Over-Extraction and Clinical Relevance?

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BI 2026 Presentation-Copenhagen

Scope of Presentation (Inverse Pyramid)

A. *What are the major scientific issues in chemical characterization of medical devices (ISO 10993-18) today?*

B. *How do solvent choices affect uncertainties of identification and quantification?*

C. *"Over-extraction", clinical relevance and tox assessment?*

D. *What are the extraction powers of human tissues?*

E. *How to streamline extraction solvents based on power of biological tissues?*

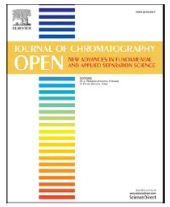
Technical contents of presentation are based on my #13 publication on Chemical Characterization

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Journal of Chromatography Open

journal homepage: www.elsevier.com/locate/jcoa



A critical review and analysis of thermodynamic and kinetic effects on extraction of medical devices by organic solvents as a sample preparation step in devices' chemical characterization

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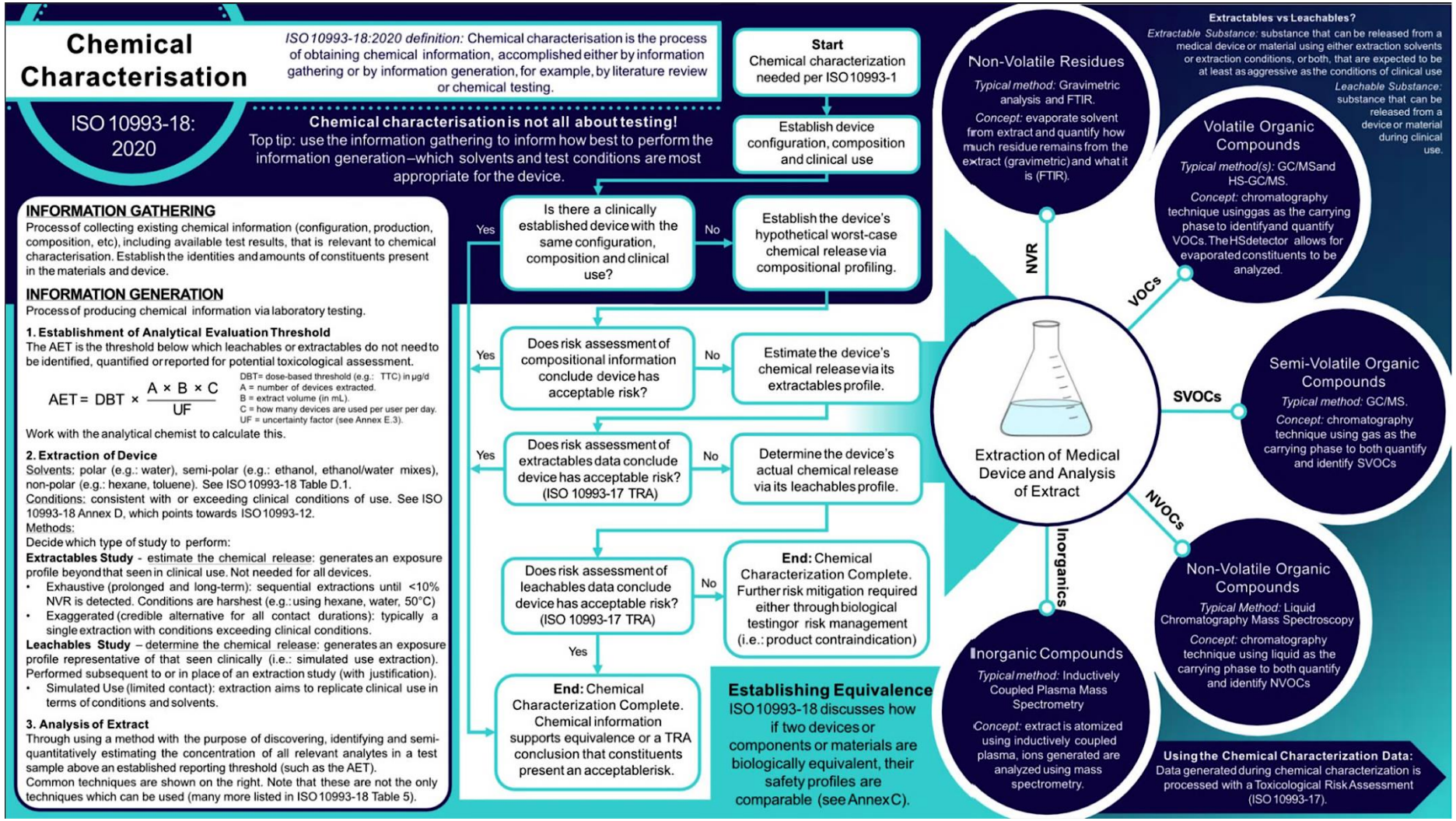
ARTICLE INFO

Keywords:
Extractables
Leachables
Chemical characterization of medical devices
Extraction solvents
Simulating solvents
Abraham's solvation parameter model

ABSTRACT

The extraction of medical devices by organic solvents as a sample preparation step is perhaps the most critical process in chemical characterization of medical devices, as the decision of solvent choice determines not only the resulting extractables profiles (e.g., the number, molecular weight, and concentration of extractables), but also the degree of analytical challenges in identification and quantification, when performing instrumental analysis of extracts. Both concentration and chemical identities of all extractables are used in subsequent toxicological risk assessment, which is required to support regulatory submission and approval of medical devices. There is currently a considerable debate on which solvent(s) should be used to balance the desired extraction and clinical relevance to biological tissue exposure due to scientific and regulatory consequences. The purpose of this article is intended to streamline solvent selection in chemical characterization, particularly on the rational development of a semipolar solvent to stimulate or exaggerate biological (storage) fatty tissues. A comprehensive review and analysis of solvent extraction of polymer materials from thermodynamic and kinetic perspectives is provided first. The solvent-material interactions (swelling) and their consequences on kinetics and thermodynamics are subsequently elaborated. The conclusions of thermodynamic and kinetic properties, together with solvent-material interactions, are used to establish solvent similarity criteria between semipolar solvents and fatty tissues. Finally, solvent solubility, degree of material swelling by solvents, diffusion coefficients in device material, partition coefficient between material and solvent, and solvent compatibility with instrumental analysis are used as the criteria to establish representative solvents to fatty tissues in chemical characterization studies. Blood simulating solvents are well established and not discussed in the article.

Processes of ISO 10993-18 - Sounds Elegant on Paper?



What are the measurement errors associated with the decisions for:

1) *Extraction solvents?*
2) *Untargeted analysis?*

By Leah Williams, PhD:
https://www.linkedin.com/feed/update/urn:li:activity:7475518129398378496/?updateEntityUrn=urn%3Ali%3Afs_updateV2%3A%28urn%3Ali%3Aactivity%3A7475518129398378496%2CFEED_DETAIL%2CEMPTY%2CDEFAULT%2Cfalse%29

The Cornerstones of Chemical Characterization

Chemical Characterization



Extraction?



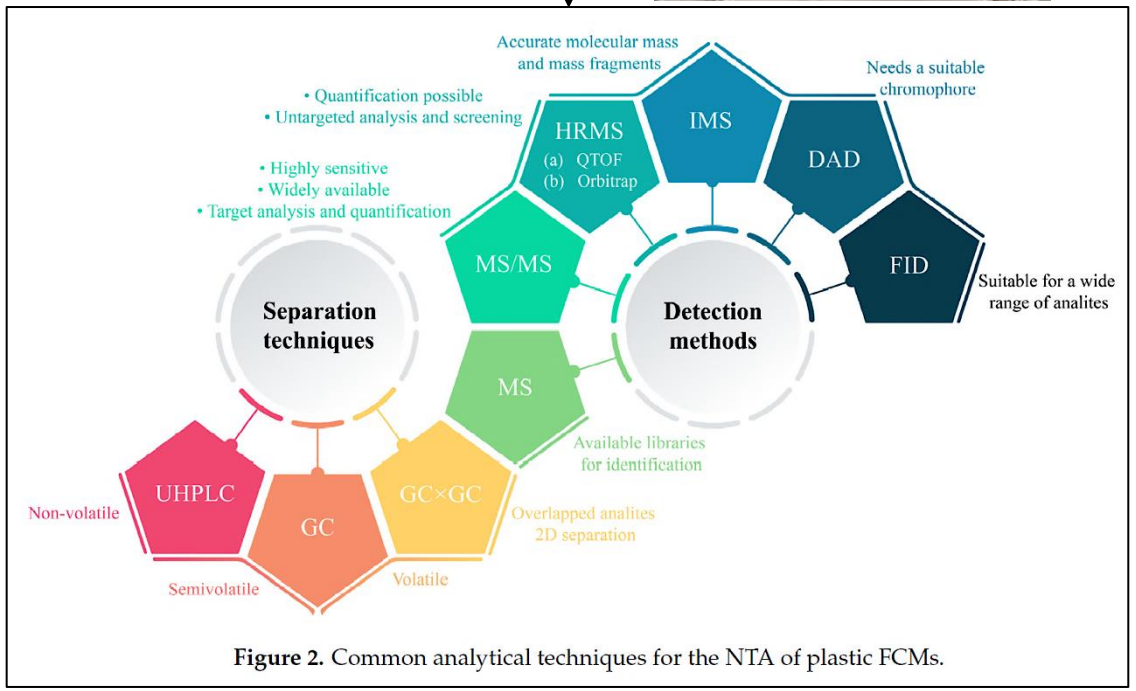


Figure 2. Common analytical techniques for the NTA of plastic FCMs.

Miralles, Pablo, et al. "Recent Trends and Challenges on the Non-Targeted Analysis and Risk Assessment of Migrant Non-Intentionally Added Substances from Plastic Food Contact Materials." *Toxics* 13.7 (2025): 543.

Major Scientific Issues

The Major Scientific Issues (1): *Solvent Choices*

V. Test Article Extraction

A. Extraction Conditions

Extraction conditions should be chosen to obtain worst-case estimates of amounts of analytes in the device to which the tissue may be exposed. You should provide a rationale for the extraction conditions selected that addresses the device exposure time and type of tissue contact. The recommended extraction approaches are provided in Table 1, which was adapted from ISO 10993-18 Table 2.

Table 1. Recommended extraction conditions.

	Duration of Contact		
	Limited (< 24 h)	Prolonged (1-30 days)	Long-Term (> 30 days)
Extraction duration/ number of cycles	Exaggerated[a] extractions or clinically relevant worst-case conditions	Exhaustive or exaggerated[a,c] extractions	Exhaustive or exaggerated[a,c] extractions
Types of solvents	Polar and non-polar[b]	Polar and non-polar[b]	Polar, semi-polar, and non-polar
Non-volatile residue (NVR) analysis recommended to demonstrate exhaustion	N/A	Yes	Yes

[a] We recommend that exaggerated conditions exceed both time and temperature of clinical use.[16]

[b] If a device cannot be evaluated in an analytically expedient polar or non-polar solvent, biological testing may be needed, but in some cases other solvents may be used with justification (Other considerations for extraction solvents can be found in Appendix B, Section IX.A.(3)).

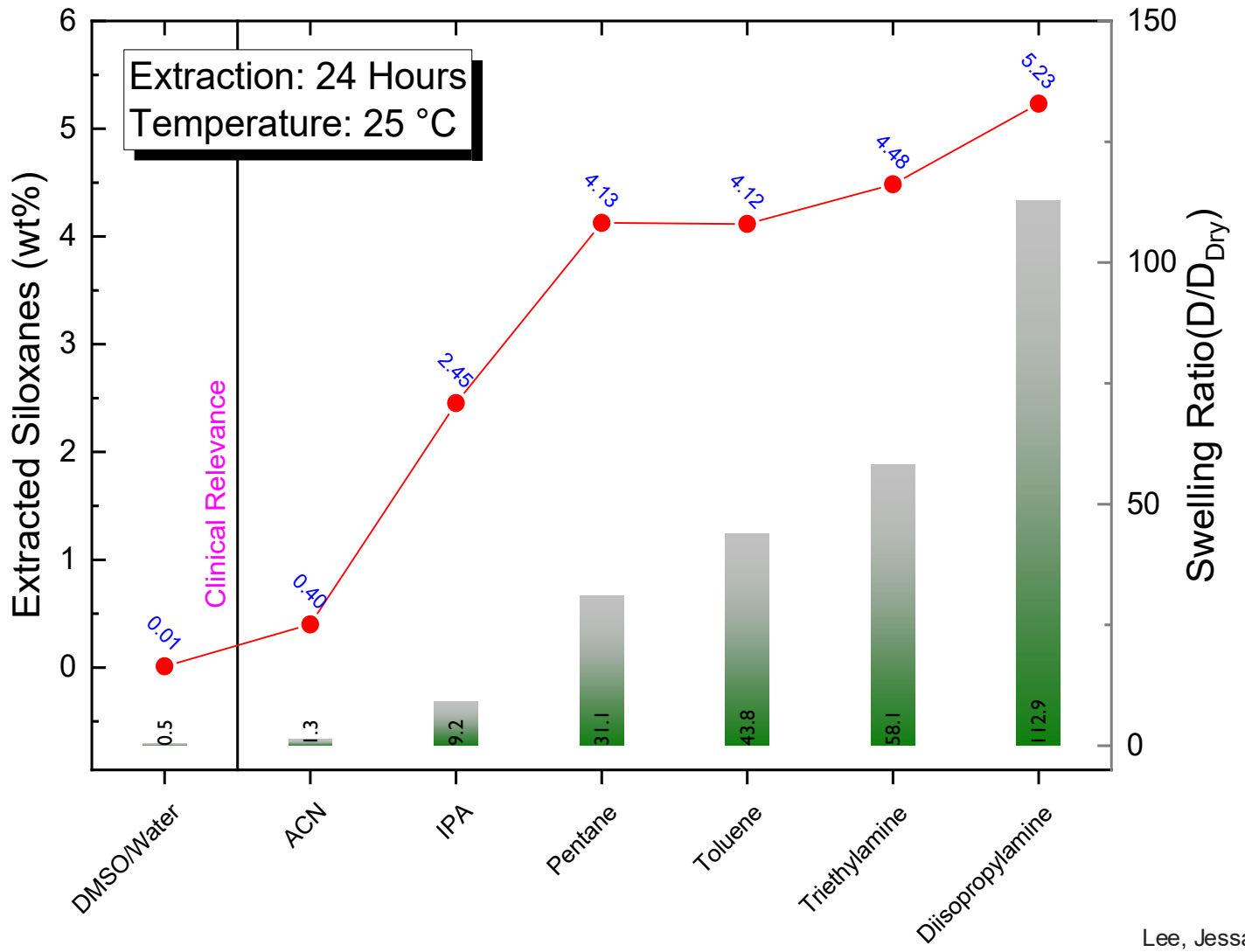
[c] See ISO 10993-18 Table 2 for examples where exhaustive extraction would not typically be warranted.

DRAFT

1) Why long-term contact warrants an additional semipolar solvent?
2) What are extraction powers of contact tissues?
3) Do we need 3 solvents?
4) *Are these solvents clinically relevant?*

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/chemical-analysis-biocompatibility-assessment-medical-devices

The Major Scientific Issues (1): *Solvent Choices, Short Contact Example*

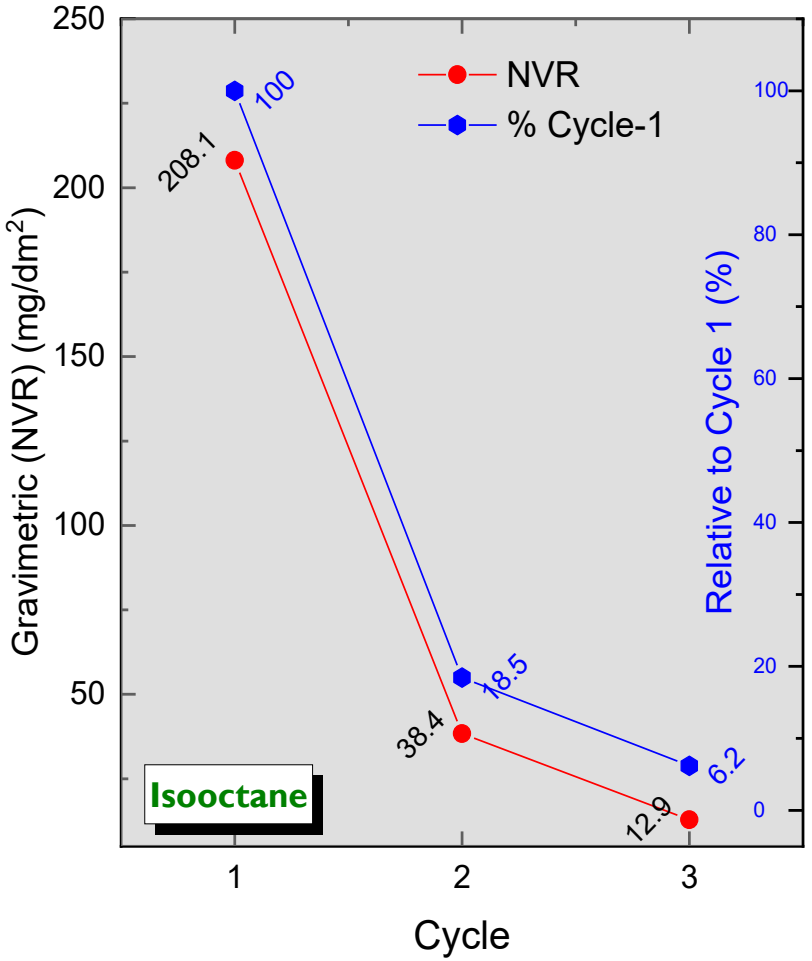


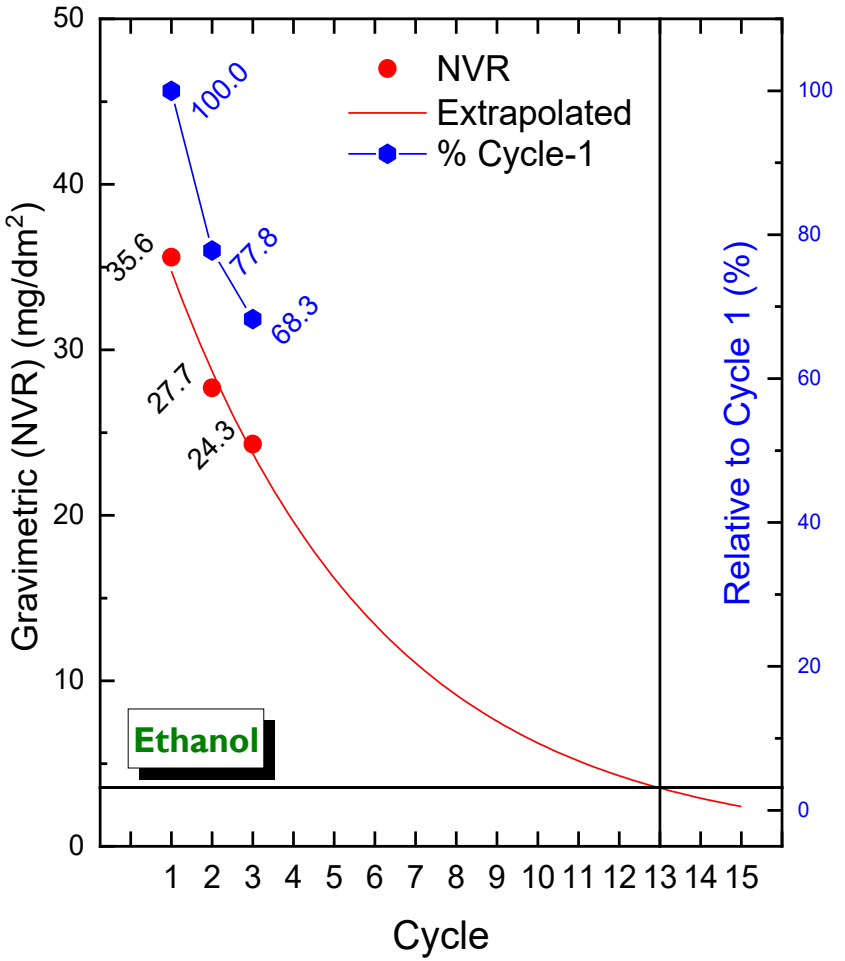
Short Tissue Contact: Surgical Tool by Silicone:

1. Water: ~0%
2. IPA: 2.45%
3. Pentene: 4.13%

Lee, Jessamine Ng, Cheolmin Park, and George M. Whitesides. "Solvent compatibility of poly (dimethylsiloxane)-based microfluidic devices." *Analytical chemistry* 75.23 (2003): 6544-6554.

The Major Scientific Issues (2): *Definition of Exhaustive Extractions (NVR)*

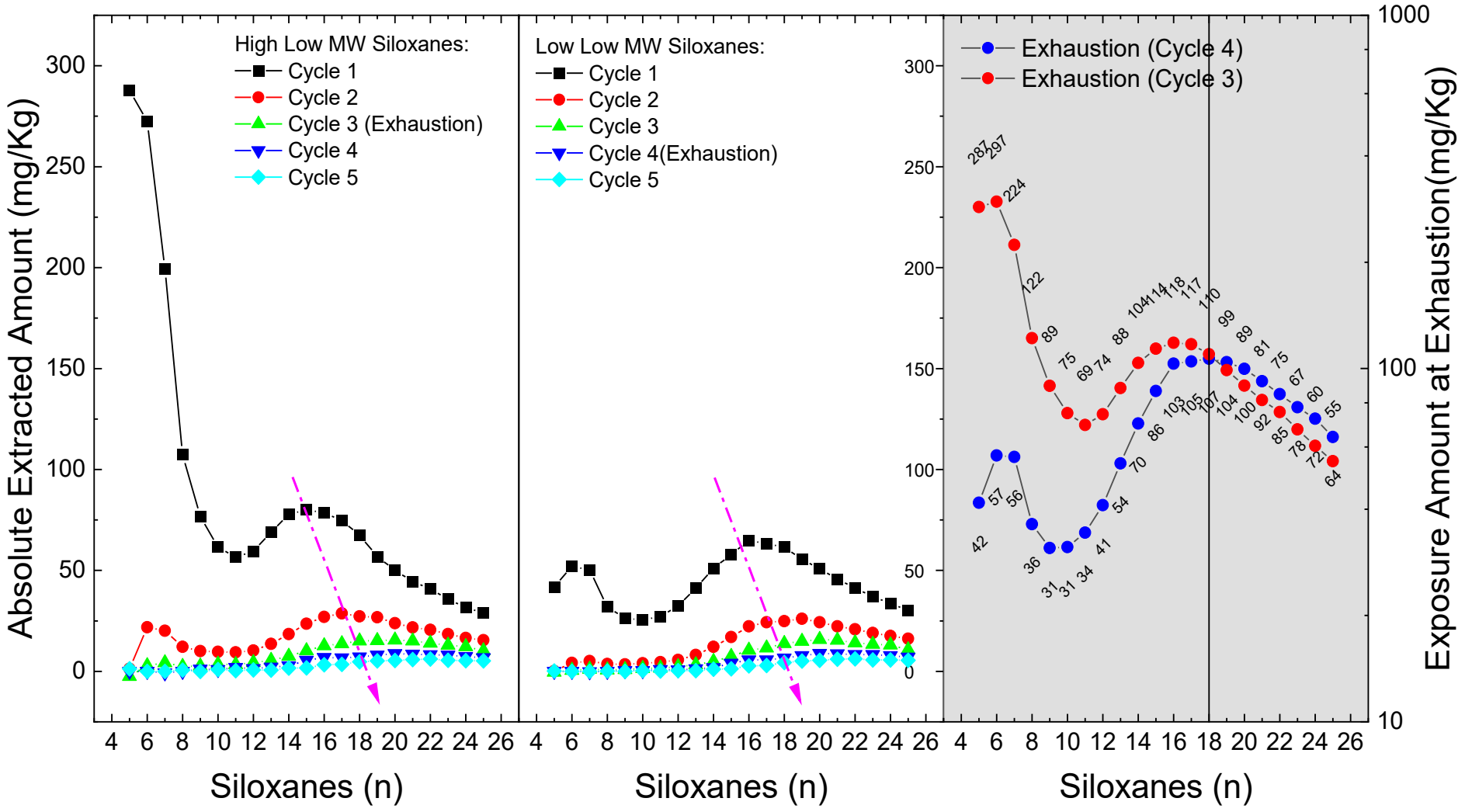




1) Solvent dependent
2) Composition dependent
3) Lack of consistency

Helling, Ruediger, et al. "Determination of the overall migration from silicone baking moulds into simulants and food using 1H-NMR techniques." *Food Additives & Contaminants: Part A* 26.3 (2009): 395-407.

