- **SAFEMTECH (EU, IAPP, Marie Curie)**
- AGL-04363 and AGL- 2012-37886 (Spanish Ministry of R&D&i)
- 4 INNPACTO Projects (Spain)
- ACTIBIOPACK
- NANOFLEXIPACK
- AGL-2015
- RTI-2018
- (RTC2019-007161-2)
- TED2021-129138B-C21
- PID2021-128089OB-I00
- FOODYPLAST (EU)
- POCTEFA-ALERT-PYR 2024-2027
- Several Companies…

- Instituto de Investigación en Ingeniería de Aragón (I3A)
- Gobierno de Aragón

Grupo GUIA (T53_23R) and
Fondo Social Europeo

GUIA group, University of Zaragoza, Spain

Muchas gracias

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