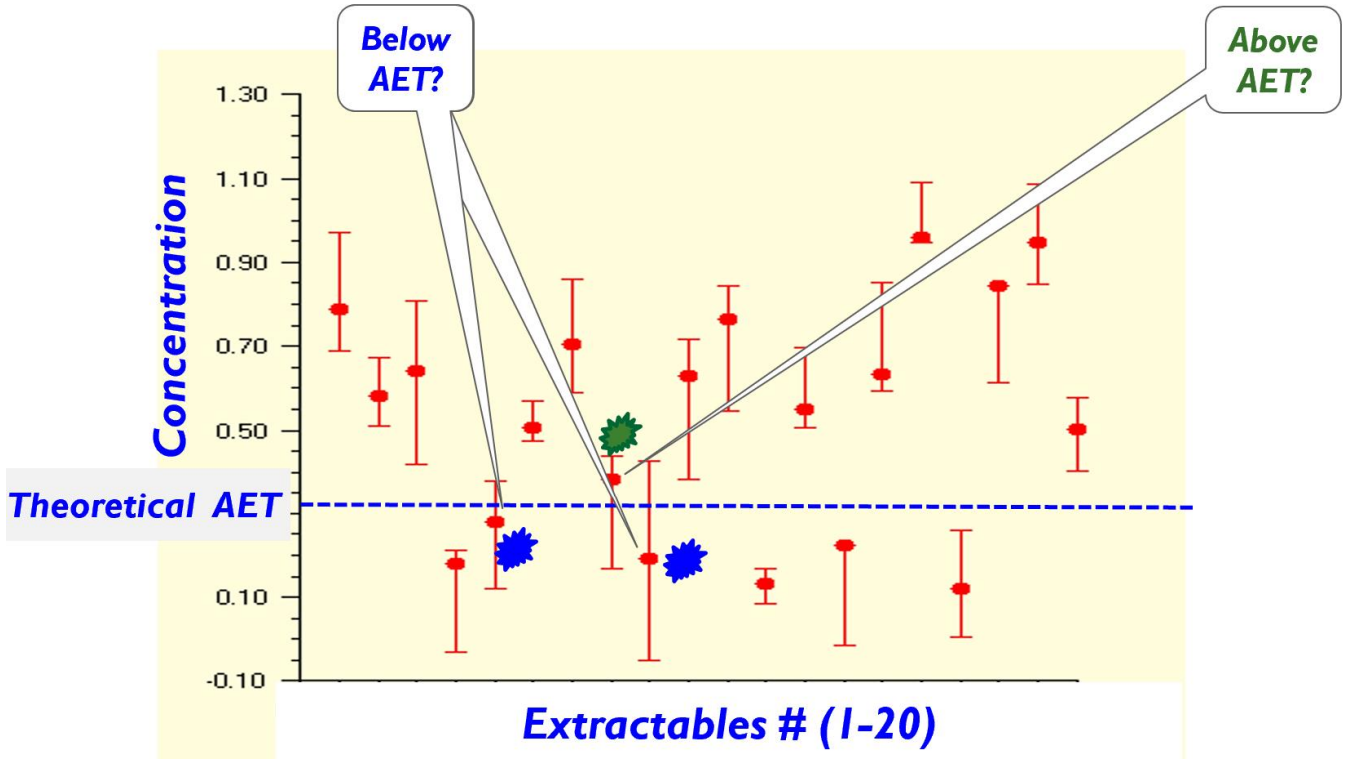
The Major Scientific Issues (2): *Definition of Exhaustive Extractions (NVR)*

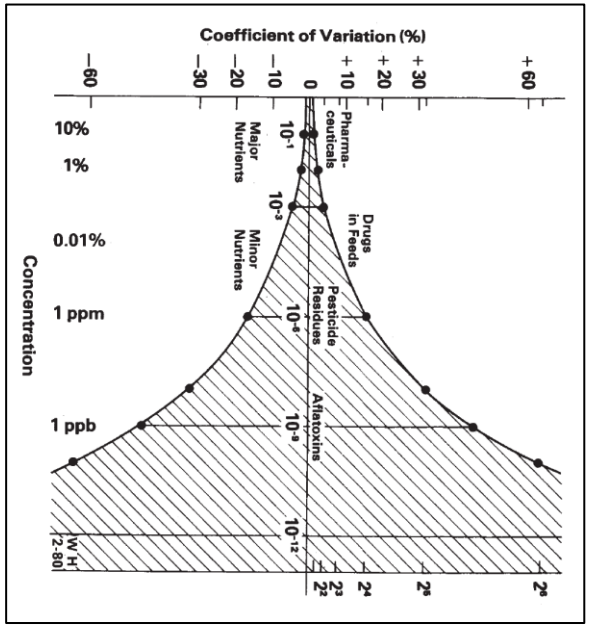


Eckardt, Martin, et al. "Migration of cyclic dimethyl siloxanes from silicone elastomers into food–determination of D4 to D25 via on-line coupled HPLC-GC-FID." *Food Additives & Contaminants: Part A* 42.12 (2025): 1764-1782.

The Major Scientific Issues (3): *The Concept of UF/ AET*

1. If response factor distribution is not symmetrical, and UF equation is invalid.
2. There are errors associated with AET line and measured concentrations. "*Report extractables ≥ AET or TTC" may not be achieved*.
3. It is more problematic if AET is very low.





Groff LC 2nd, Grossman JN, Kruve A, Minucci JM, Lowe CN, McCord JP, Kapraun DF, Phillips KA, Purucker ST, Chao A, Ring CL, Williams AJ, Sobus JR. Uncertainty estimation strategies for quantitative non-targeted analysis. Anal Bioanal Chem. 2022 Jul;414(17):4919-4933.

Horwitz, William, and Richard Albert. "The Horwitz ratio (HorRat): a useful index of method performance with respect to precision." *Journal of AOAC International* 89.4 (2006): 1095-1109.0

González, A. Gustavo, and M. Ángeles Herrador. "A practical guide to analytical method validation, including measurement uncertainty and accuracy profiles." *TrAC Trends in Analytical Chemistry* 26.3 (2007): 227-238.

The Major Scientific Issues (4): *Untargeted Instrumental Analysis*

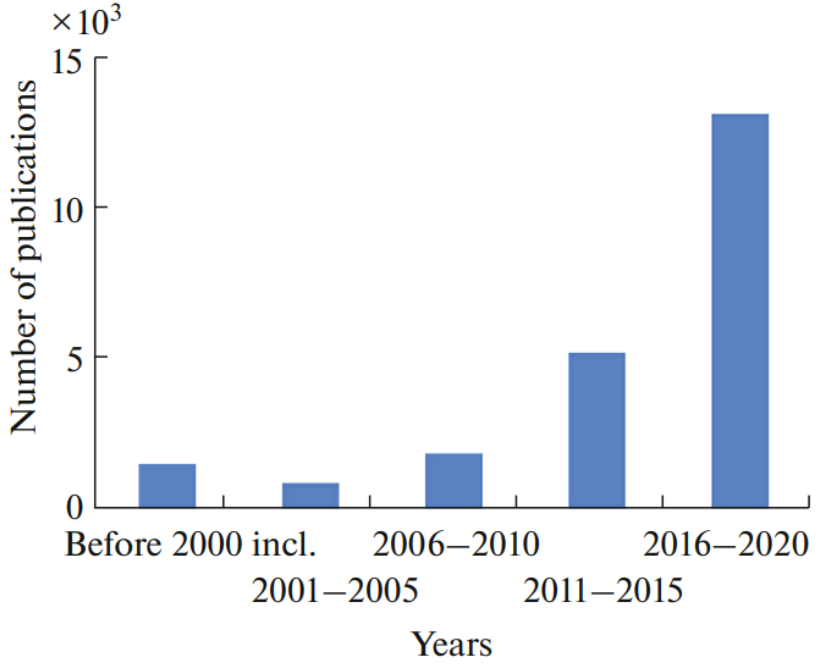


Fig. 1. Dynamics of the number of publications in the field of non-target chemical analysis. Data as of the beginning of 2021 assessed by summing up the number of articles and other documents found in the Google Scholar system for various English terms denoting this type of analysis (see Table 1).

- Risk assessments are mostly based extractables data.
- They are acquired by non-targeted analysis.
- *2021-2025: 17K pubs.*
- *Medical devices: 3-12*

Table 2. Main fields of non-targeted chemical analysis and the corresponding objects of analysis

Field	Object/matrix			
	air, water, soil, sediments, waste, garbage	food and beverages	urine, blood, tissues, and other biomatrices	samples of plant and animal origin
Environmental objects [3–9]	++		+	+
Food, food raw materials, beverages [10–12]	+	++	+	+
Pharmaceuticals, drugs, doping [13–15]*			++	
Toxicology [13–15]*	+	+	++	+
Metabolomics [16–18]		+	++	+
Natural compounds [19, 20]	+			++

++, the main matrix; +, more rare analysis.
* Combined in forensic medicine.

Milman, B. L., and I. K. Zhurkovich. "Present-day practice of non-target chemical analysis." *Journal of Analytical Chemistry* 77.5 (2022): 537-549.

The Major Scientific Issues (5): *Measurement Errors of Untargeted Analysis*

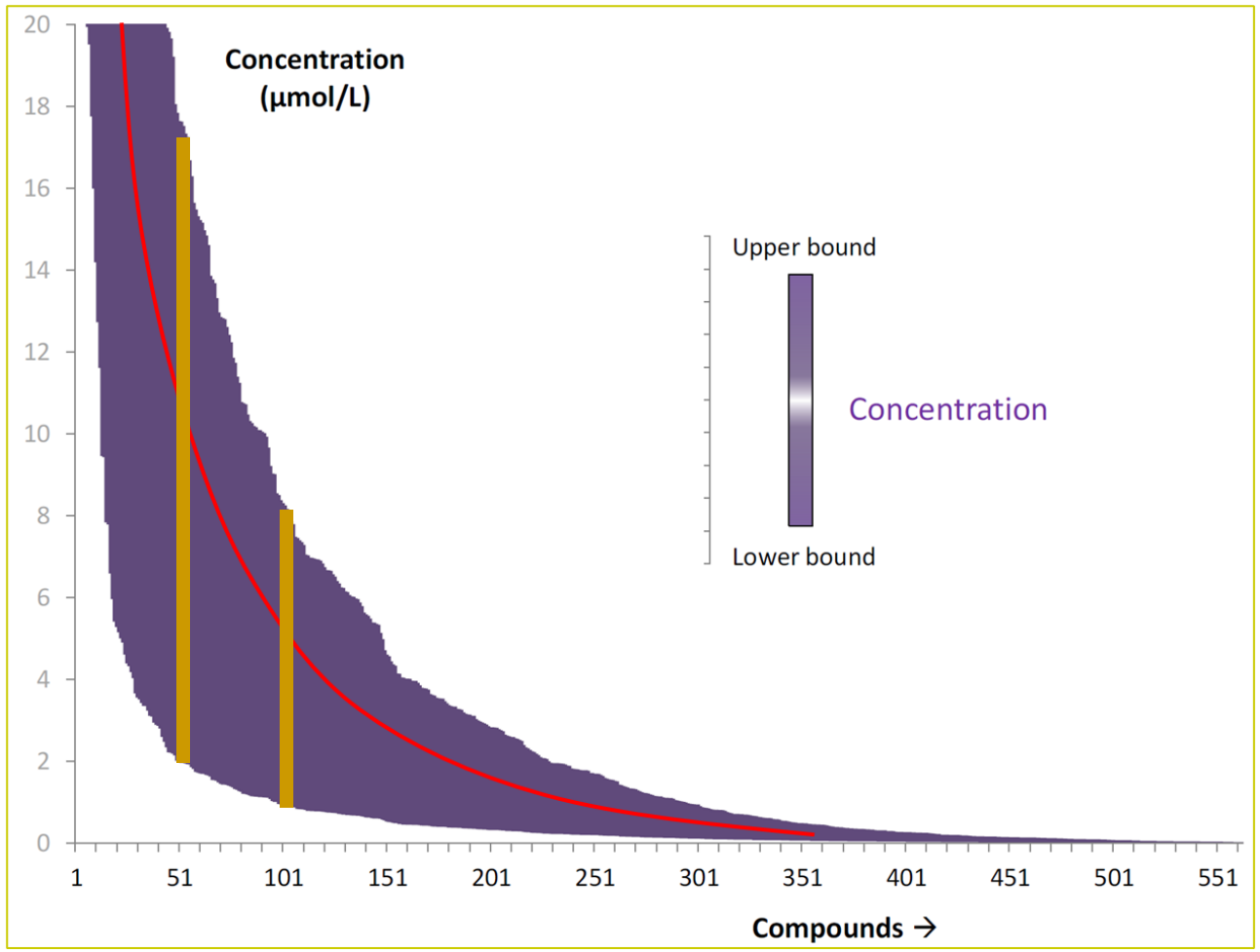
1. Profile: The value of P_{NTA} is the indicator of true positive results, which in test experiments with mixtures produced by the U.S. EPA did not exceed 65% for methods based on HPLC–HRMS.
2. Identification:
   a. *GC-MS, The trueness of identifying volatile compounds from the libraries of reference EI mass spectra is generally ~80%, and ~70% by first search ranking score.*
   b. *LC-MS, For nonvolatile analytes and ESI-MS^2 mass spectra, the situation is more uncertain, the proportion of true-positive results varies widely. Most labs rely on library search.*
3. Quantitation (NTA): The errors by LC-MS can be 3-fold in "best cases". 60-70% with less than 10-fold error. Using surrogates via GC-MS often yields semi-quantitative data with significant errors, typically ranging from 0.5- to 2.0-fold.

$$P_{NTA}\,(\%) = 100 \times \frac{(\text{Number of identified compounds})}{(\text{Number of sample components})}.$$

Milman, B. L., and I. K. Zhurkovich. "Present-day practice of non-target chemical analysis." *Journal of Analytical Chemistry* 77.5 (2022): 537-549.
Sobus, Jon R., et al. "Using prepared mixtures of ToxCast chemicals to evaluate non-targeted analysis (NTA) method performance." *Analytical and bioanalytical chemistry* 411.4 (2019): 835-851.
Milman, Boris L. *Chemical identification and its quality assurance*. Berlin, Heidelberg: Springer Berlin Heidelberg, 2011.
Malm, Louise, et al. "Quantification approaches in non-target LC/ESI/HRMS analysis: an interlaboratory comparison." *Analytical chemistry* 96.41 (2024): 16215-16226.

The Major Scientific Issues (5): *Measurement Errors of Untargeted Analysis*

Topic B



Eelco N. Pieke, Kit Granby, Xenia Trier, Jørn Smedsgaard, A framework to estimate concentrations of potentially unknown substances by semi-quantification in liquid chromatography electrospray ionization mass spectrometry, Analytica Chimica Acta, Volume 975, 2017, Pages 30-41, ISSN 0003-2670, https://doi.org/10.1016/j.aca.2017.03.054.

- The figure on the right shows the measurement errors on reported data in one lab by LC-MS (ESI).
- The LC-ESI responses are maximized for standards and samples to minimize the impact of different responses between standards and extractables.
- A method expectation: "extractables and surrogate standards matches were similar in RF without having detailed knowledge about extractables".
- *Overall, the error bar of LC-MS is very wide.*
- Implication to tox: TSL: 120/600 µg/day

Solvent Choices vs. Uncertainty of Identification and Quantification

Extraction Solvents and Measurement Uncertainty (1)

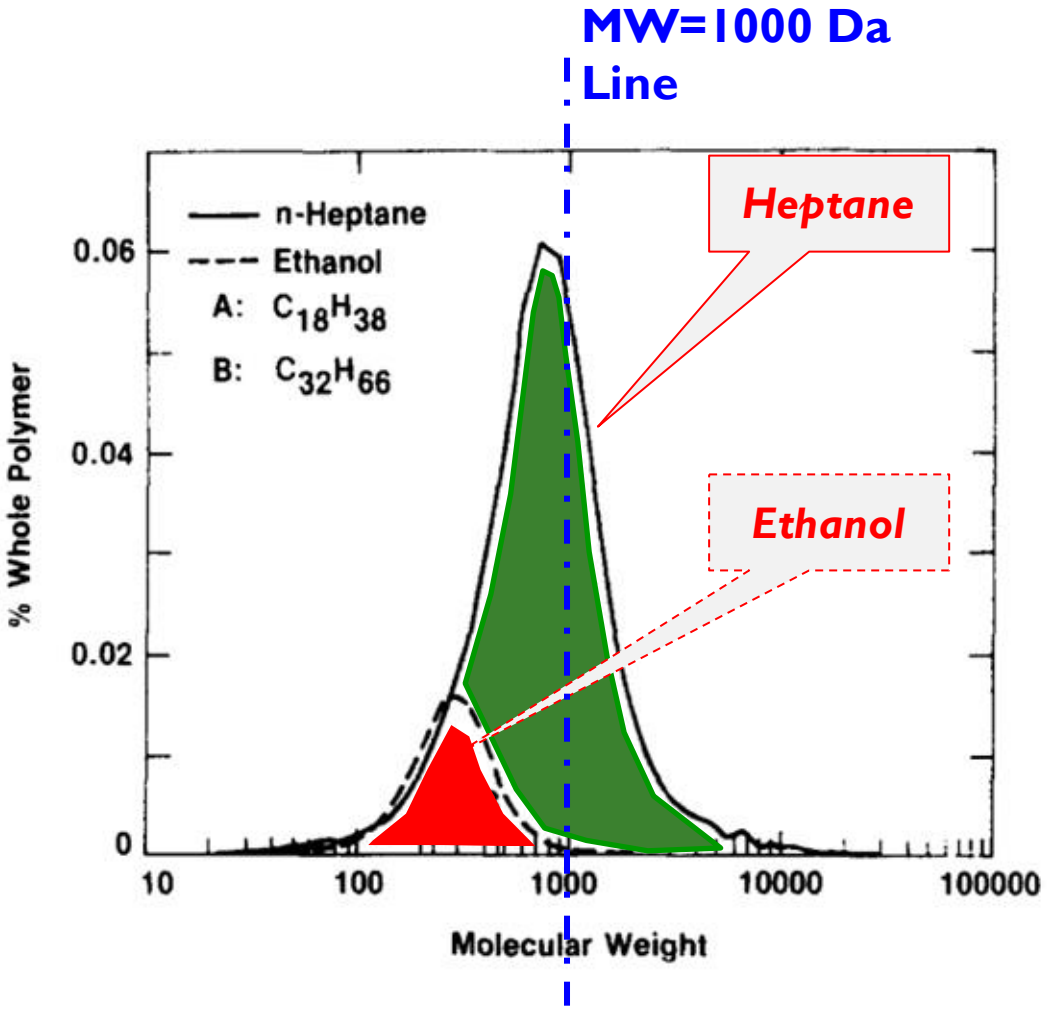


Figure 3 Molecular weight distribution of 70°C ethanol (– – –) and n-heptane (————) extracts of linear polyethylene

- Chromatography Issue
- Quantification issue with many overlapped/unresolved compounds
- Difficulty in identification due to extensive background noises
- *The thicker the materials, the more over-extraction*

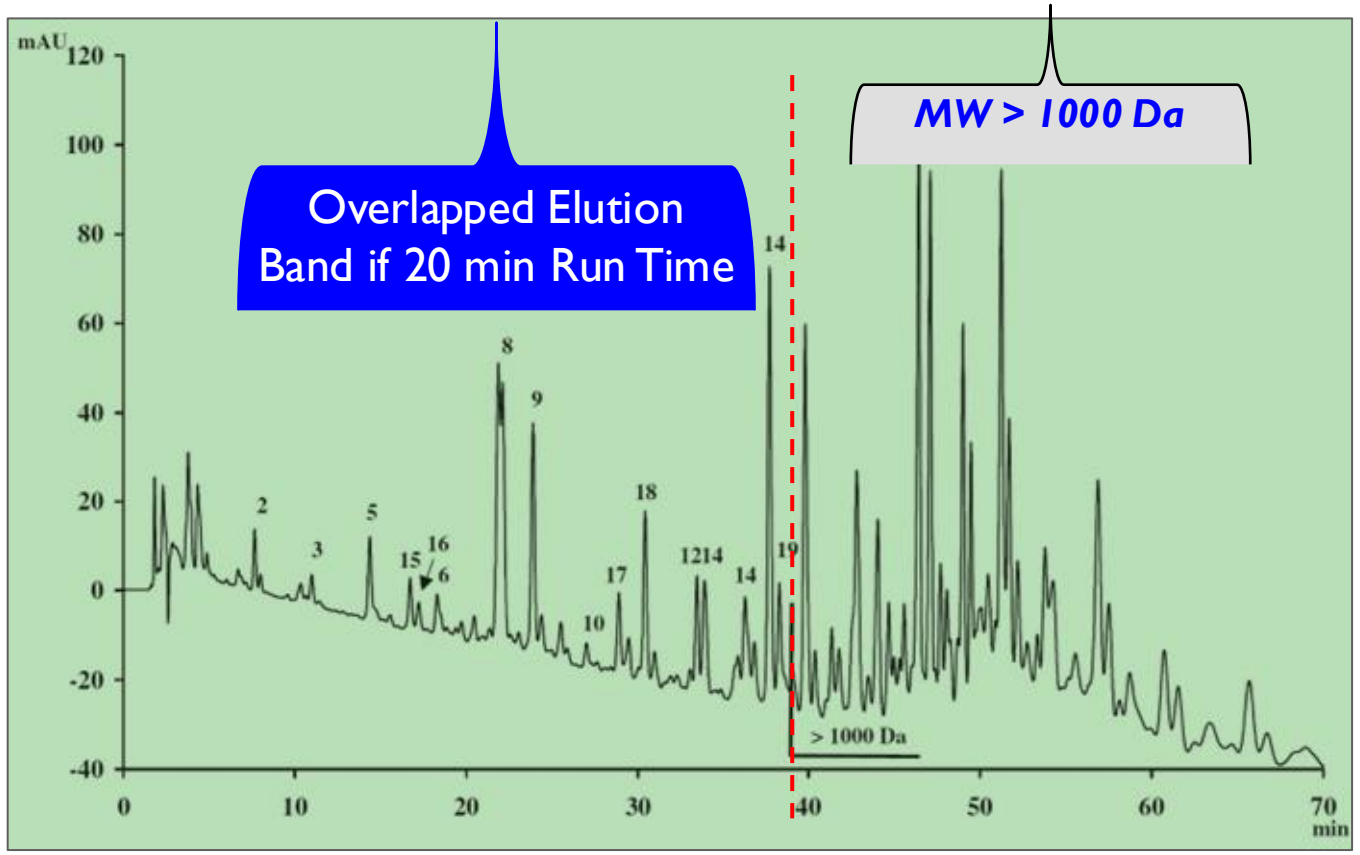
Note: Upper MW range by ethanol: ~1000 Da and 30,000 Da by n-heptane

Chang, Shu-Sing, Walter J. Pummer, and John R. Maurey. "Fat-simulating and accelerating solvents for polyolefins and MWD of solvent extracts of polyethylenes." *Polymer* 24.10 (1983): 1267-1272.

Reynier, Alain, P. Dole, and A. Feigenbaum. "Integrated approach of migration prediction using numerical modelling associated to experimental determination of key parameters." *Food Additives & Contaminants* 19.S1 (2002): 42-55.

Extraction Solvents and Measurement Uncertainty (2)

Material: polyester coating on metal cans
Extracted by ACN



1. *Over-extraction may produce unknowns of > 1000 Da*
2. *They can be lost during chromatographic analysis.*
3. *NVR can detect all*
4. *Chromatography-based techniques may not, creating mass imbalance issue.*

Schaefer A, Simat TJ. Migration from can coatings: part 3. Synthesis, identification and quantification of migrating epoxy-based substances below 1000 Da. Food Addit Contam. 2004 Apr;21(4):390-405. doi: 10.1080/02652030310001657388. PMID: 15204563.

Solvent Choices (*Nonpolar Solvent*) and Over Extraction/ Tox Assessment

Jianwei Li, Li, J. Evaluation of Thermodynamic and Kinetic Contributions to Over-Extraction of Extractables by Nonpolar Organic Solvents in Comparison to Lipids in Exhaustive and Exaggerated Extractions of Medical Devices Based on Abraham Solvation Model and Solvent–Material Interactions Using Low-Density Polyethylene as a Representative Material. Liquids 2024, 4, 117–147. https://doi.org/10.3390/liquids4010006

Over Extraction/Tox Assessment (1): *LDPE*

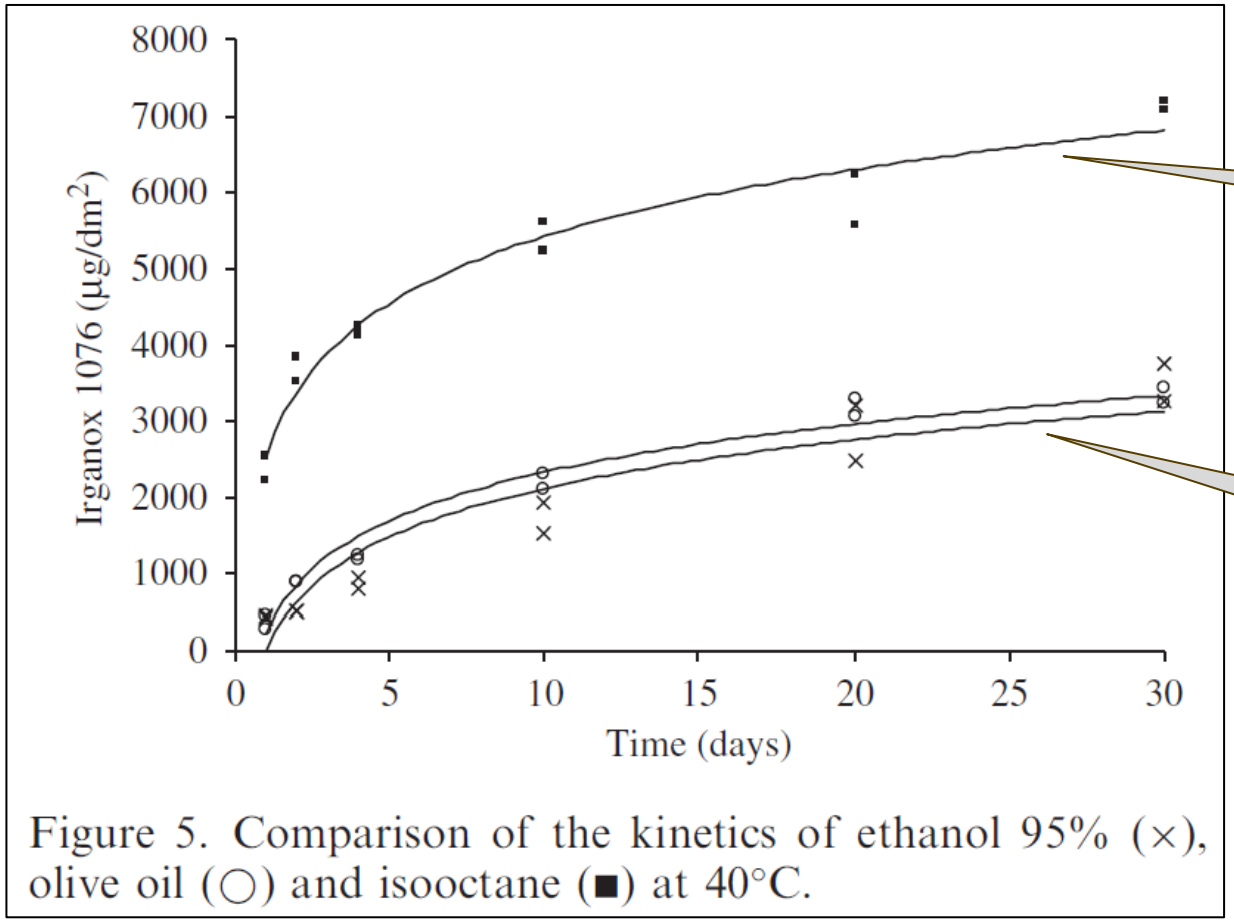


Figure 5. Comparison of the kinetics of ethanol 95% (×), olive oil (○) and isooctane (■) at 40°C.

Isooctane

Ethanol and Olive oil

Beldi, Giorgia, et al. "Time-and temperature-dependent migration studies of Irganox 1076 from plastics into foods and food simulants." *Food Additives & Contaminants: Part A* 29.5 (2012): 836-845.

Over Extraction/Tox Assessment (2): *Silicone*

Total: 73.38

Total: 259.4

Total: 87.6

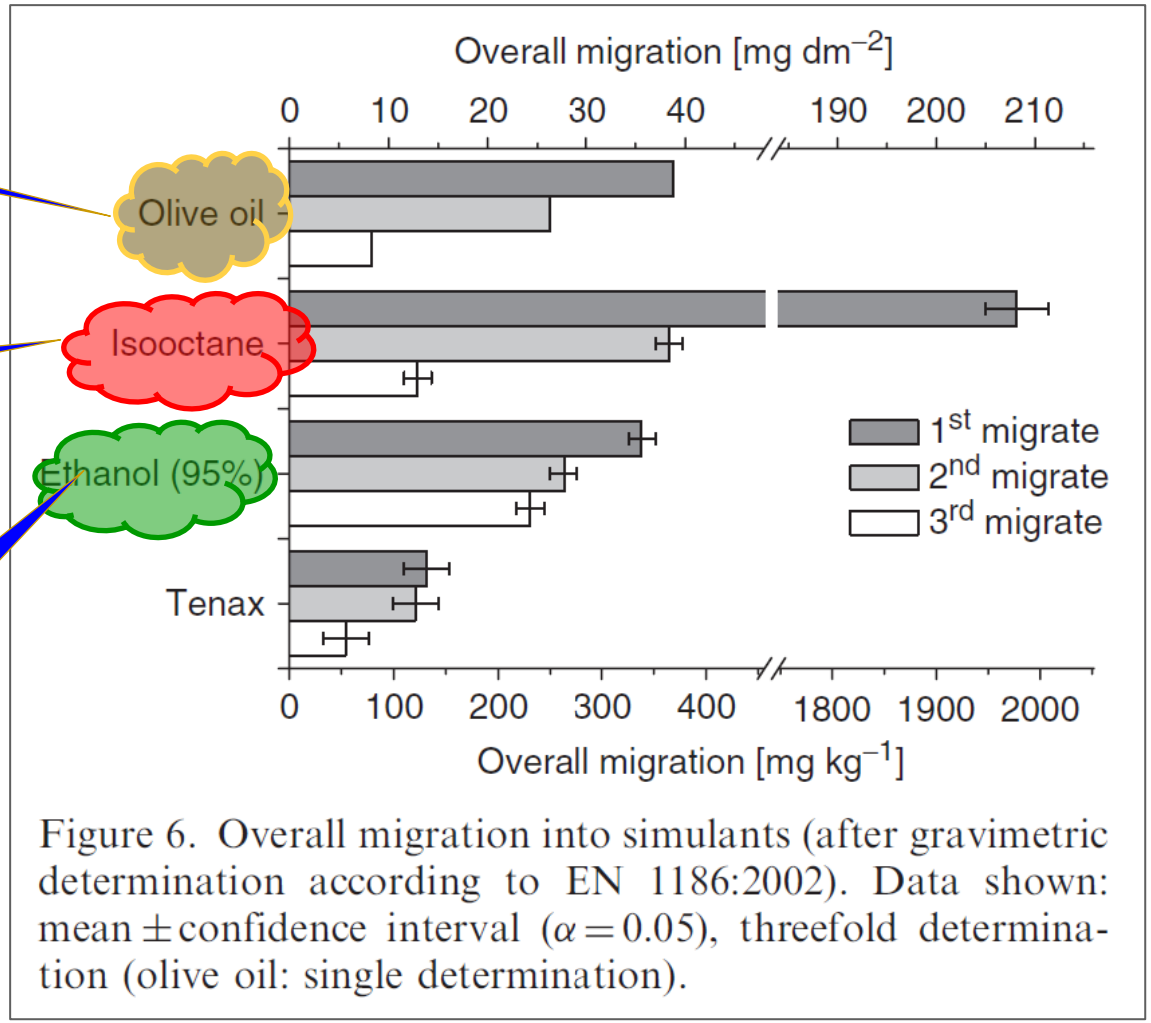
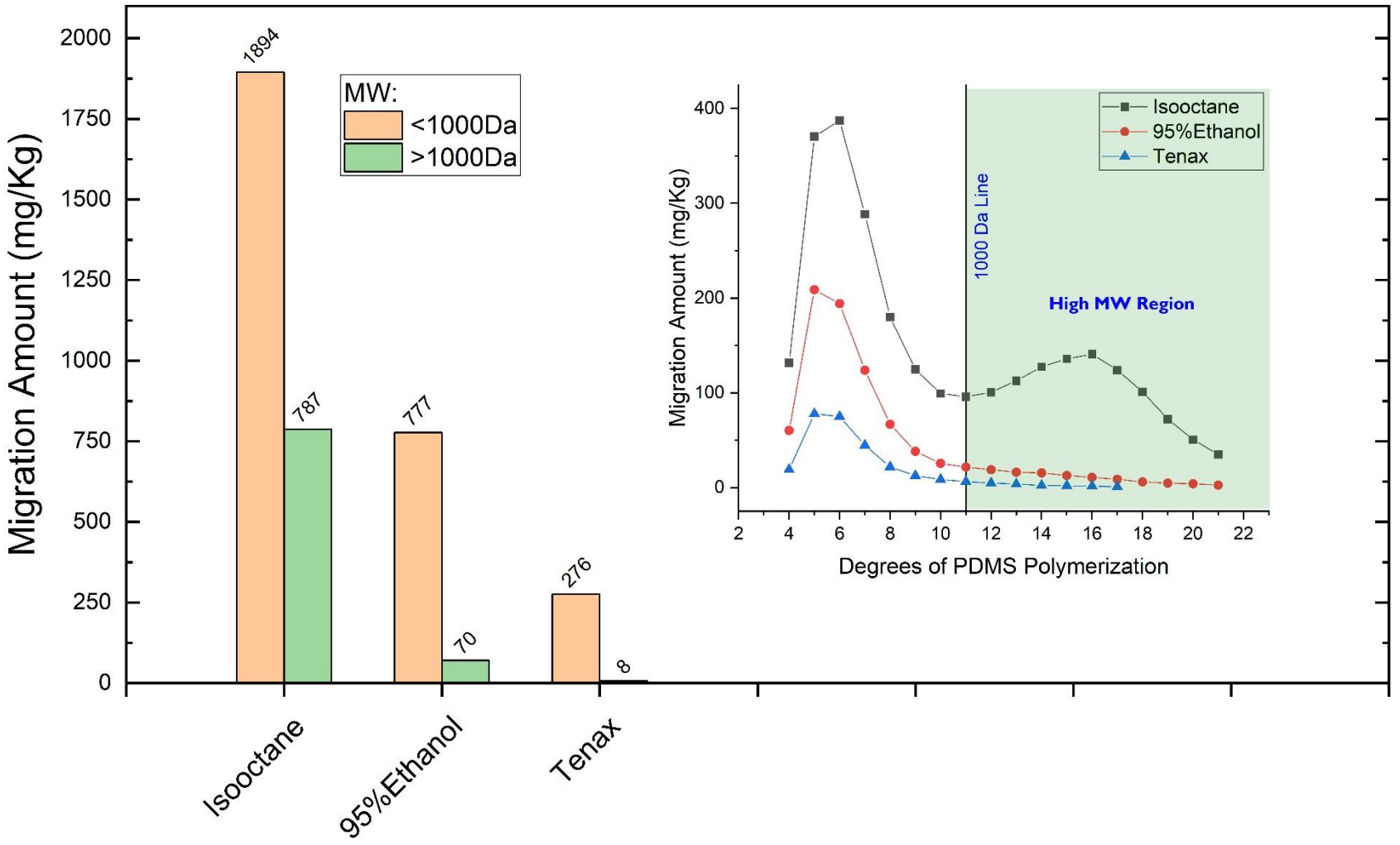


Figure 6. Overall migration into simulants (after gravimetric determination according to EN 1186:2002). Data shown: mean ± confidence interval ($\alpha = 0.05$), threefold determination (olive oil: single determination).

Helling, Ruediger, et al. "Determination of the overall migration from silicone baking moulds into simulants and food using 1H-NMR techniques." *Food Additives & Contaminants: Part A* 26.3 (2009): 395-407.

Over Extraction/Tox Assessment (3): *PDMS*

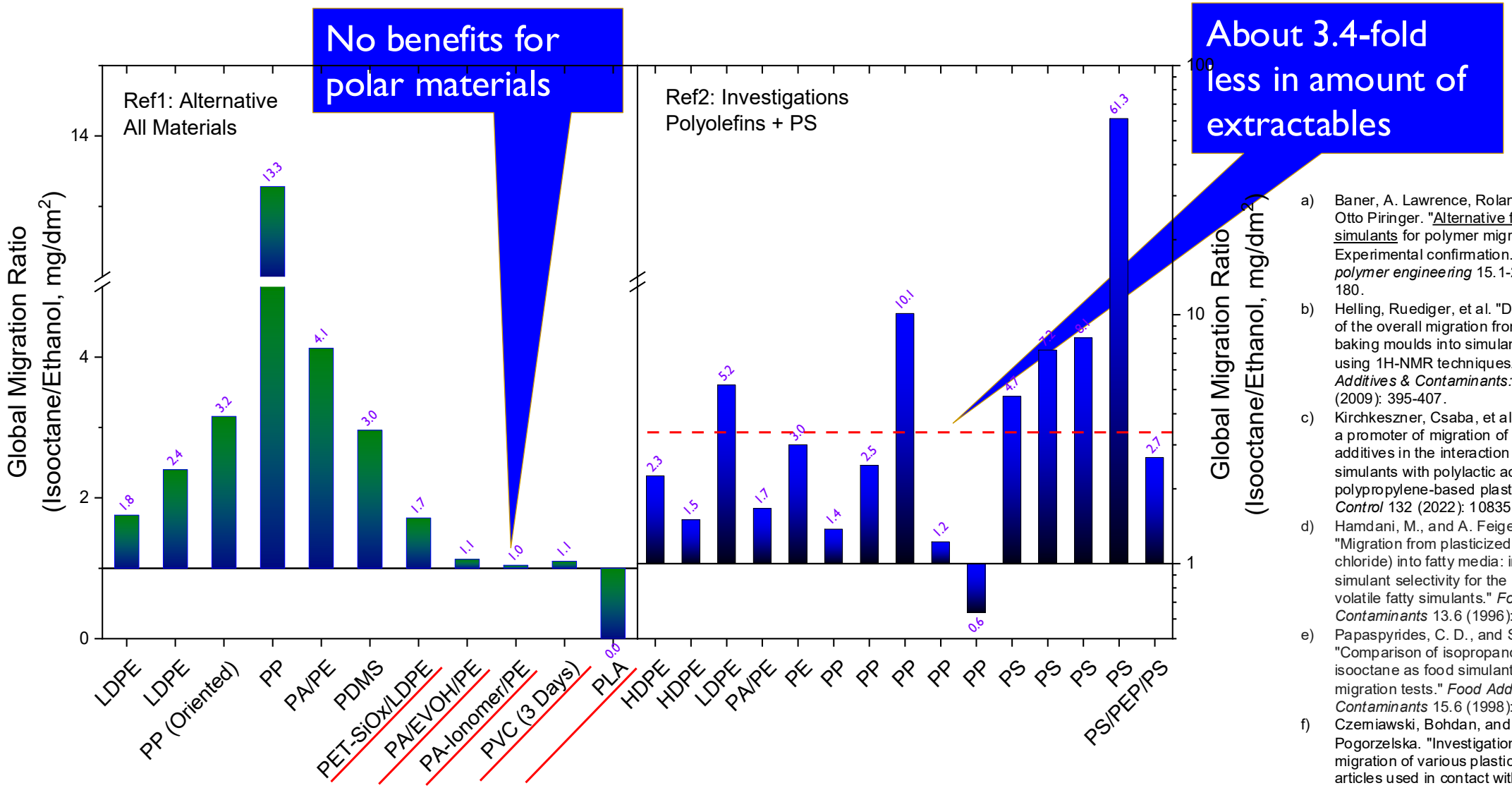


Isooctane vs Ethanol:

- Siloxane range: D4-D25
- Total amount by isooctane ~3-fold higher
- High MW siloxanes ~10-fold higher

Liu, Yi-Qi, et al. "Influence of cooking conditions on the migration of silicone oligomers from silicone rubber baking molds to food simulants." *Food Chemistry* 347 (2021): 128964.

Over Extraction/Tox Assessment (4): *"Different" Materials*



Filename: ALTERNATIVE FATTY FOOD SIMULANTS-All Ratios-UPDATED

a) Baner, A. Lawrence, Roland Franz, and Otto Piringer. "Alternative fatty food simulants for polymer migration testing: Experimental confirmation." *Journal of polymer engineering* 15.1-2 (1995): 161-180.

b) Helling, Ruediger, et al. "Determination of the overall migration from silicone baking moulds into simulants and food using 1H-NMR techniques." *Food Additives & Contaminants: Part A* 26.3 (2009): 395-407.

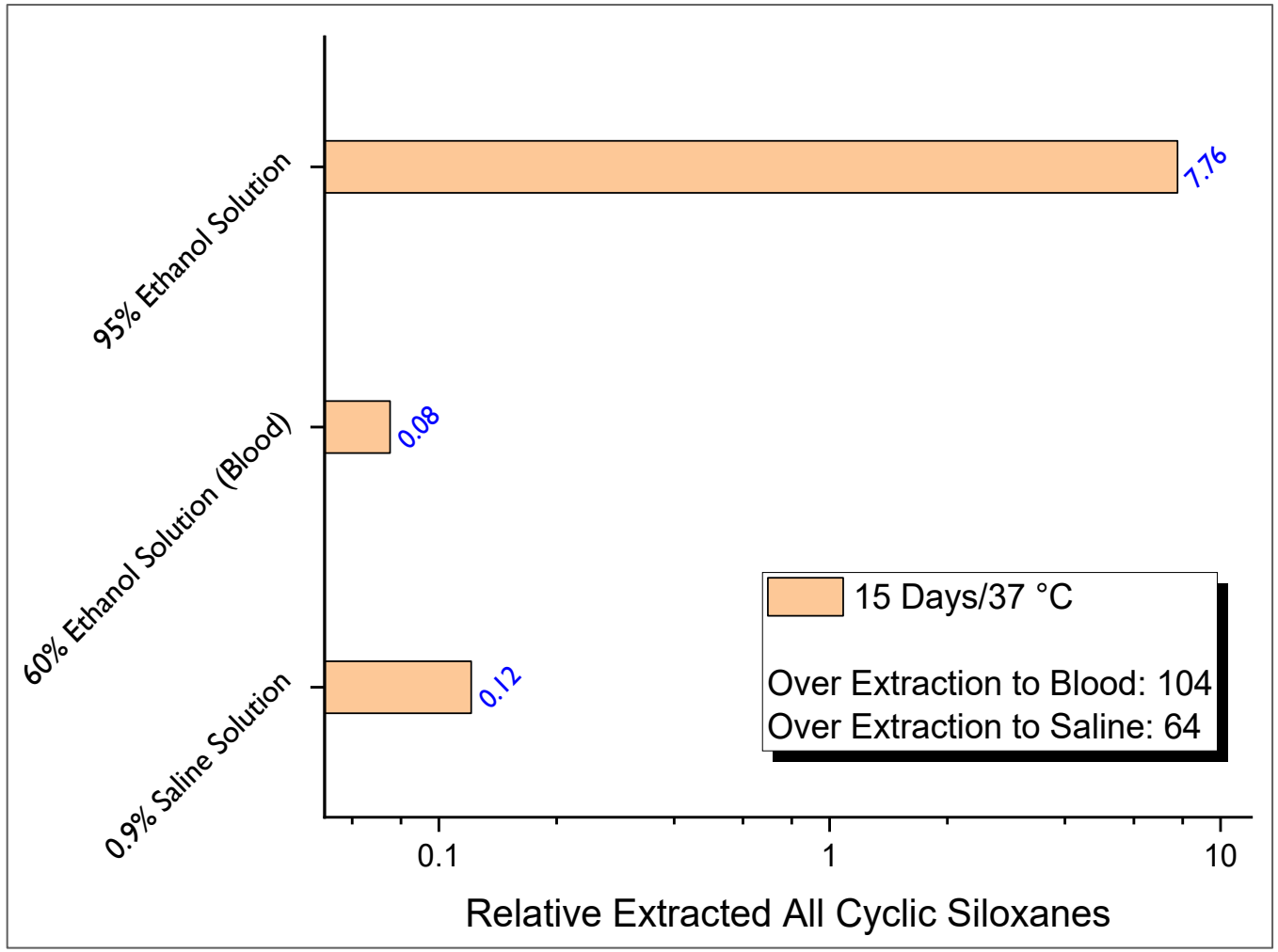
c) Kirchkeszner, Csaba, et al. "Swelling as a promoter of migration of plastic additives in the interaction of fatty food simulants with polylactic acid-and polypropylene-based plastics." *Food Control* 132 (2022): 108354.

d) Hamdani, M., and A. Feigenbaum. "Migration from plasticized poly (vinyl chloride) into fatty media: importance of simulant selectivity for the choice of volatile fatty simulants." *Food Additives & Contaminants* 13.6 (1996): 717-729.

e) Papaspyrides, C. D., and S. G. Tingas. "Comparison of isopropanol and isooctane as food simulants in plasticizer migration tests." *Food Additives & Contaminants* 15.6 (1998): 681-689.

f) Czerniawski, Bohdan, and Zofia Pogorzelska. "Investigations on overall migration of various plastic materials and articles used in contact with foodstuffs." *Packaging Technology and Science: An International Journal* 10.5 (1997): 261-270.

Over Extraction/Tox Assessment (5): *Blood*

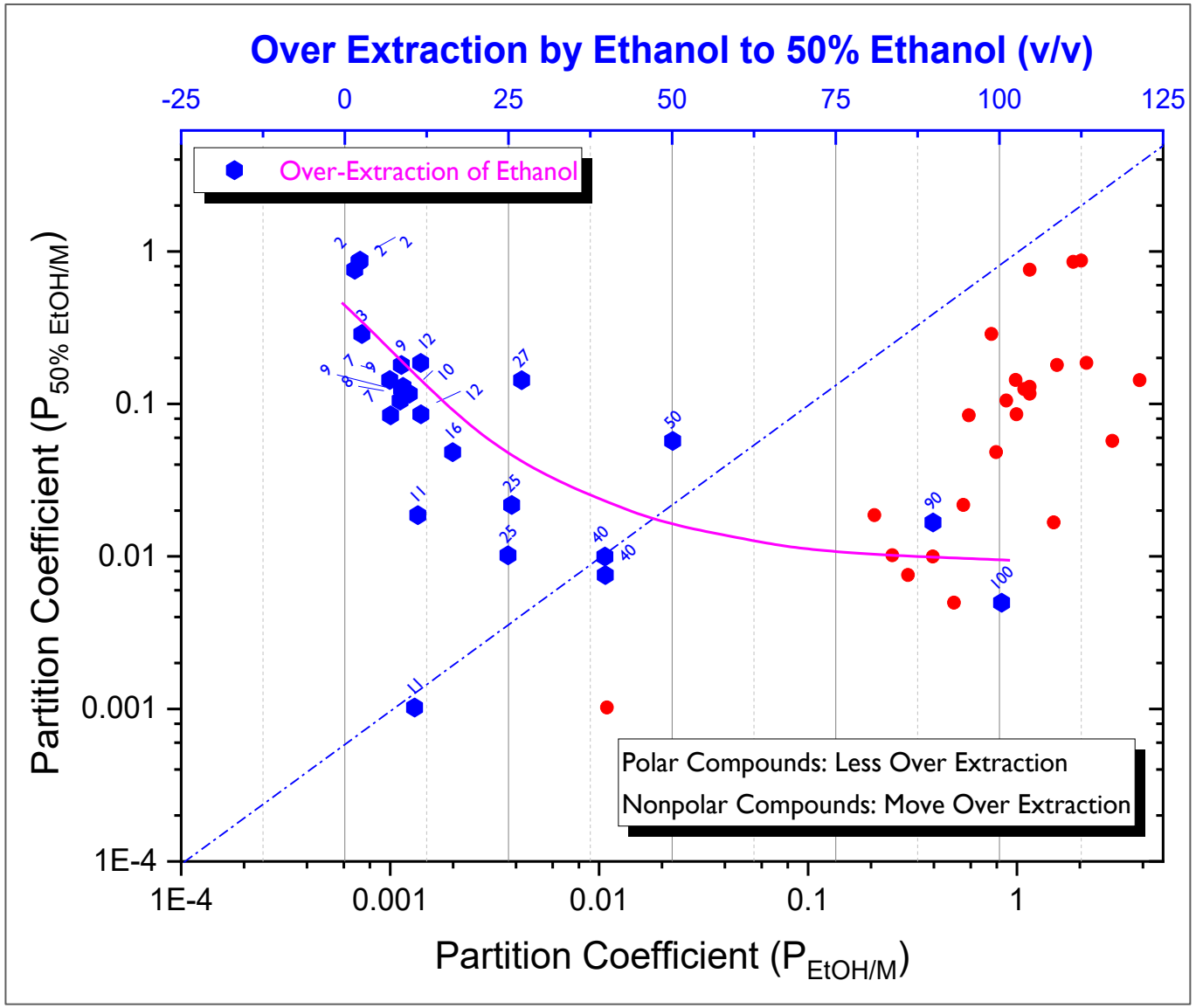


Ethanol vs. Ethanol (50% v/v) as Blood Simulating Solvent:

- Over extraction of cyclic siloxanes by ethanol is ~100-fold to blood
- Material: Silicone

Guenu, Sophie, et al. "Mass spectrometry and scanning electron microscopy study of silicone tunneled dialysis catheter integrity after an exposure of 15 days to 60% ethanol solution." *Rapid Communications in Mass Spectrometry: An International Journal Devoted to the Rapid Dissemination of Up-to-the-Minute Research in Mass Spectrometry* 21.2 (2007): 229-236.

Over Extraction/Tox Assessment (5): *Blood*



Ethanol vs. Ethanol (50% v/v) as Blood Simulating Solvent:

- Over extraction of cyclic siloxanes by ethanol is ~100-fold to blood
- Materials: EVA/EVOH/PE/PA

Nguyen, Phuong-Mai, Samuel Dorey, and Olivier Vitrac. "The ubiquitous issue of cross-mass transfer: applications to single-use systems." *Molecules* 24.19 (2019): 3467.

Tissue Extraction Power

Extraction Power of Human Tissues (1): *Human Tissue Compositions*

Compositions of Tissues and Other Biological Phases (vol %)					
Tissue	***Water***	***Neutral lipid***	***Phospholipid***	***Serum albumin***	***Other proteins***
Whole blood	81	0.13	0.22	1.6	16
plasma	96	0.15	0.08	2.9	1.5
muscle	78	0.43	0.45	0.13	17
lungs	84	1.02	0.98	0.54	5.5
kidneys	78	1.2	3.5	0.24	16
liver	73	1.9	4.6	0.19	17
milk	91	4.2	0	0.02	2.4
brain	79	4.3	6.7	0.004	8.0
skin	62	8.7	0.97	0.33	28
adipose	16	79	0.22	0.15	5.2

- Low diffusion rate into materials due to large MW
- MW cutoff of polymer~1000 Da
- Lipids MW range: 700-1500 Da

a) Schmitt, W. General approach for the calculation of tissue to plasma partition coefficients. Toxicol. In Vitro 2008, 22 (2), 457−467

b) Endo, Satoshi, Trevor N. Brown, and Kai-Uwe Goss. "General model for estimating partition coefficients to organisms and their tissues using the biological compositions and polyparameter linear free energy relationships." *Environmental science & technology* 47.12 (2013): 6630-6639.

Extraction Power of Tissues (2): *Human Tissues Solvation Scale*

Tissue or Fluid	Oiliness Index
Water	0.00
Plasma	0.08
Lung	0.16
Blood	0.26
Muscle tissue	0.42
Kidney tissue	0.46
Brain homogenate	0.46
Liver tissue	0.50
Human fat	0.93
Olive oil	1.00

50% Ethanol/ Water (v/v)

Butanone and Dioxane

"oiliness index" of the given biological tissue (as solvent), defined approximately as solubility in olive oil over total solubility in "water and olive oil", reflecting the relative hydrophilic/lipophilic nature of the body organ, fluid, or tissue

a) Abraham, Michael H., et al. "Solubility properties in polymers and biological media. 2. The correlation and prediction of the solubilities of nonelectrolytes in biological tissues and fluids." *Journal of medicinal chemistry* 28.7 (1985): 865-870.

b) Tamlet MJ, Abraham DJ, Doherty RM, Taft RW, Abraham MH. Solubility properties in polymers and biological media: 6. An equation for correlation and prediction of solubilities of liquid organic nonelectrolytes in blood. J Pharm Sci. 1986 Apr;75(4):350-5. doi: 10.1002/jps.2600750406.

c) Li, Jianwei. "Evaluation of fatty tissue representative solvents in extraction of medical devices for chromatographic analysis of devices' extractables and leachables based on Abraham general solvation model." *Journal of Chromatography A* 1676 (2022): 463240.

Extraction Power of Tissues (3): Deep Brain Leads (PU) into Brain Tissues

GC-MS on MDI

180 Days/37 °C

LC-MS on Soft Segments

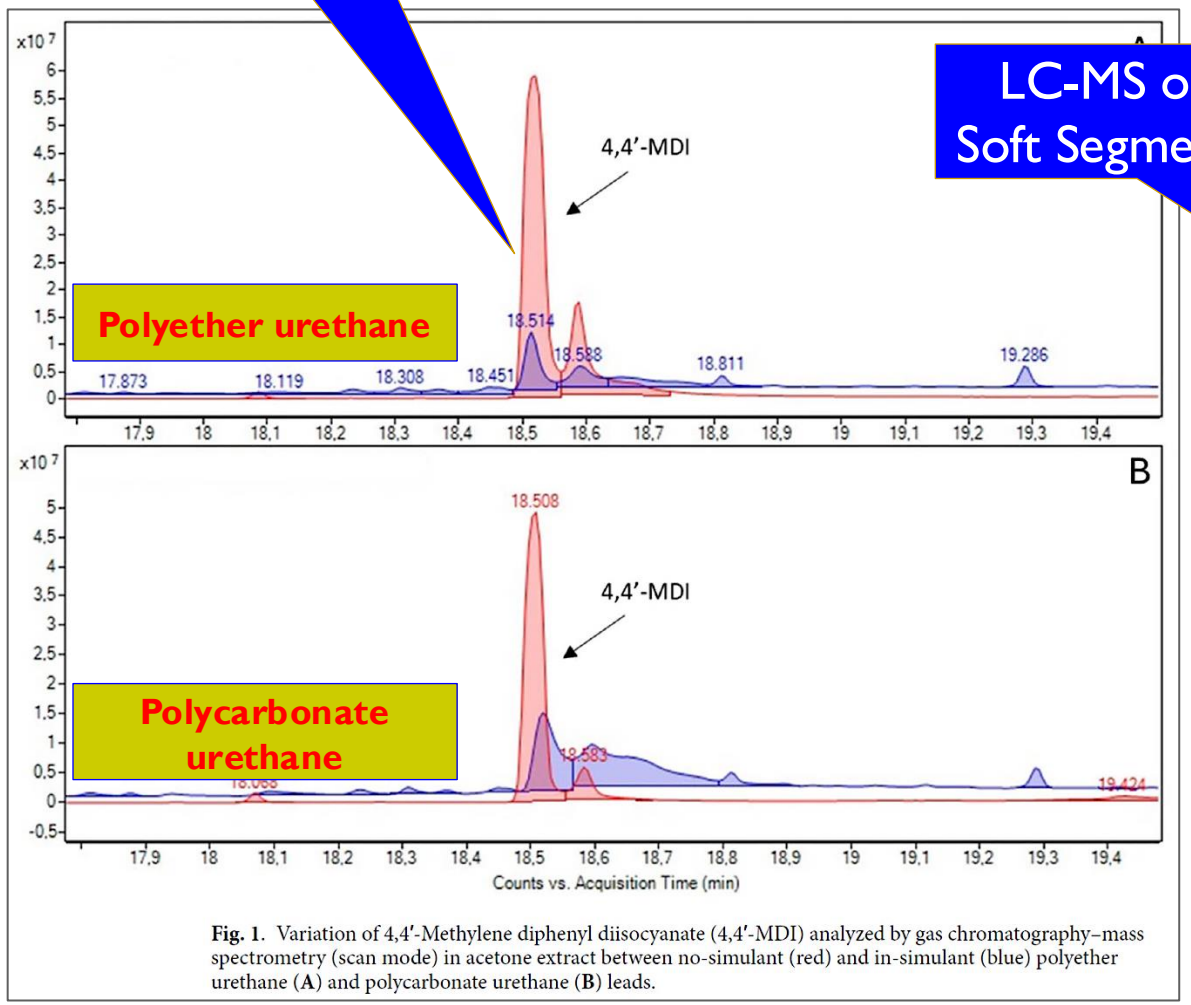


Fig. 1. Variation of 4,4′-Methylene diphenyl diisocyanate (4,4′-MDI) analyzed by gas chromatography–mass spectrometry (scan mode) in acetone extract between no-simulant (red) and in-simulant (blue) polyether urethane (**A**) and polycarbonate urethane (**B**) leads.

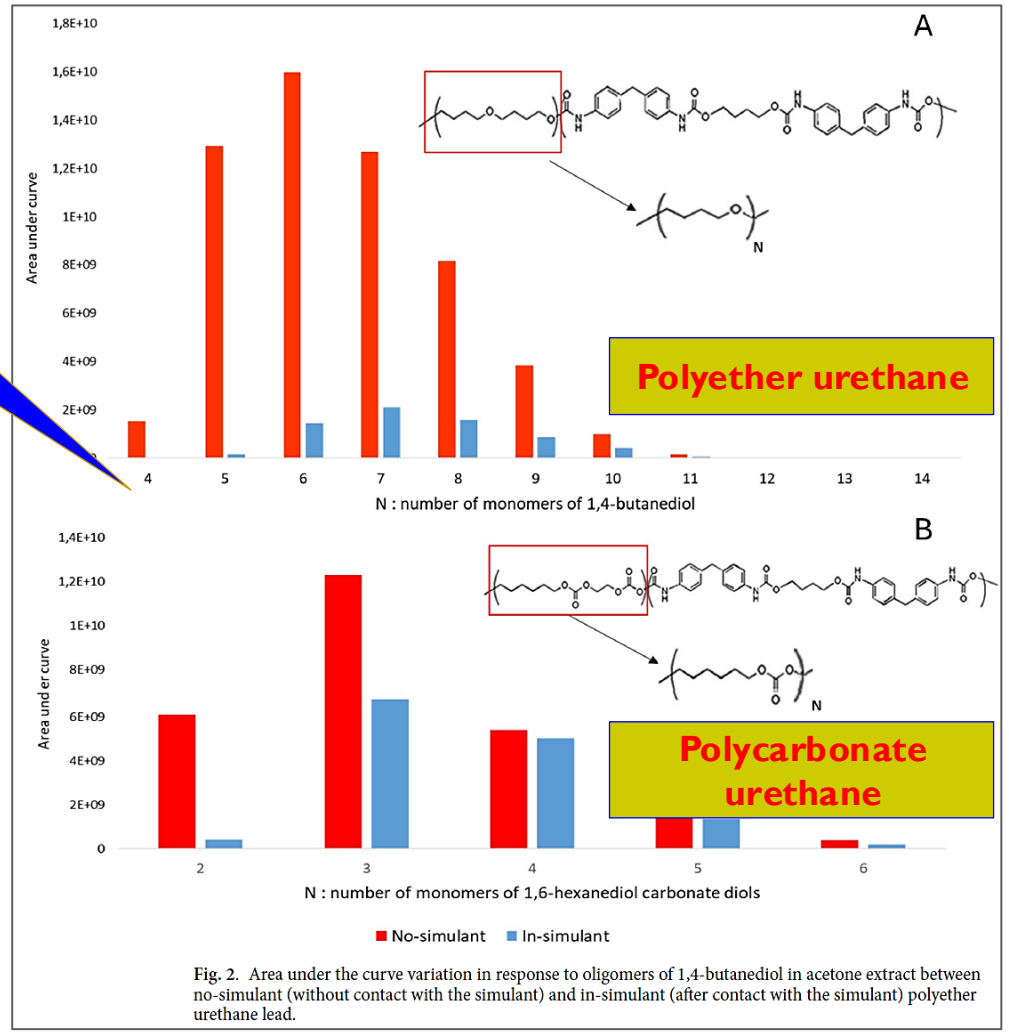
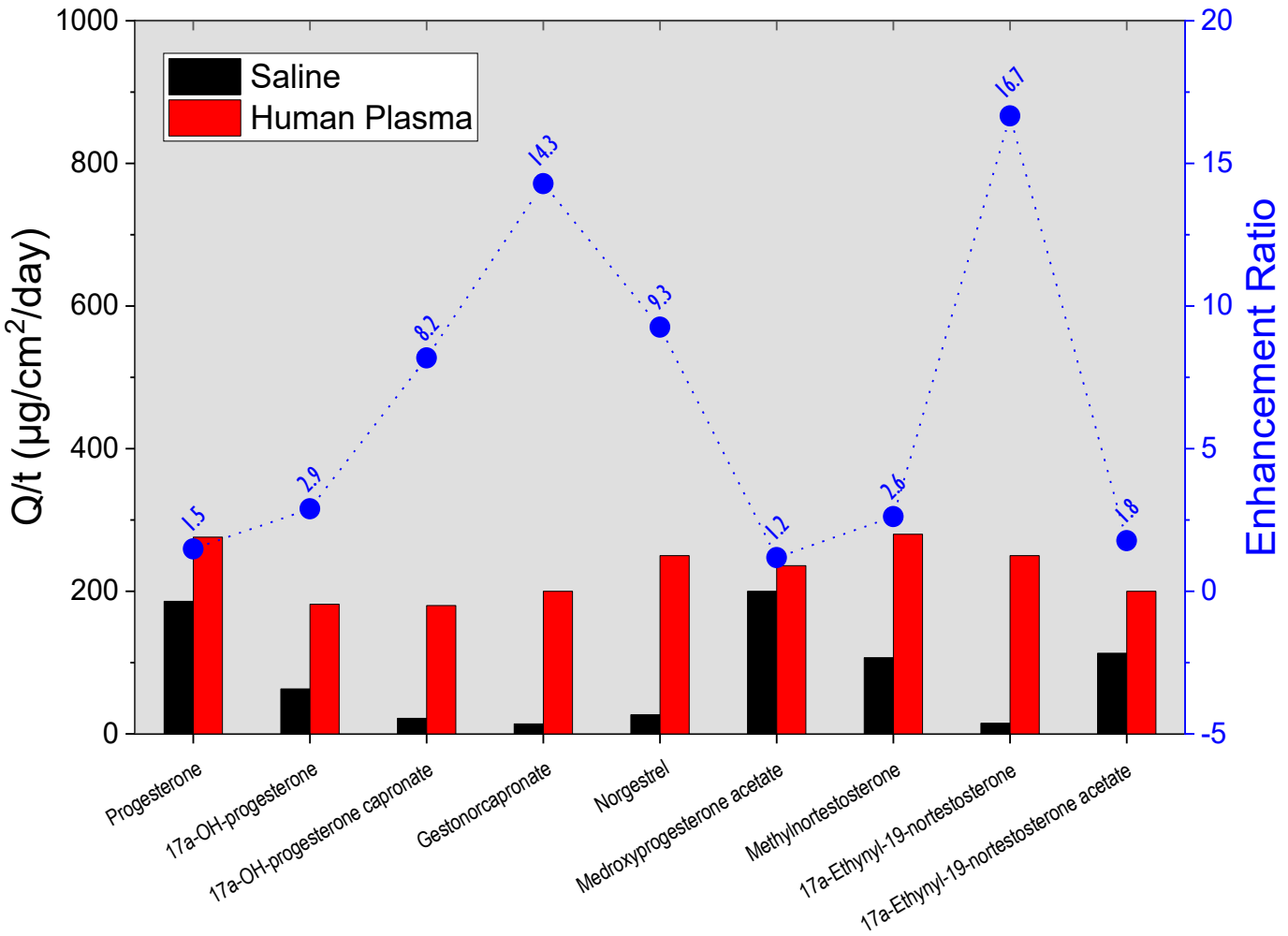


Fig. 2. Area under the curve variation in response to oligomers of 1,4-butanediol in acetone extract between no-simulant (without contact with the simulant) and in-simulant (after contact with the simulant) polyether urethane lead.

Bouattour, Yassine, et al. "Screening for compounds released from deep brain stimulation probes by contact with a brain simulant." *Scientific Reports* (2026).

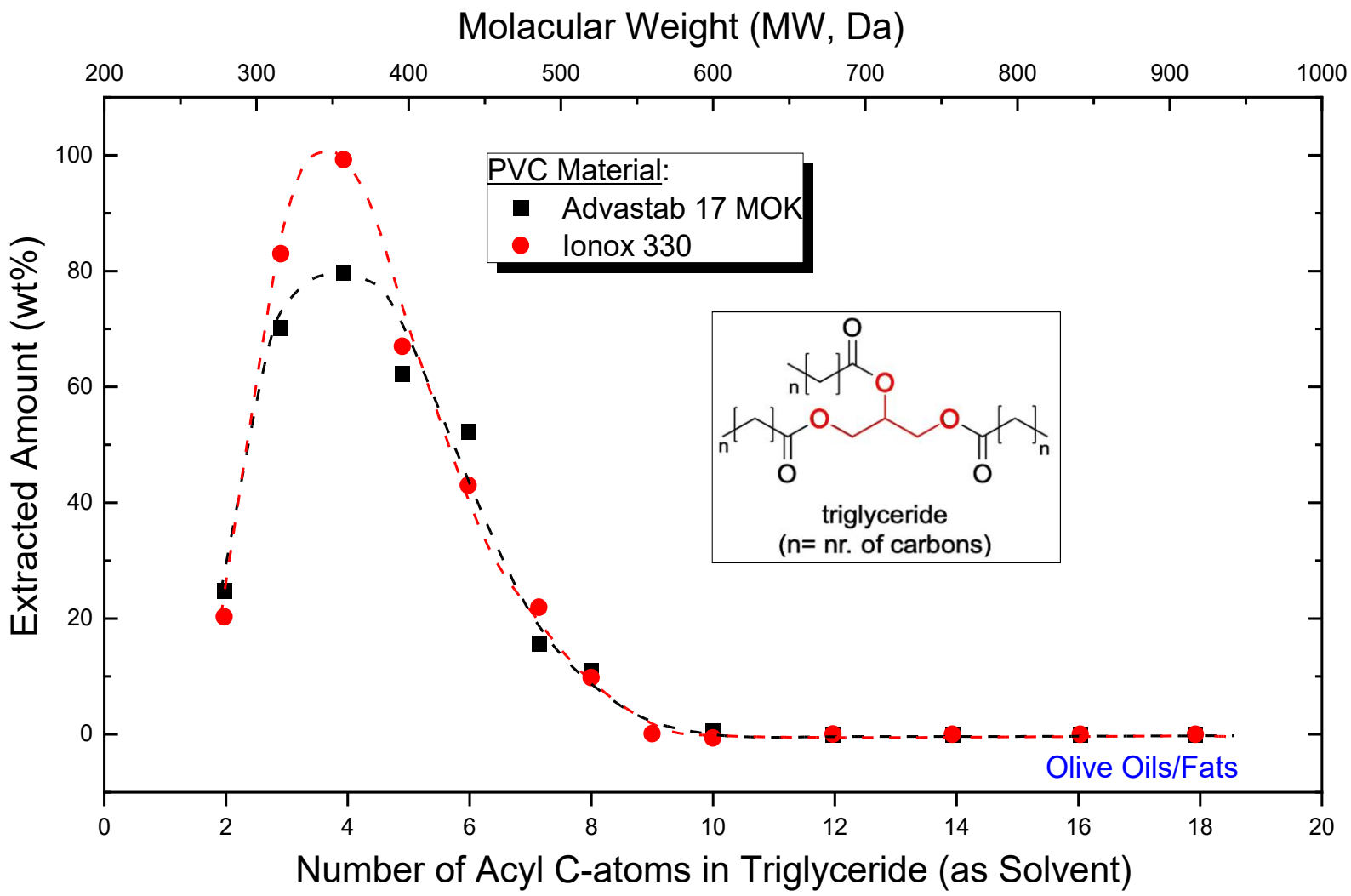
Extraction Power of Tissues (3): Silicone Drug Device into Blood



Albumin is highly water-soluble but contains hydrophobic binding pockets, it acts as a crucial "depot" or "transporter" for molecules that cannot dissolve well in blood plasma. Albumin can bind to and carry a wide variety of hydrophobic molecules that would otherwise not dissolve in blood plasma.

a) Source: Compiled from the data by Schuhman and Taubert, Acta Biol. Med. Germ., 24:897 (1970)
b) Kamlet, Mortimer J., et al. "Solubility properties in polymers and biological media: 6. An equation for correlation and prediction of solubilities of liquid organic nonelectrolytes in blood." *Journal of pharmaceutical sciences* 75.4 (1986): 350-355.
c) Asrorov, Akmal M., et al. "Albumin is a reliable drug-delivering molecule: Highlighting points in cancer therapy." *Medicine in Drug Discovery* 22 (2024): 100186.
d) Makriyannis, Alexandros, Jianxin Guo, and Xiaoyu Tian. "Albumin enhances the diffusion of lipophilic drugs into the membrane bilayer." *Life sciences* 77.14 (2005): 1605-1611.

Extraction Power of Tissues (3): *Extraction Power of Fatty Tissues (PVC)*

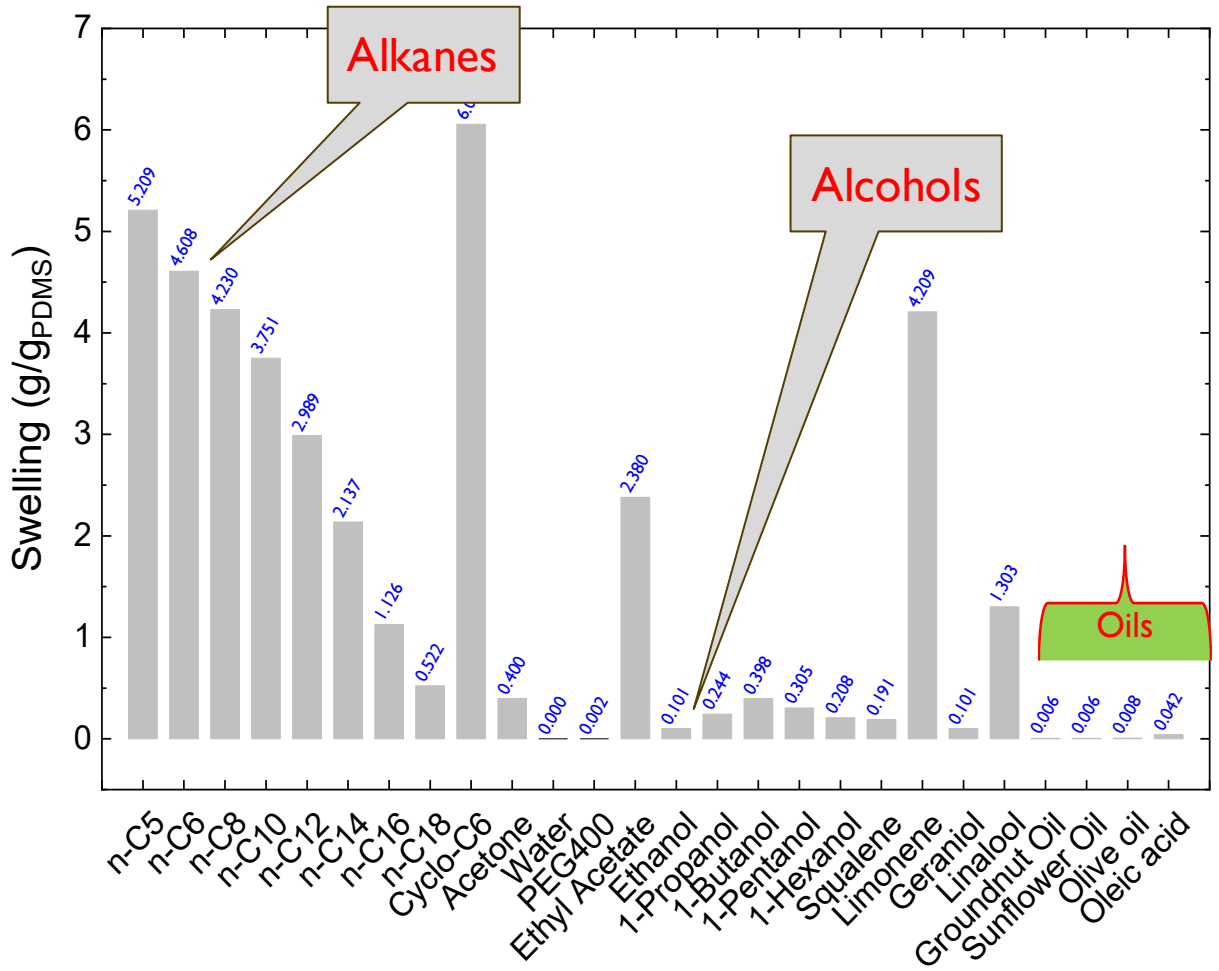


As solvent MW increases *(65 °C/5 Hour~1 day at 37 C)*,

- Its polarity remains similar or decreases.
- Its viscosity increases
- Its swelling increases and then decreases
- Extraction power determined by solvent (tissue)-PVC interactions

Figge, K. "Migration of components from plastics-packaging materials into packed goods—test methods and diffusion models." *Progress in polymer science* 6.4 (1980): 187-252.
Shepherd, M. J. "Trace contamination of foods by migration from plastics packaging—A review." *Food chemistry* 8.2 (1982): 129-145.

Extraction Power of Tissues (4): *Solvent Absorption/Swelling*



- This size exclusion characteristic of polymers is the reason for extremely low diffusion rates of fats.
- The molecular size limitation of silicone is ~ 500-700 Daltons.
- Viscosity of fats is high, leading to slow penetration.

Regardless of their polarity, the size and viscosity of fatty tissues dominantly controls their interactions with plastics.

a) Cocchi, Giovanni, Maria Grazia De Angelis, and Ferruccio Doghieri. "Solubility and diffusivity of liquids for food and pharmaceutical applications in crosslinked polydimethylsiloxane (PDMS) films: I. Experimental data on pure organic components and vegetable oil." *Journal of membrane science* 492 (2015): 600-611.

b) Smedes, Foppe, et al. "Partitioning of hydrophobic organic contaminants between polymer and lipids for two silicones and low density polyethylene." *Chemosphere* 186 (2017): 948-957.

c) Barcelo, Damia, and Yolanda Pico, eds. *Sample Handling and Trace Analysis of Pollutants: Innovations to Determine Organic Contaminants*. Elsevier, 2024.

Extraction Power of Tissues (5): *Storage Fatty Tissue Absorption in Silicone*

Table 5. *Mean Lipid Wt.% in 28 Silicone Implants for Joints Other Than Finger Joints*

DURATION OF IMPLANTATION (MONTHS)	INTACT IMPLANTS		FRACTURED IMPLANTS		P VALUE
	No. Impl.	*Wt.% X ± S.E.*	*No. Impl.*	*Wt.% X ± S.E.*	
1–60	20	0.505 ± 0.069	8	0.405 ± 0.081	$p > 0.01$

NOTES:

- All (storage) fats of different types and sources have the same solvation properties.
- Fats are equivalent to vegetable oils such as olive oils.

Swanson, Alfred B., et al. "Durability of silicone implants—an in vivo study." *Orthopedic Clinics of North America* 4.4 (1973): 1097-1112.

Extraction Power of Tissues (6): *Simulating Solvent of Fats for Polyolefins*

Hint from Food Industries:

Yes, ethanol, specifically 95%, is widely recognized as a proxy simulant for fatty foods for polyolefins in food contact and packaging safety assessments.

a) FDA, 2016. Guidance Documents & Regulatory Information by Topic - Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations. http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm081818.htm.

b) Chang, Shu-Sing, Walter J. Pummer, and John R. Maurey. "Fat-simulating and accelerating solvents for polyolefins and MWD of solvent extracts of polyethylenes." *Polymer* 24.10 (1983): 1267-1272.

c) Baner, A., et al. "Alternative fatty food simulants for migration testing of polymeric food contact materials." *Food Additives & Contaminants* 9.2 (1992): 137-148.

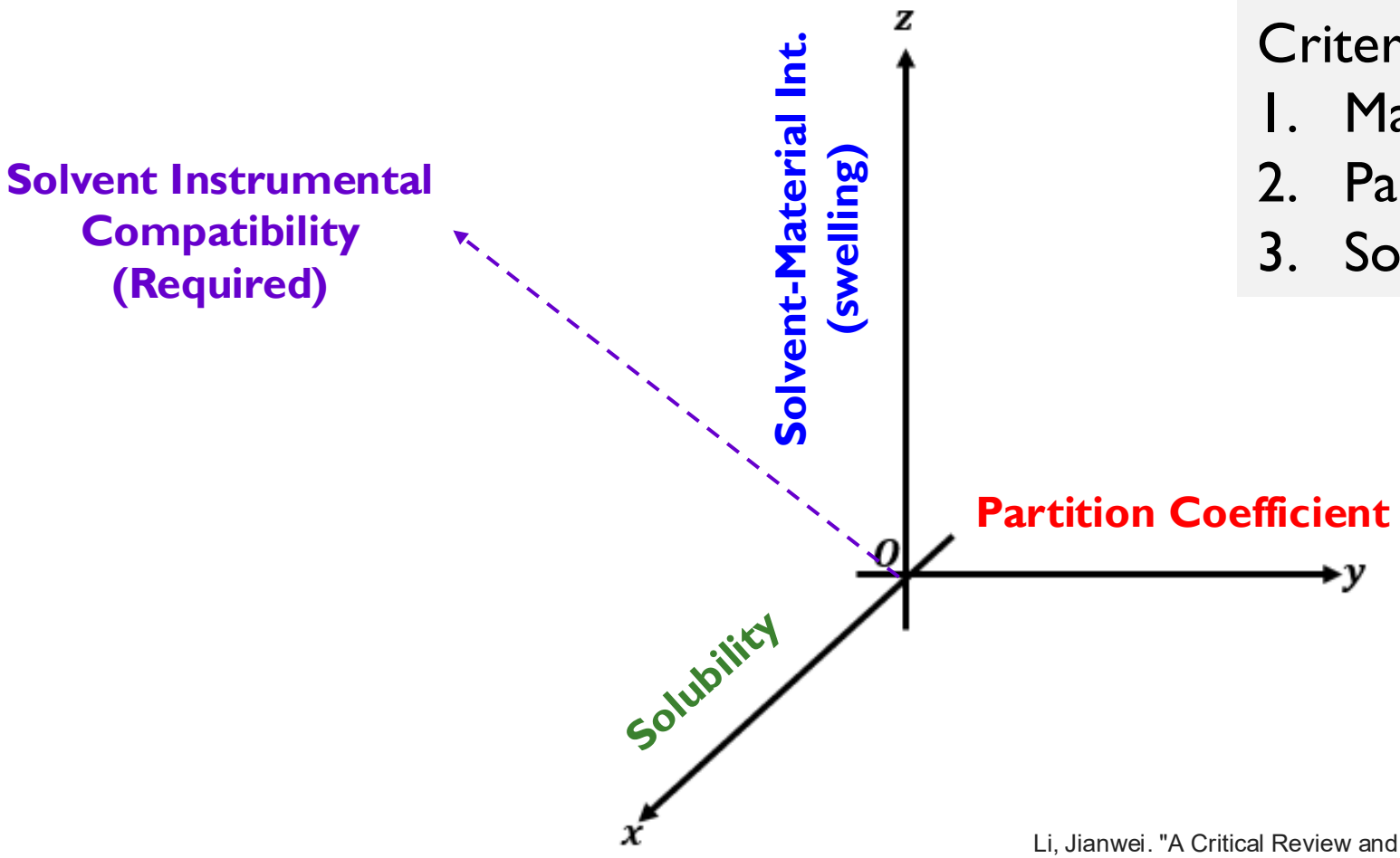
d) Ernstoff, Alexi S., et al. "High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools." *Food and Chemical Toxicology* 109 (2017): 428-438.

e) Seiler, Annika, et al. "Correlation of foodstuffs with ethanol–water mixtures with regard to the solubility of migrants from food contact materials." *Food Additives & Contaminants: Part A* 31.3 (2014): 498-511.

f) Cooper, Ian, Anne Goodson, and Anthony O'Brien. "Specific migration testing with alternative fatty food simulants." *Food Additives & Contaminants* 15.1 (1998): 72-78.

Simplify Extraction Solvents

How to Streamline and Establish Solvent Similarity (3D)?



Criteria for solvent similarity:

1. Material swelling by solvent
2. Partition
3. Solubility

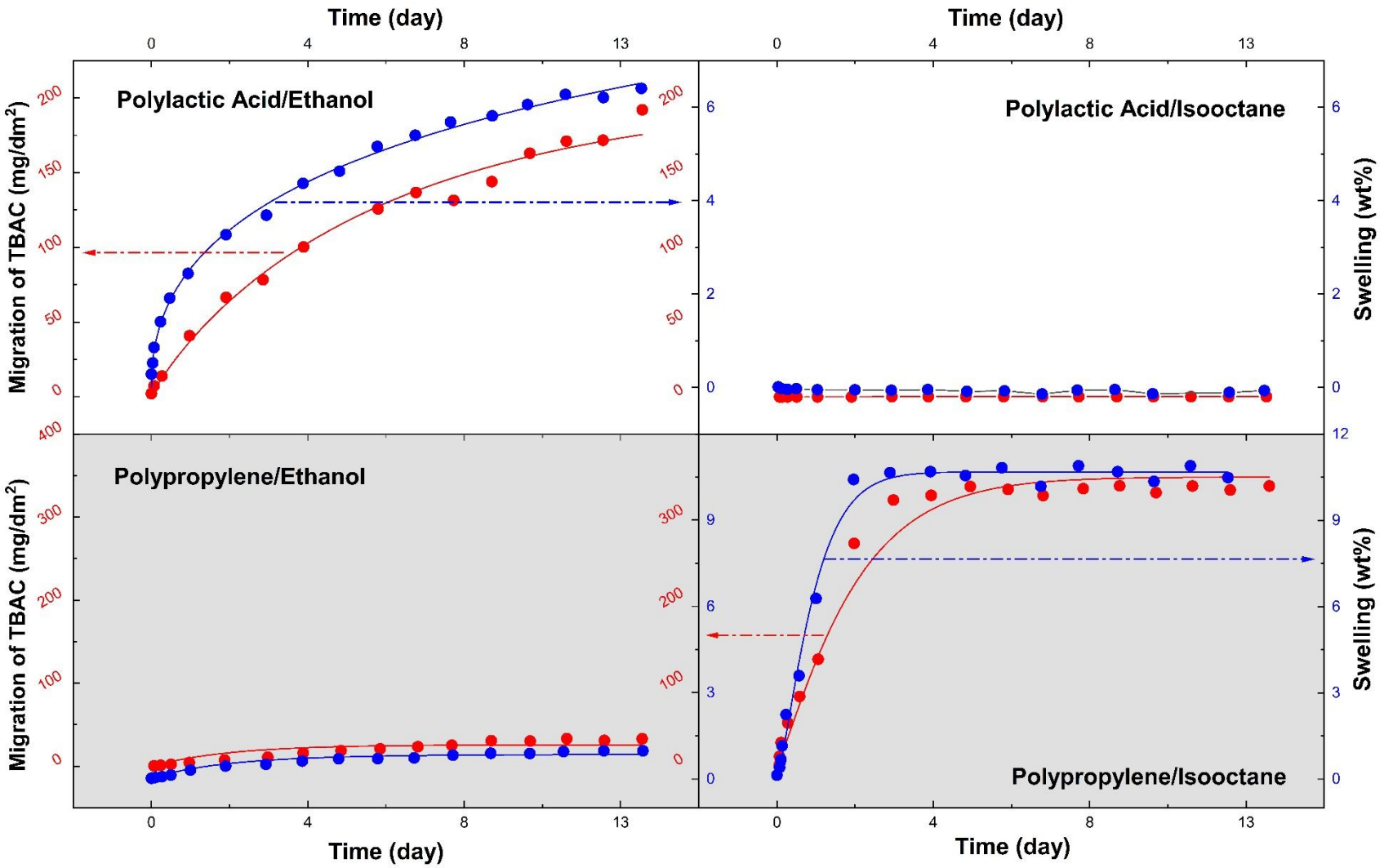
Li, Jianwei. "A Critical Review and Analysis of Thermodynamic and Kinetic Effects on Extraction of Medical Devices by Organic Solvents as a Sample Preparation Step in Devices' Chemical Characterization." *Journal of Chromatography Open* (2026): 100309.

How to Establish Solvent Similarity: Blood as Example

For biocompatibility testing of blood-contacting medical devices, ethanol/water mixtures between ***20% and 40% (v/v)*** are typically used to represent the extracting power of human blood. The specific percentage chosen depends on the target compounds being tested and the standard guidelines followed:

20% Ethanol (v/v)	Jordi, Mark Anderson, et al. "Comparison of Binary Alcohol/Water Solvent Systems to Blood for Extractions of Blood-Contacting Medical Devices." PDA Journal of Pharmaceutical Science and Technology 78.5 (2024): 560-571.
40% Ethanol (v/v)	Luo, Hongyu, et al. "Evaluation of the Di (2-ethylhexyl) phthalate released from polyvinyl chloride medical devices that contact blood." Springerplus 3.1 (2014): 58
17.2% Ethanol (v/v)	(a) Badding, Melissa A., et al. "Toxicological risk assessment of bisphenol a released from dialyzers under simulated-use and exaggerated extraction conditions." Regulatory Toxicology and Pharmacology 118 (2020): 104787. (b) Haishima, Yuji, et al. "Elution of bisphenol-A from hemodialyzers consisting of polycarbonate and polysulfone resins." Journal of Biomedical Materials Research: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials 58.2 (2001): 209-215.
40% Ethanol (v/v)	ISO 10993-12/18
50-60% Ethanol (v/v)	Li, Jianwei. "Evaluation of blood simulating solvents in extractables and leachables testing for chemical characterization of medical devices based on Abraham general solvation model." *Journal of Molecular Liquids* 345 (2022): 116995.

Solvent Similarity (1): Significance of Swelling on Migration (PLA/PP)



Migration of TBTC into ethanol and isooctane from PLA and PP.

TBTC: tributyl acetyl citrate

Kirchkeszner, Csaba, et al. "Swelling as a promoter of migration of plastic additives in the interaction of fatty food simulants with polylactic acid-and polypropylene-based plastics." *Food Control* 132 (2022): 108354.

Solvent Similarity (1): Swelling Map of Materials by Different Solvents

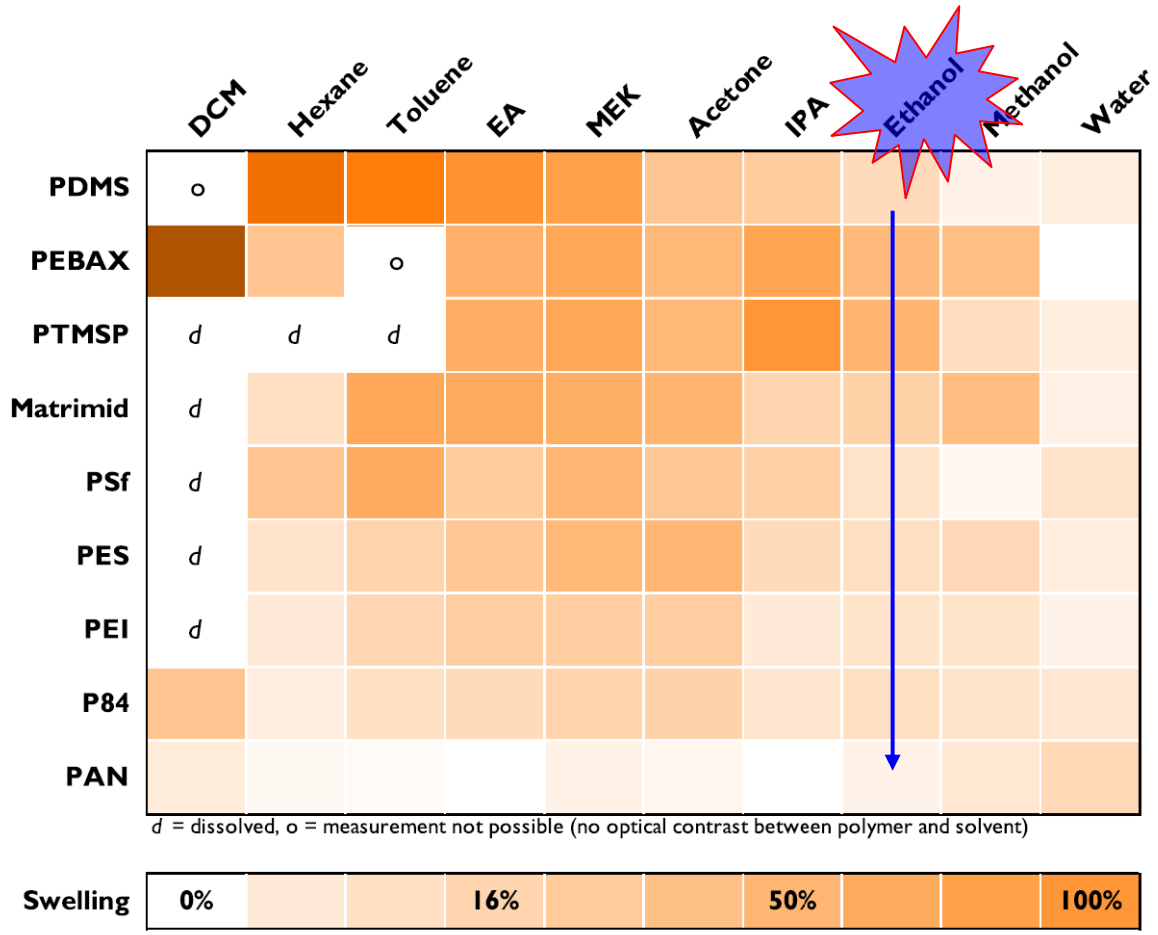


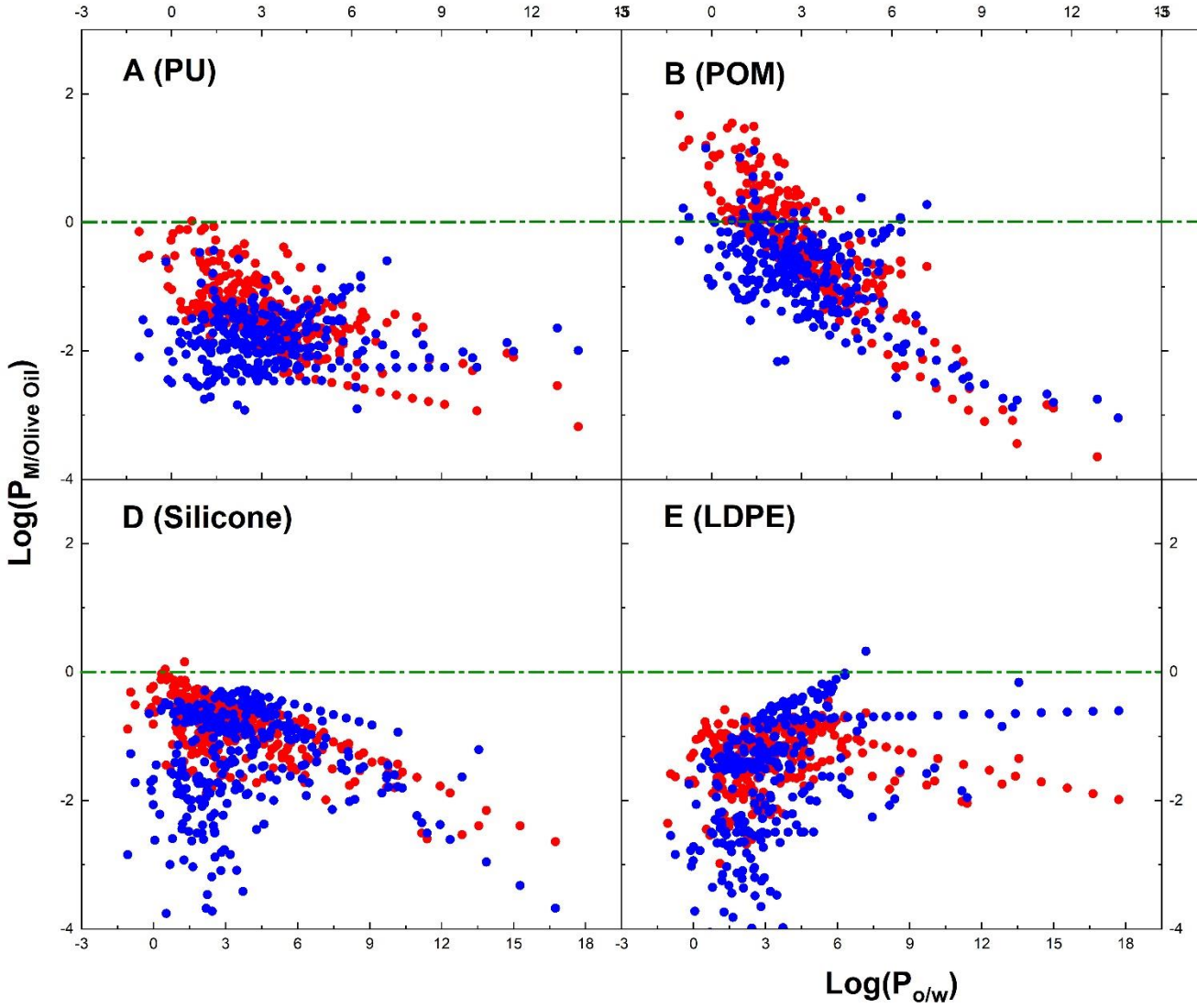
Fig. 22. Overview of all swelling degrees measured after long-term exposure to the respective solvents. For each polymer-solvent combination, the last measured data point was taken. 'o' indicates absence of a measurement due to lack of optical contrast, 'd' indicates dissolution of the polymer in the solvent.

Ethanol is considered as a general solvent by swelling

Poly(acrylonitrile) (PAN)
Poly(sulfone) (PSf)
Poly(ether sulfone) (PES)
Polydimethylsiloxane (PDMS)
Poly(ether imide) (PEI)
Poly (ether block amide) (trade name: PEBAX)
Poly(imide) (P84 and Matrimid)
Poly[1-(trimethylsilyl)-1-propyne] (PTMSP)

Kappert, Emiel J., et al. "Swelling of 9 polymers commonly employed for solvent-resistant nanofiltration membranes: A comprehensive dataset." *Journal of membrane science* 569 (2019): 177-199.

Solvent Similarity (2): Partition Coefficient of Ethanol and Olive Oil



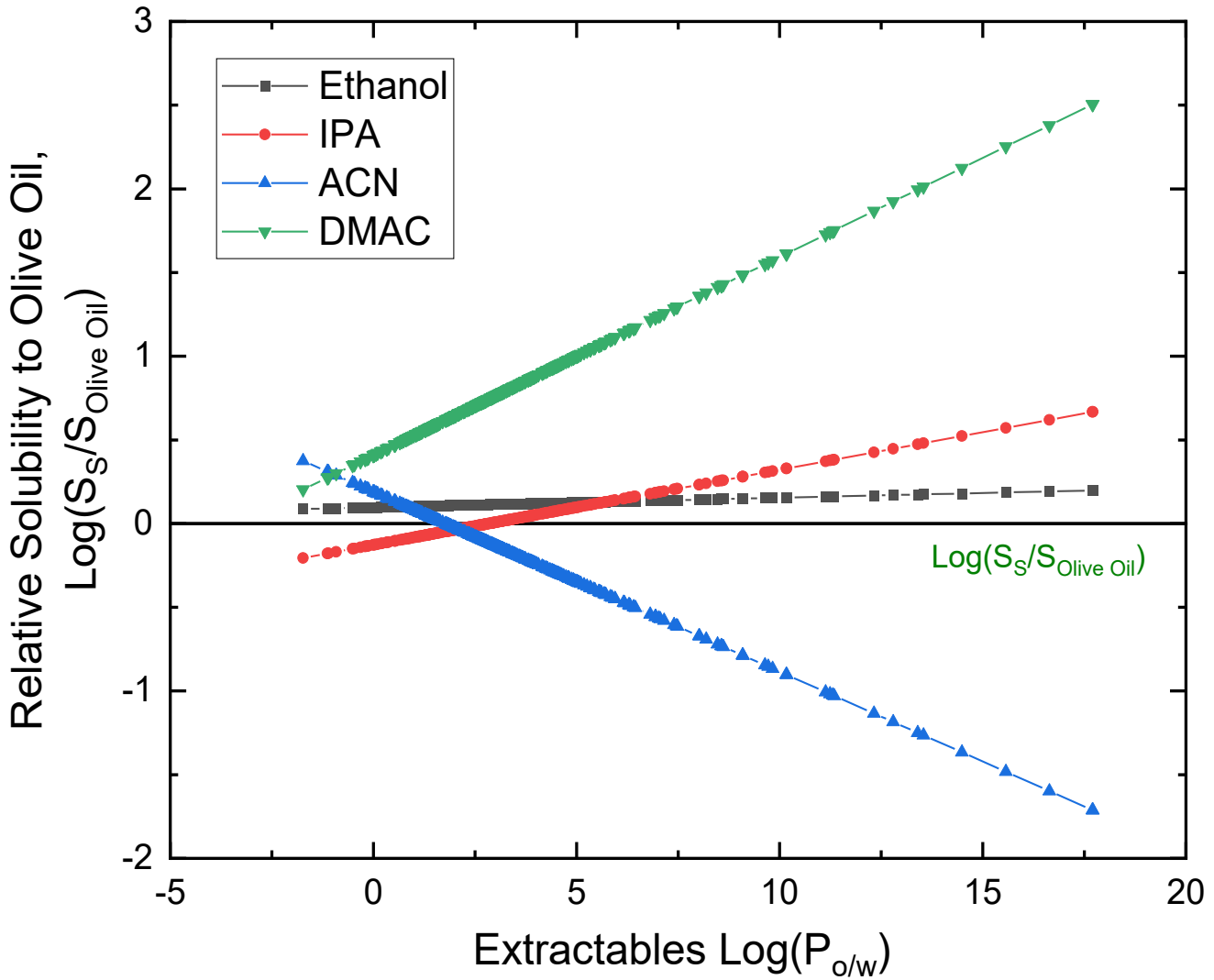
Ethanol has equivalent or better partition properties to fats

Olive Oil
Ethanol

LDPE: low density polyethylene
Silicone: PDMS
PU: Poly(ether)urethane
POM: Polyoxymethylene
PA: Polyacrylate

Li, Jianwei. "A Critical Review and Analysis of Thermodynamic and Kinetic Effects on Extraction of Medical Devices by Organic Solvents as a Sample Preparation Step in Devices' Chemical Characterization." *Journal of Chromatography Open* (2026): 100309.

Solvent Similarity (3): Comparison of Solubility of Ethanol and Olive Oil



Ethanol has equivalent solubility properties to fats

Conclusion:

Ethanol is same as (storage) fatty tissue!

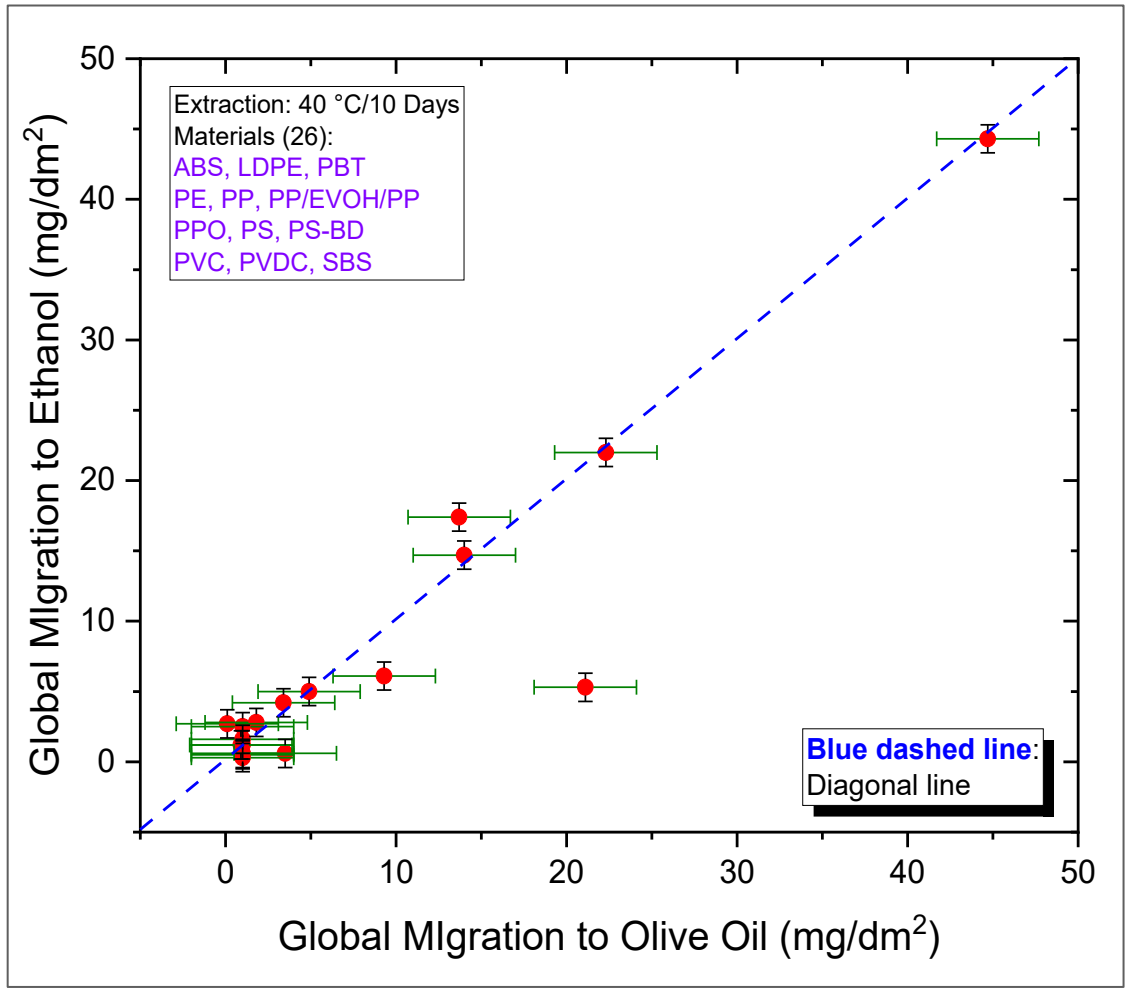
Li, Jianwei. "A Critical Review and Analysis of Thermodynamic and Kinetic Effects on Extraction of Medical Devices by Organic Solvents as a Sample Preparation Step in Devices' Chemical Characterization." *Journal of Chromatography Open* (2026): 100309.

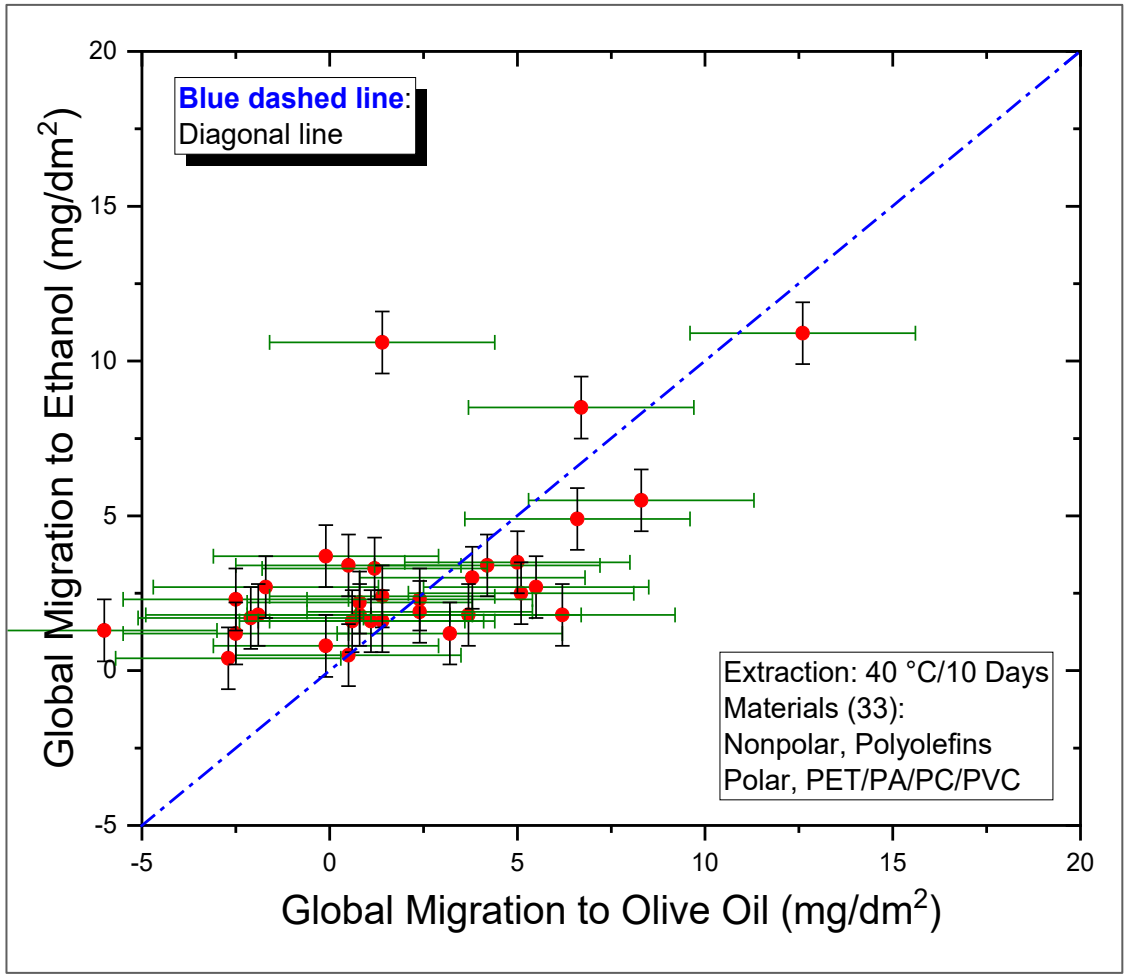
How to Streamline Chemical Characterization?

Tissue (Contact)	Simulating Solvents
Blood	Water Ethanol/water 50/50 (v/v)
(Storage) fatty tissues	Water Ethanol

Show Me the Money

Correlation between Ethanol vs. Olive oil (Fats)-Overall Migration

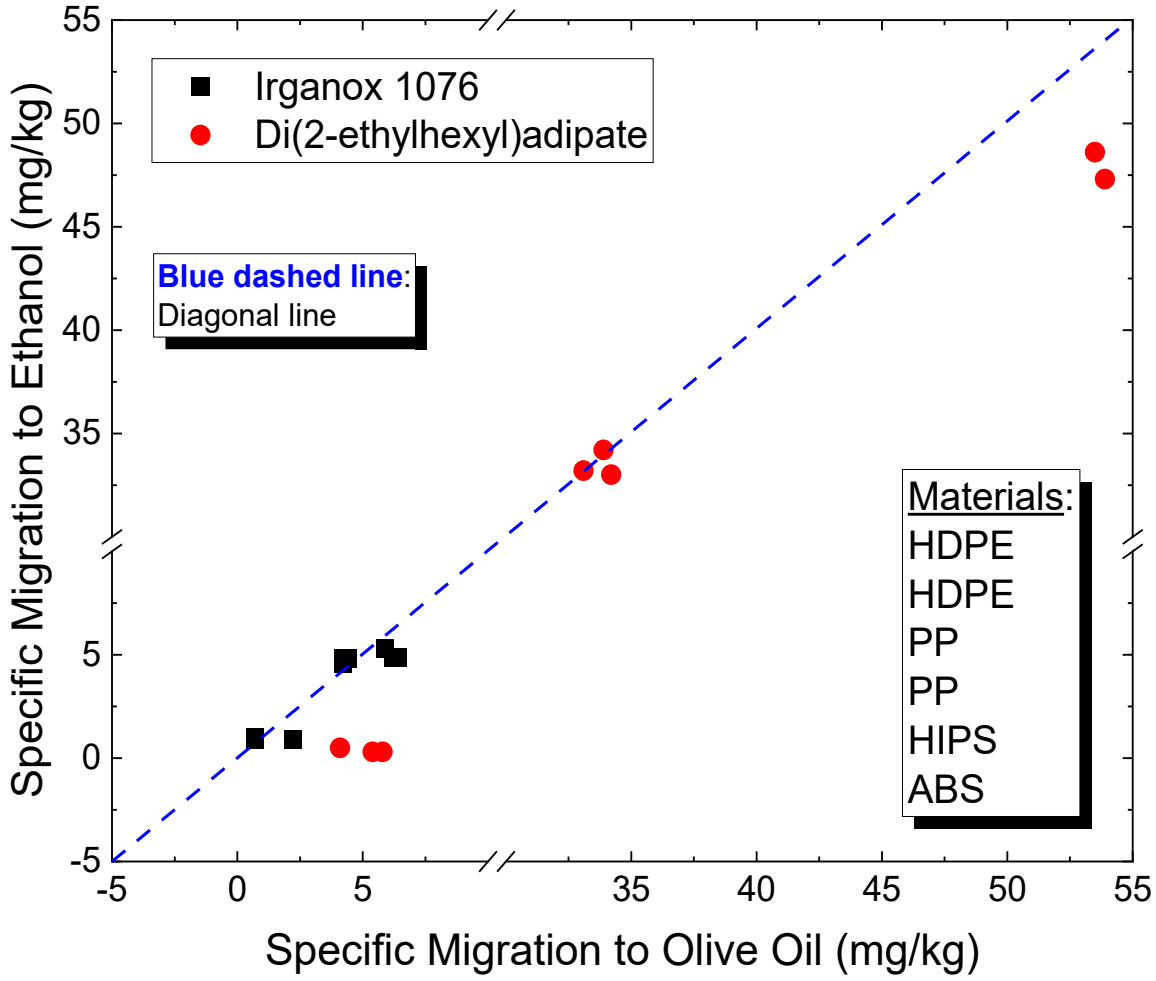




a) de Kruijf, Nico, and Rinus Rijk. "The suitability of alternative fatty food simulants for overall migration testing under both low-and high-temperature test conditions." *Food Additives & Contaminants* 14.6-7 (1997): 775-789.

b) Baner, A. Lawrence, Roland Franz, and Otto Piringer. "Alternative fatty food simulants for polymer migration testing: Experimental confirmation." *Journal of polymer engineering* 15.1-2 (1995): 161-180.

Correlation between Ethanol vs. Olive oil (Fats)-Specific Migration



Cooper, Ian, Anne Goodson, and Anthony O'Brien. "Specific migration testing with alternative fatty food simulants." *Food Additives & Contaminants* 15.1 (1998): 72-78.

Other Relevant References on Ethanol vs Fats

a) FDA, 2016. Guidance Documents & Regulatory Information by Topic - Guidance for Industry: Preparation of Premarket Submissions for Food Contact Substances: Chemistry Recommendations. http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm081818.htm.

b) Chang, Shu-Sing, Walter J. Pummer, and John R. Maurey. "Fat-simulating and accelerating solvents for polyolefins and MWD of solvent extracts of polyethylenes." *Polymer* 24.10 (1983): 1267-1272.

c) Baner, A., et al. "Alternative fatty food simulants for migration testing of polymeric food contact materials." *Food Additives & Contaminants* 9.2 (1992): 137-148.

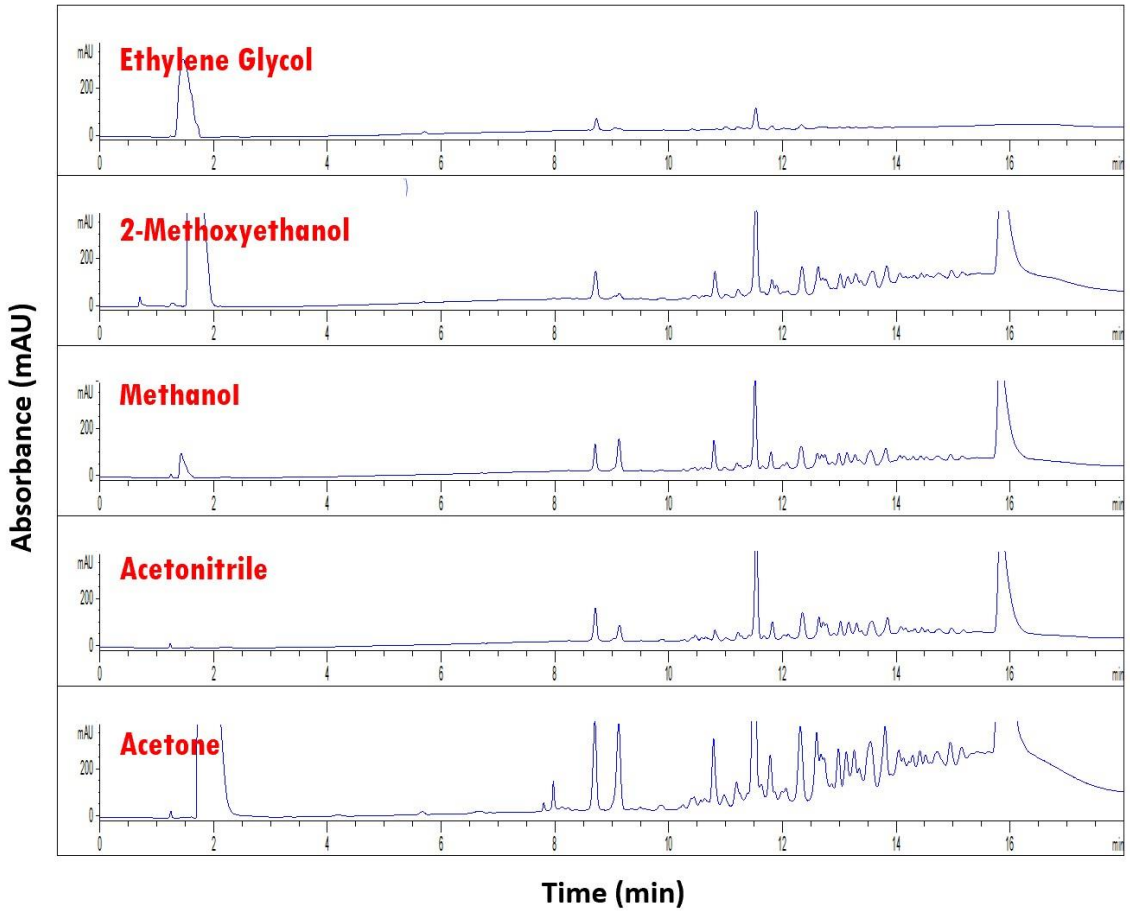
d) Ernstoff, Alexi S., et al. "High-throughput migration modelling for estimating exposure to chemicals in food packaging in screening and prioritization tools." *Food and Chemical Toxicology* 109 (2017): 428-438.

e) Seiler, Annika, et al. "Correlation of foodstuffs with ethanol–water mixtures with regard to the solubility of migrants from food contact materials." *Food Additives & Contaminants: Part A* 31.3 (2014): 498-511.

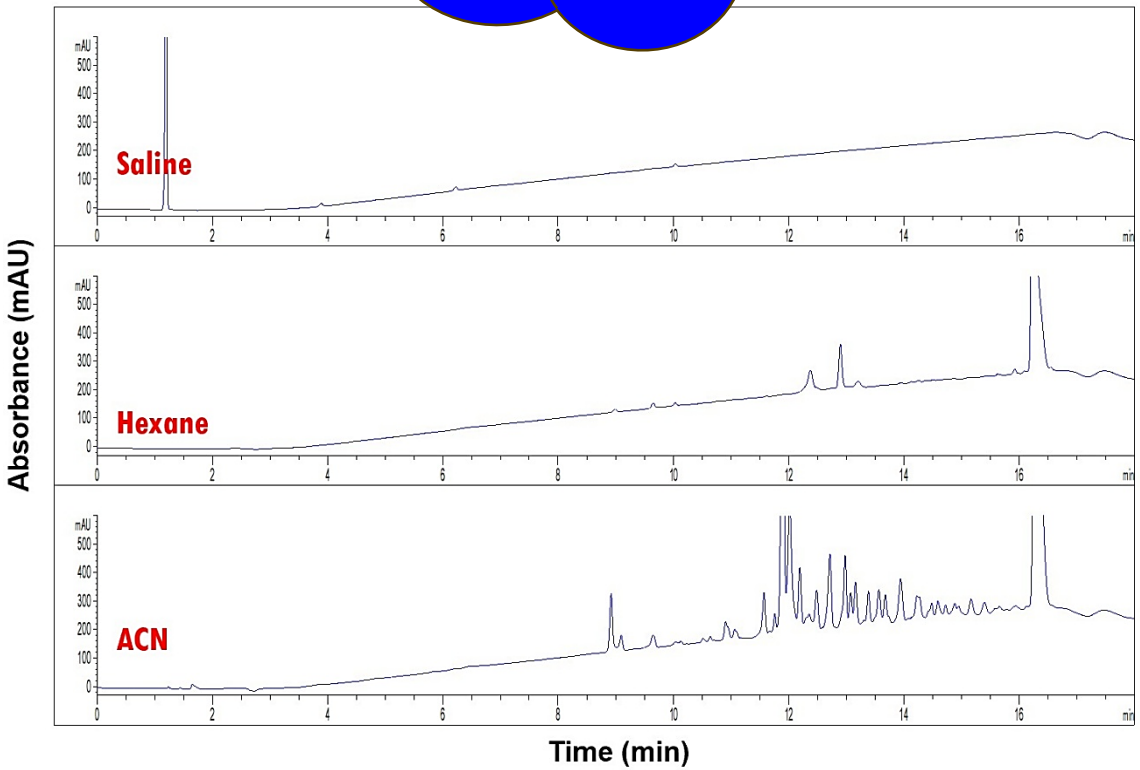
f) Cooper, Ian, Anne Goodson, and Anthony O'Brien. "Specific migration testing with alternative fatty food simulants." *Food Additives & Contaminants* 15.1 (1998): 72-78.

g) Guazzotti, Valeria, et al. "Migration testing of GPPS and HIPS polymers: Swelling effect caused by food simulants compared to real foods." *Molecules* 27.3 (2022): 823.

You Don't Need Alkanes for Polar Polymers-PU/PVC/PET



Ethanol is a stronger solvent than alkanes for "moderately polar or polar" materials!



Note: Ethanol data not collected. Ethanol~Methanol~2-Methoxyethanol

Li, Jianwei. "A Critical Review and Analysis of Thermodynamic and Kinetic Effects on Extraction of Medical Devices by Organic Solvents as a Sample Preparation Step in Devices' Chemical Characterization." *Journal of Chromatography Open* (2026): 100309.

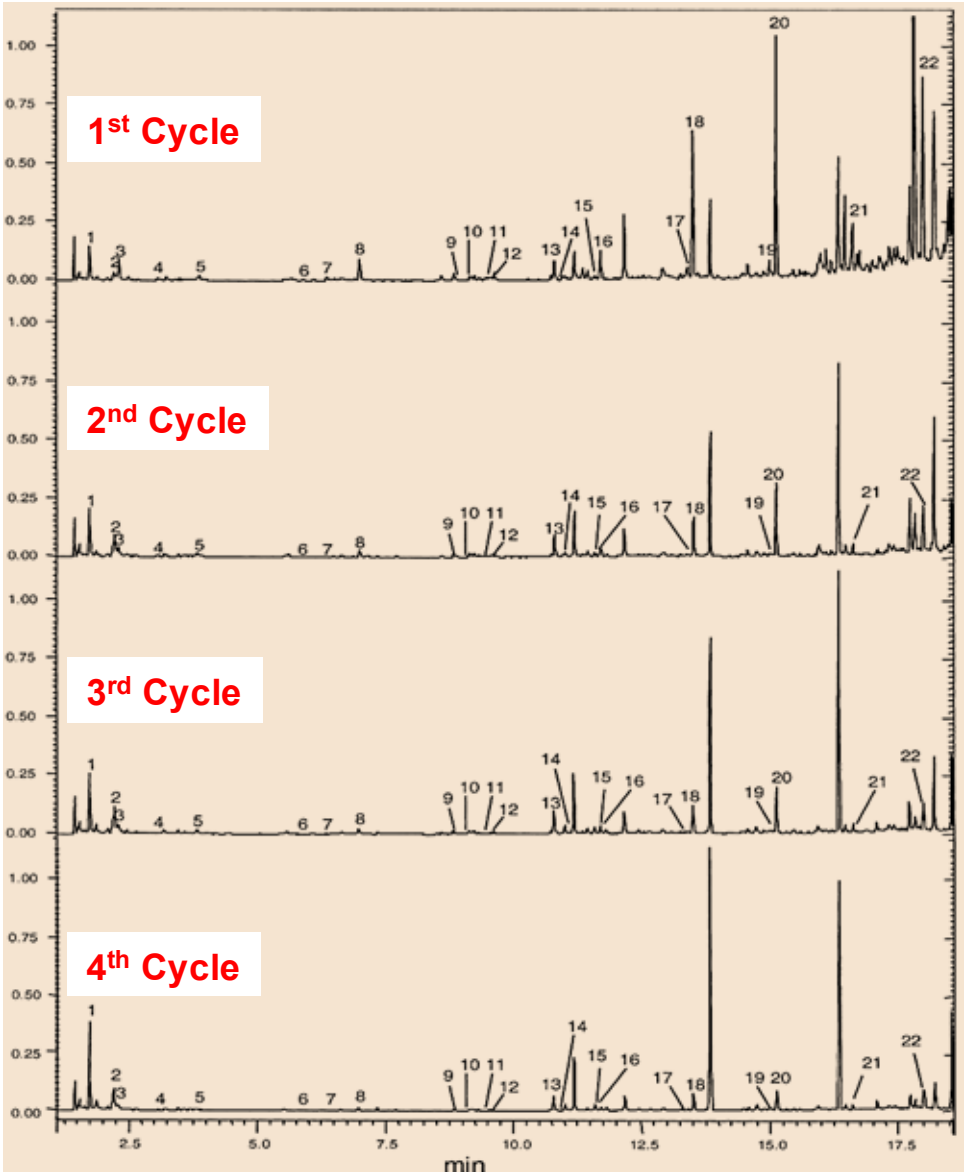
End/Questions



Exaggeration Using Tissue Equivalent/Relevant Solvent

(1) Appropriately Challenging/(2) Scientifically Justified/(3) Capable of Generating Meaningful Evidence

How to Improve Degree of Extraction by Ethanol w/o Alkanes?



1) Temperature: 50 °C (D ↑~4)

2) Sequential extraction (K↑~1-100)

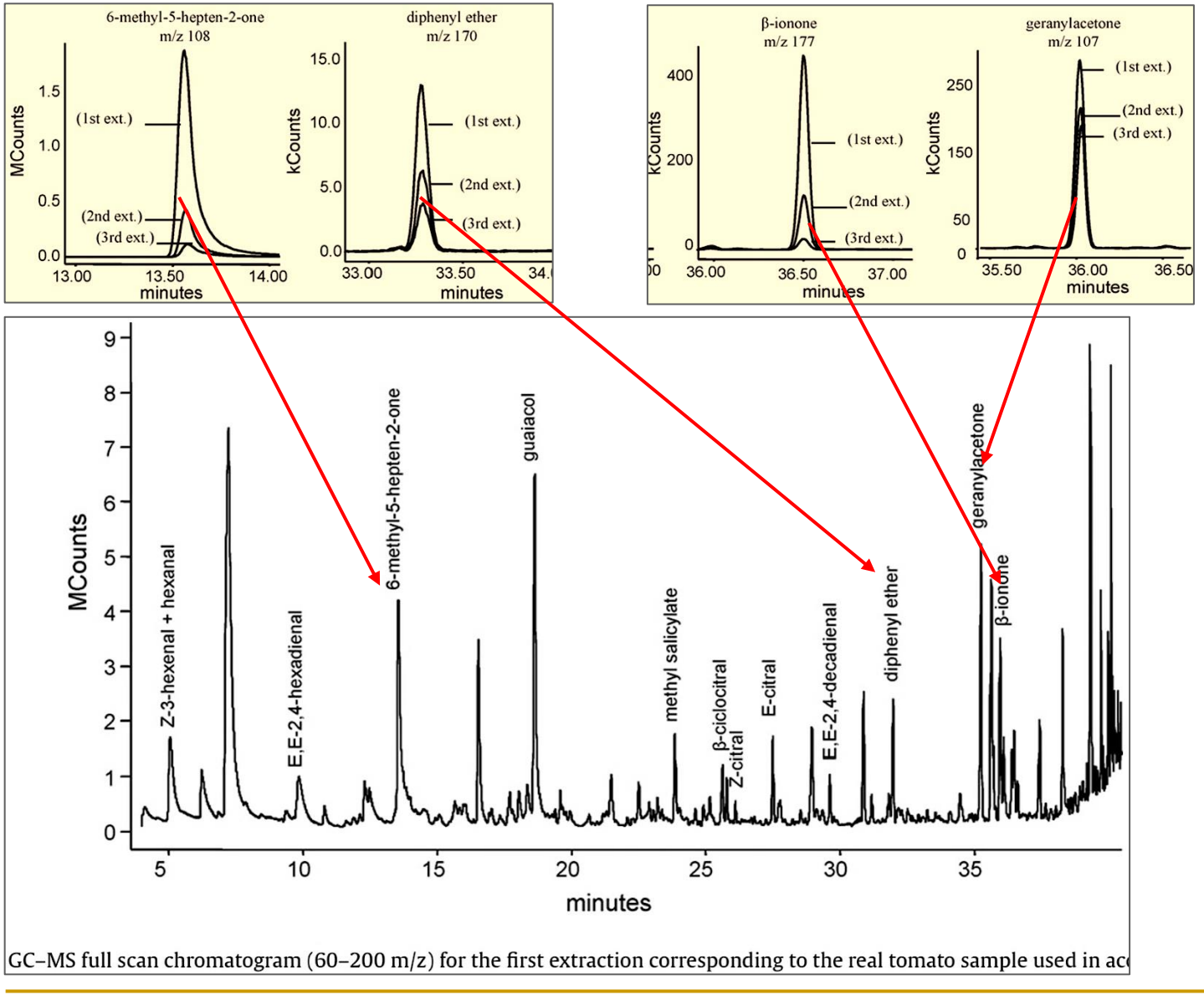
3) Duration: 24 hours (not 72 hours) (↑~3)

4) Viscosity (olive oil, 30-43 cP vs ethanol, 0.83 cP) at 40 °C

5) Mass transfer at interfacial layer

Ezquerro, Óscar, Begoña Pons, and María Teresa Tena. "Multiple headspace solid-phase microextraction for the quantitative determination of volatile organic compounds in multilayer packagings." *Journal of Chromatography A* 999.1-2 (2003): 155-164.

Repeated Extraction and Exhaustion Determination

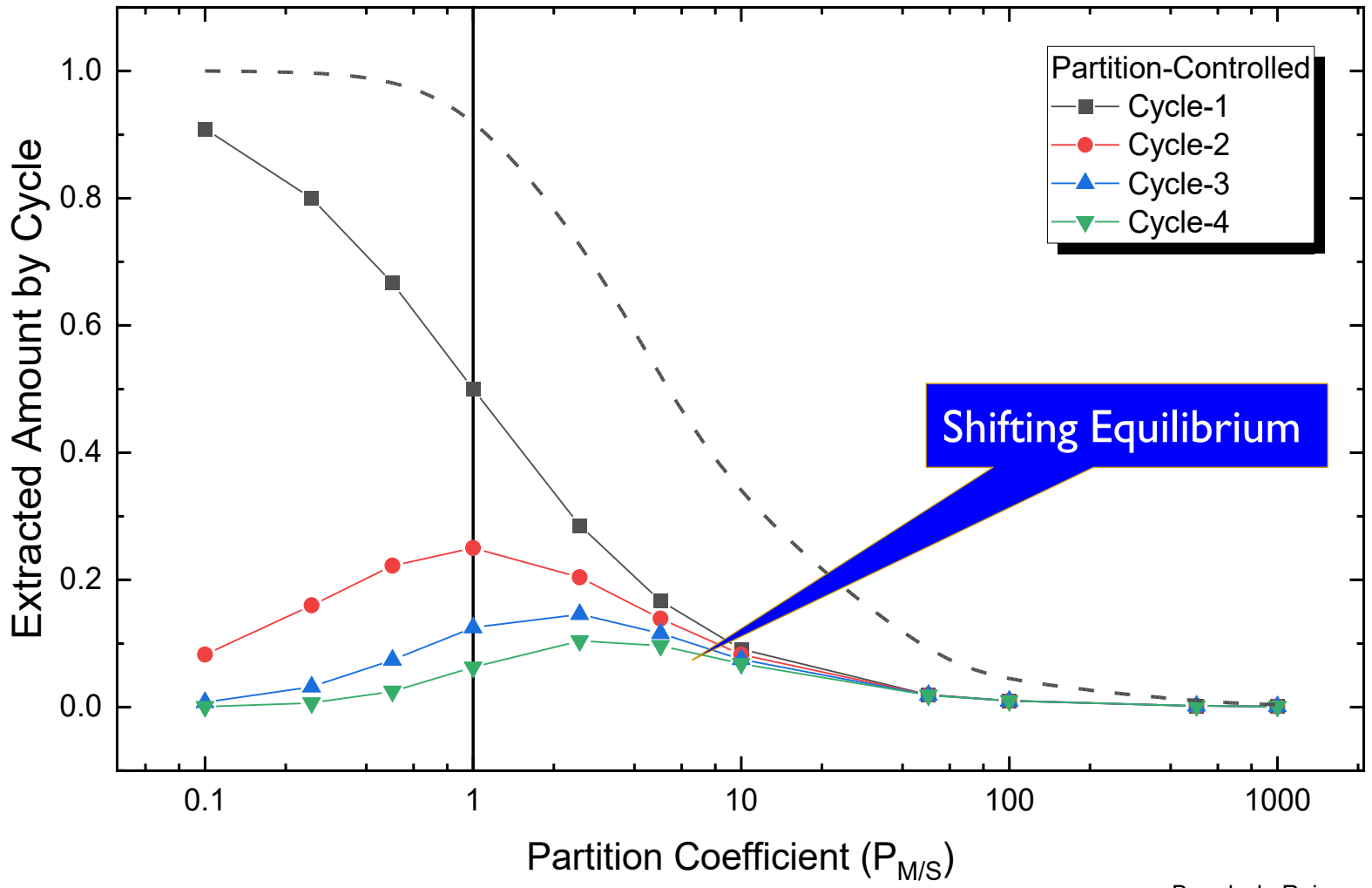


GC–MS full scan chromatogram (60–200 m/z) for the first extraction corresponding to the real tomato sample used in ac

Exhaustion determination by monitoring individual peaks

Serrano, Ernesto, J. Beltrán, and F. Hernández. "Application of multiple headspace-solid-phase microextraction followed by gas chromatography–mass spectrometry to quantitative analysis of tomato aroma components." *Journal of Chromatography A* 1216.1 (2009): 127-133.

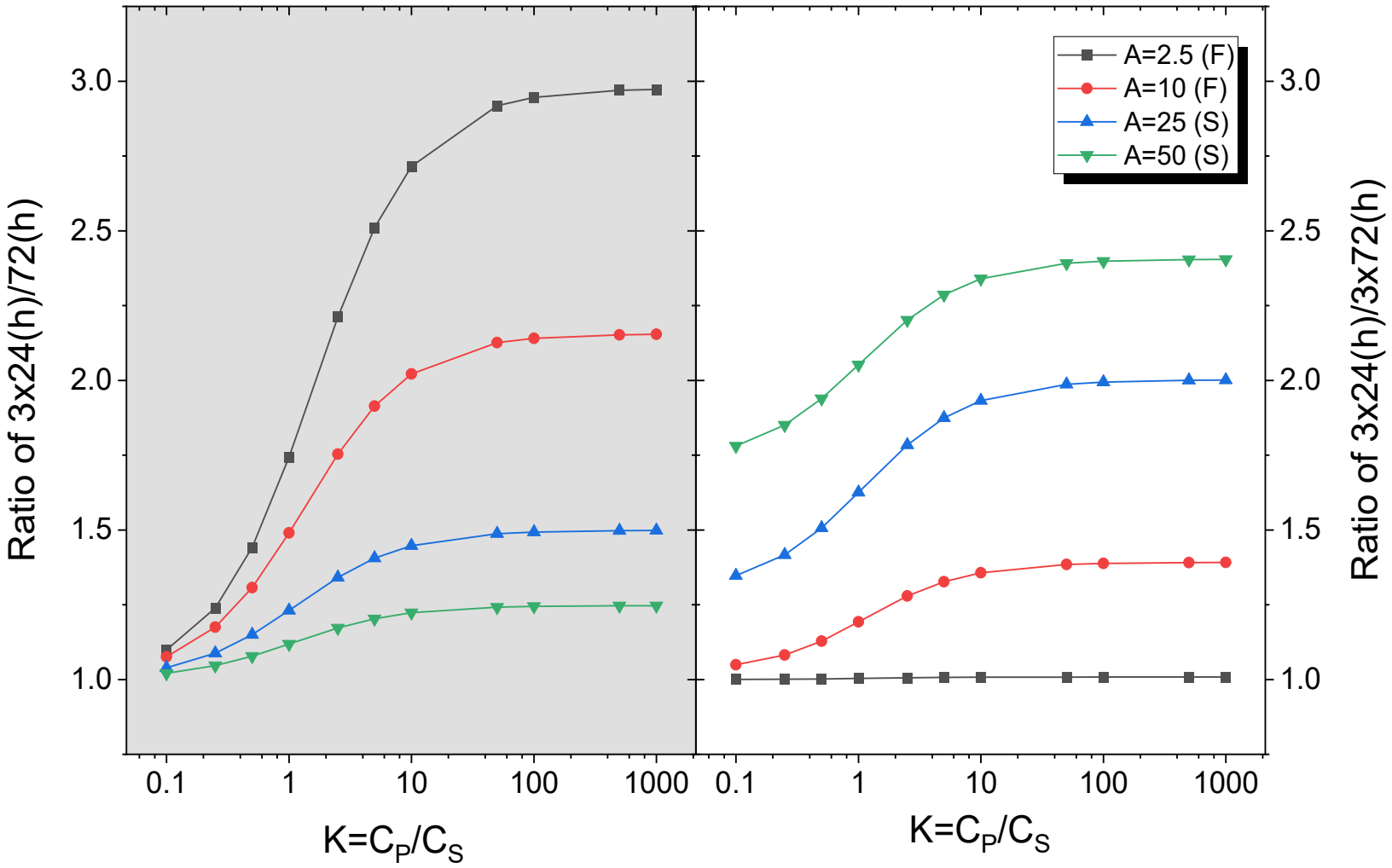
Thermodynamics and Kinetics of Extraction, Repeated Extractions



- Repeated extraction useful K~1 compounds.
- Repeated extraction improves thermodynamics with fast kinetics.

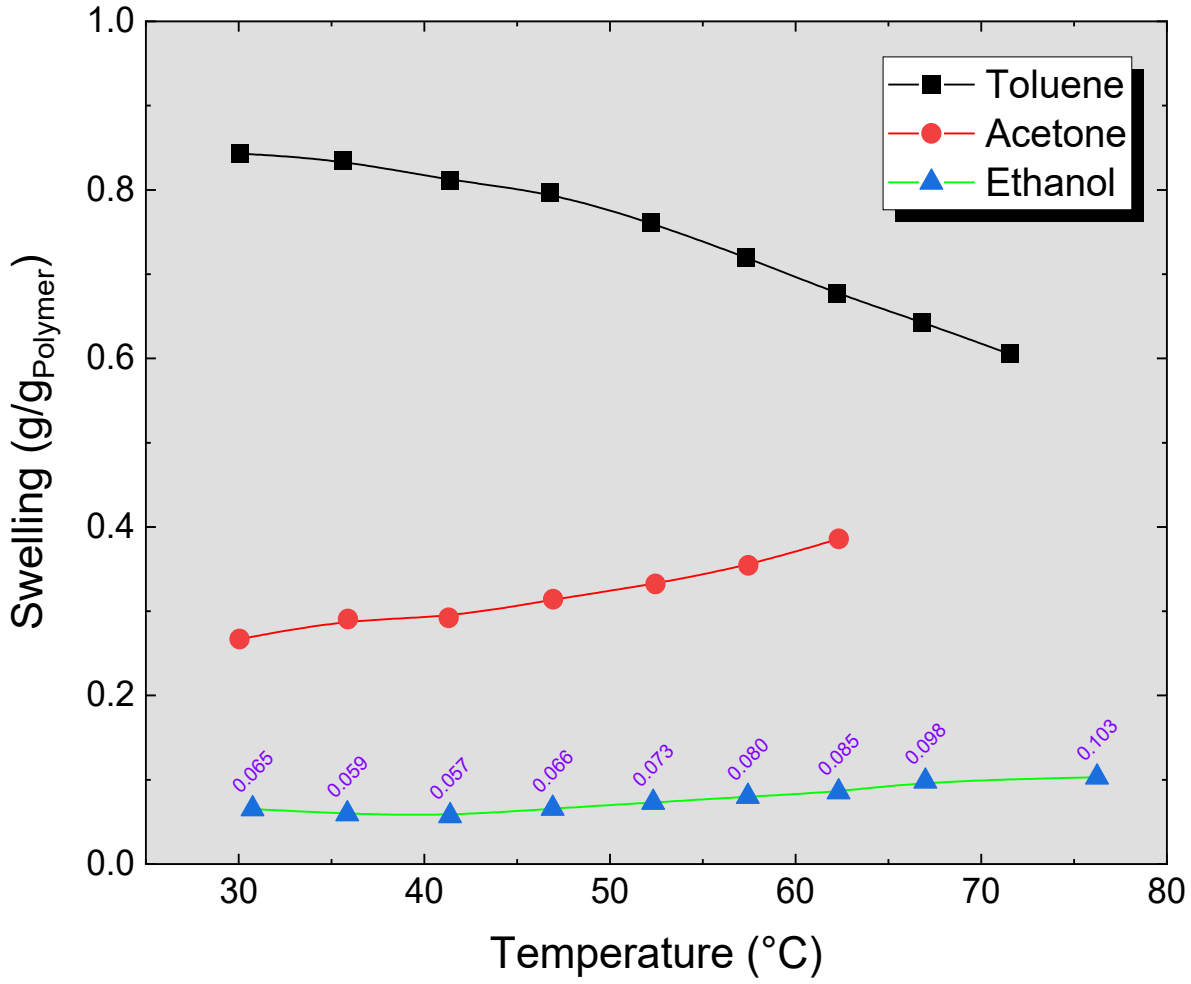
Brandsch, Rainer, et al. "Impact of partitioning in short-term food contact applications focused on polymers in support of migration modelling and exposure risk assessment." *Molecules* 27.1 (2021): 121.

Thermodynamics and Kinetics of Extraction, 24 h vs 72 h



- Repeated 24 extraction is more efficient, particularly for "fast" extractables.
- 72 hours are useful for very slow-release extractables.

Effect of Temperature on Swelling



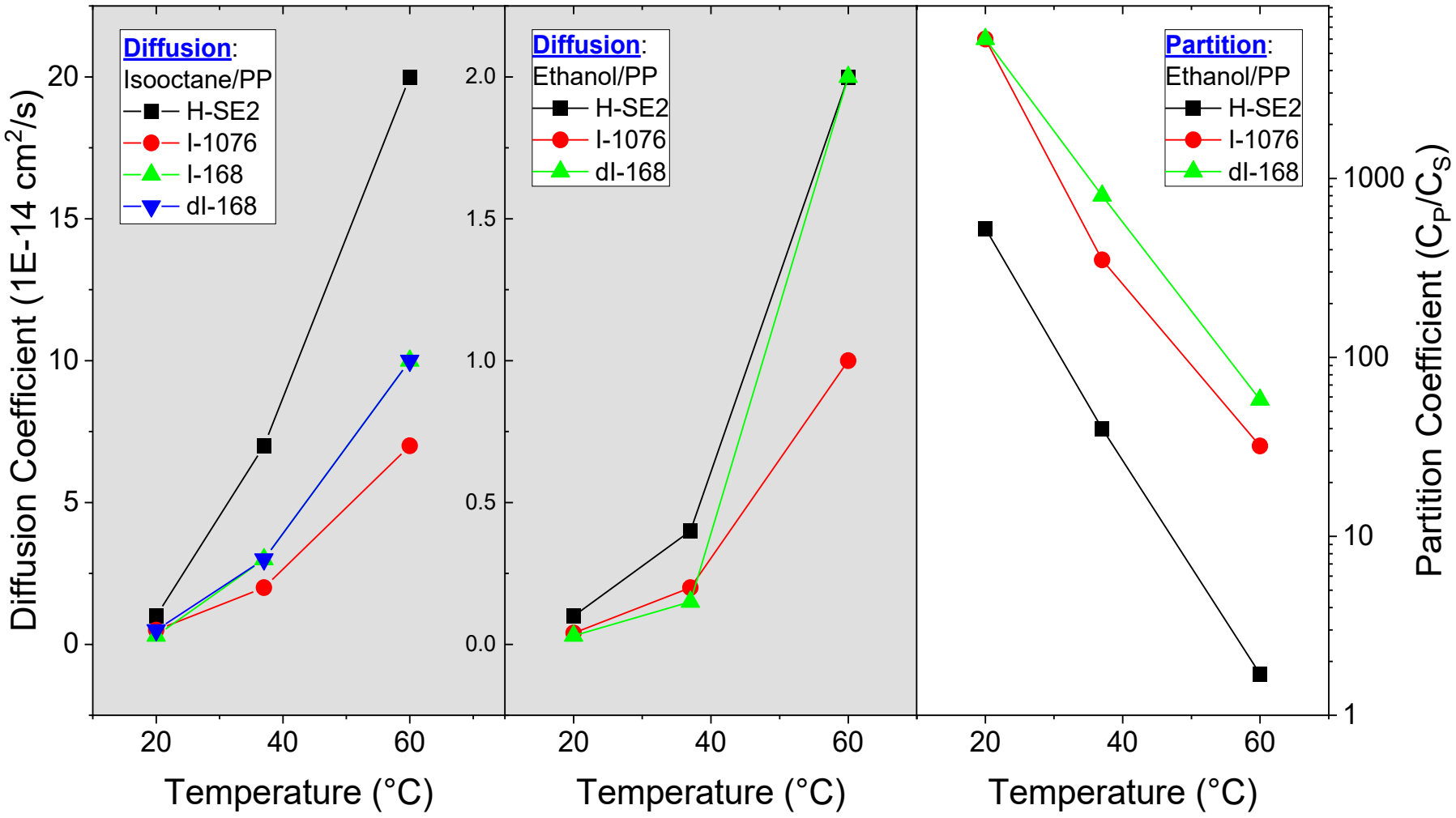
Silicone swelling by different solvents and at different temperature

Table 1. Physico-chemical properties of the pure solvents investigated, corresponding swelling (S) exerted on PDMS and PDMS–solvent interaction parameter (χ) at 40°C

Solvent	V	δ_s	S	χ
Hexamethyldisiloxane	214.00	10.8	0.882	0.743
Pentane	115.26	14.0	0.851	0.712
Heptane	146.60	14.8	0.734	0.759
Octane	162.60	15.2	0.650	0.794
Methylisobutylketone	124.90	16.8	0.738	0.795
Tetrachloromethane	96.500	17.2	2.174	0.712
Toluene	106.30	17.8	0.812	0.791
Ethyl acetate	97.800	18.1	0.750	0.820
Methylpropyketone	106.10	18.2	0.930	0.746
Benzene	88.900	18.4	0.750	0.814
Methylethylketone	89.600	18.5	0.562	0.869
Trichloromethane	79.700	18.6	1.530	0.771
Cyclohexanone	101.00	19.7	0.343	1.112
Acetone	73.300	19.8	0.295	1.089
2-Methyl-2-propanol	93.940	20.4	0.523	0.884
1-Octanol	157.66	20.6	0.073	1.893
2-Butanol	91.700	21.6	0.371	1.212
1-Pentanol	108.20	21.7	0.230	1.007
1-Methylpropanol	92.500	22.2	0.241	1.183
1-Butanol	91.500	22.8	0.200	1.277
1-Propanol	76.100	23.9	0.162	1.374
Ethanol	58.400	25.5	0.063	1.967

Favre, E. "Swelling of crosslinked polydimethylsiloxane networks by pure solvents: influence of temperature." *European polymer journal* 32.10 (1996): 1183-1188.

Effect of Temperature on Diffusion and Partition

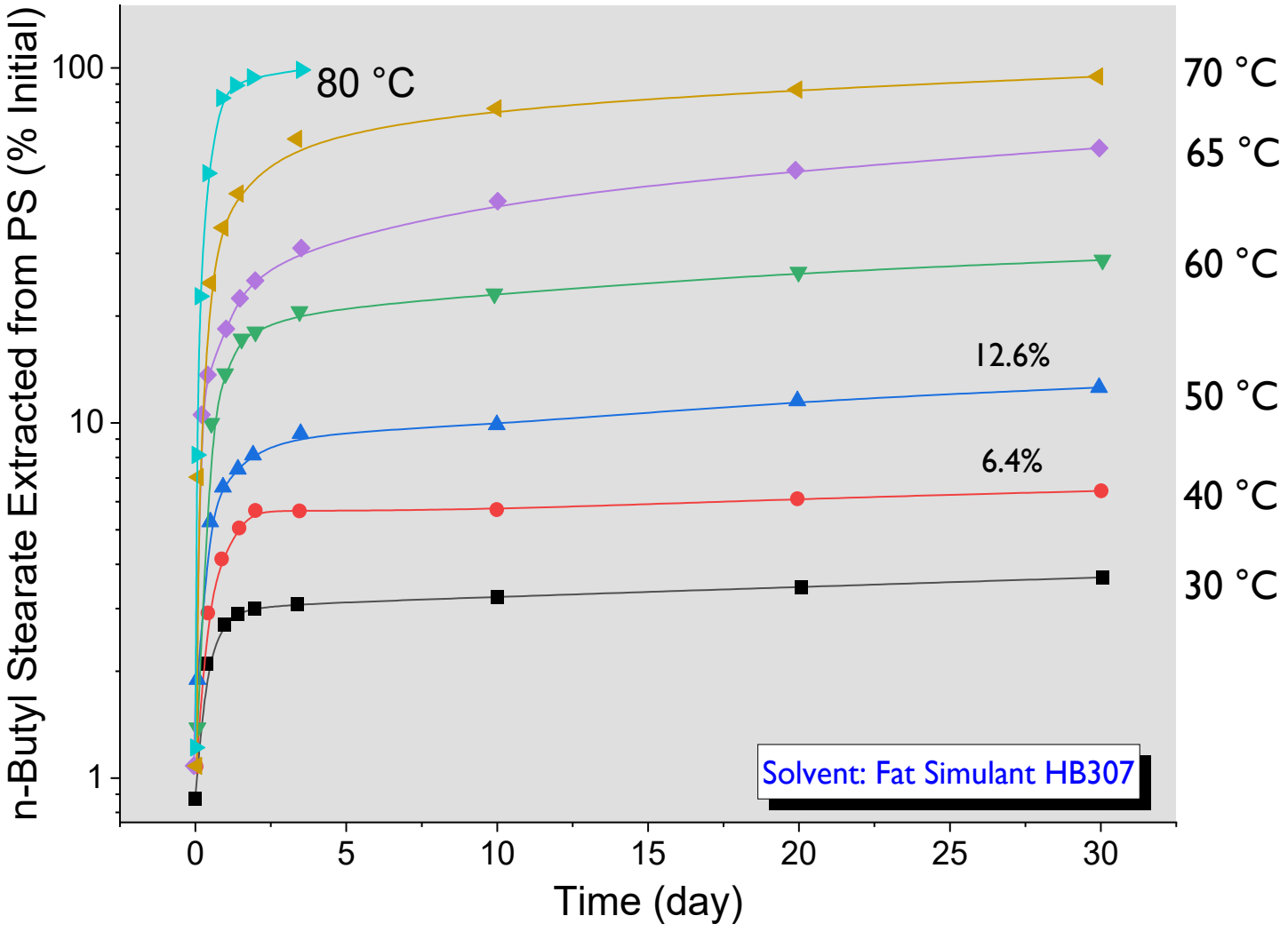


Extraction of polypropylene by isooctane and ethanol

Left two graphs: Diffusion
Right Graph: Partition

Garde, JosÉ A., et al. "Characterizing the migration of antioxidants from polypropylene into fatty food simulants." *Food Additives & Contaminants* 18.8 (2001): 750-762.

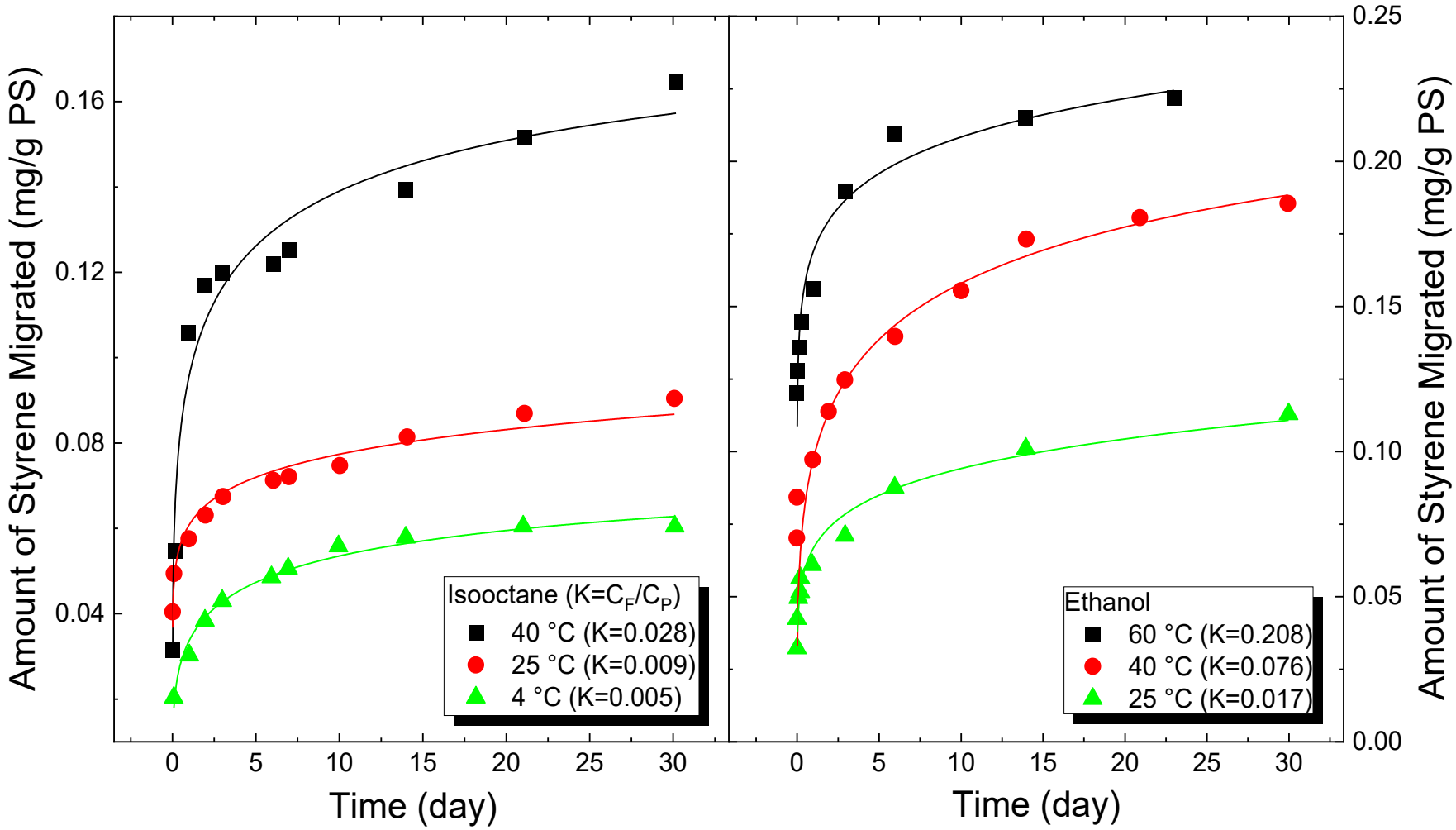
Effect of Temperature on Amount Extracted



Extracted amounts of n-Butyl Stearate from polystyrene at different temperature

Figge, K., and J. Koch. "Effect of some variables on the migration of additives from plastics into edible fats." *Food and Cosmetics Toxicology* 11.4 (1973): 975-988.

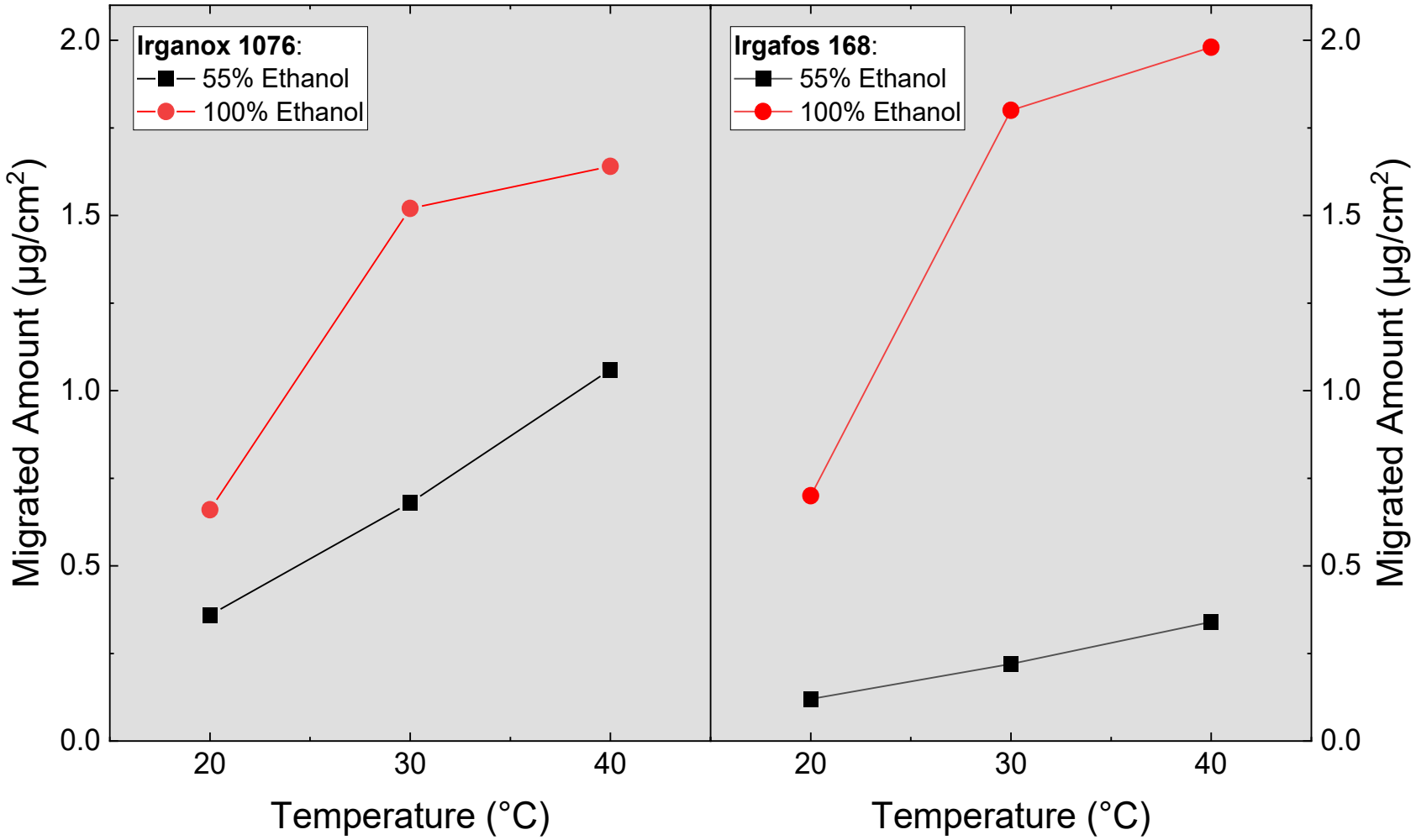
Effect of Temperature on Amount Extracted



Extraction of polystyrene by isooctane and ethanol

Paraskevopoulou, Despoina, Dimitris S. Achilias, and Adamantini Paraskevopoulou. "Migration of styrene from plastic packaging based on polystyrene into food simulants." *Polymer International* 61.1 (2012): 141-148.

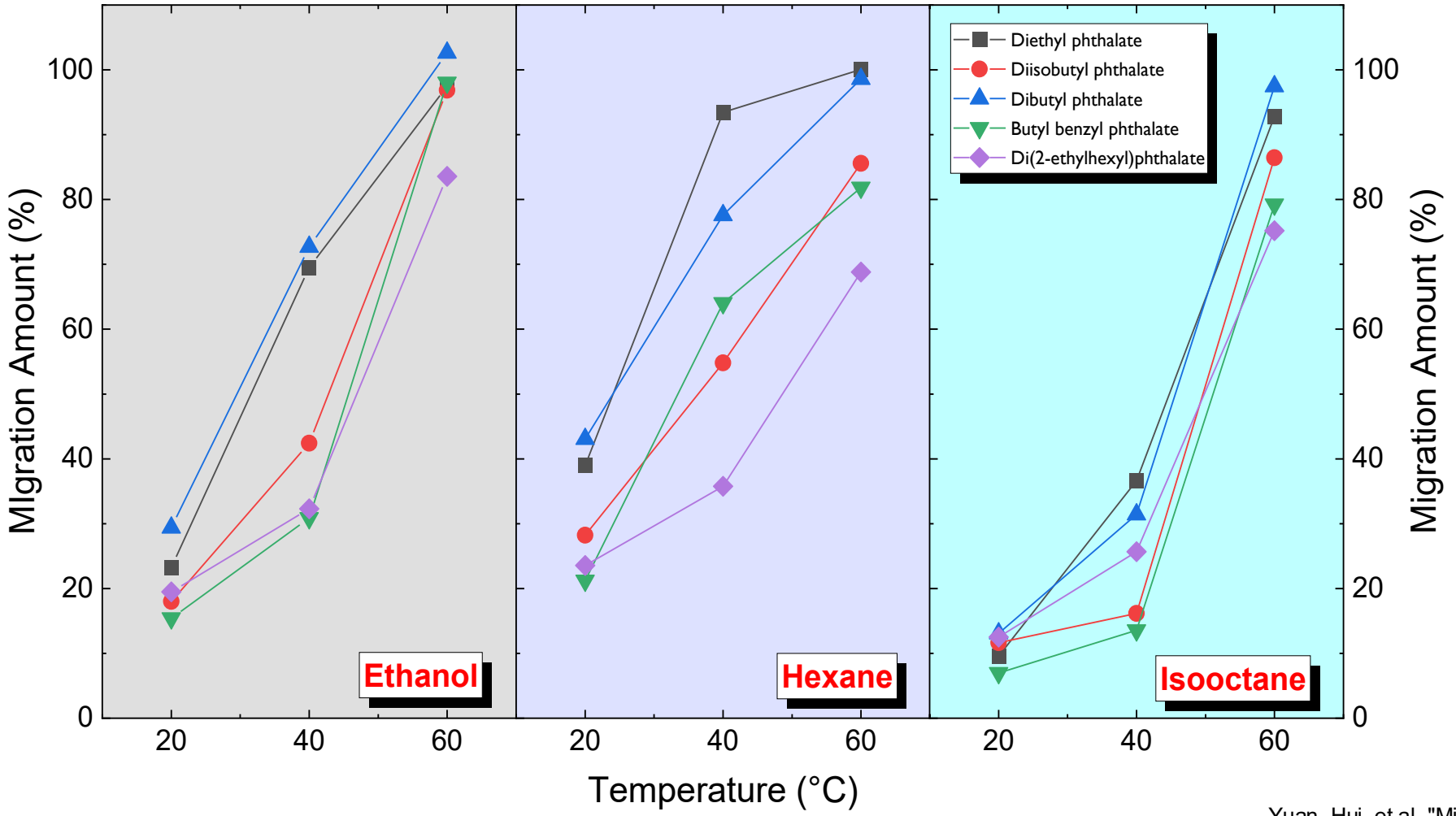
Effect of Temperature on Amount Extracted



Extraction of Polyolefins by 55% ethanol and 100% ethanol

Linssen, J. P. H., J. C. E. Reitsma, and J. L. Cozijnsen. "Research note—migration of antioxidants from polyolefins into ethanolic simulants." *Packaging Technology and Science: An International Journal* 11.5 (1998): 241-245.

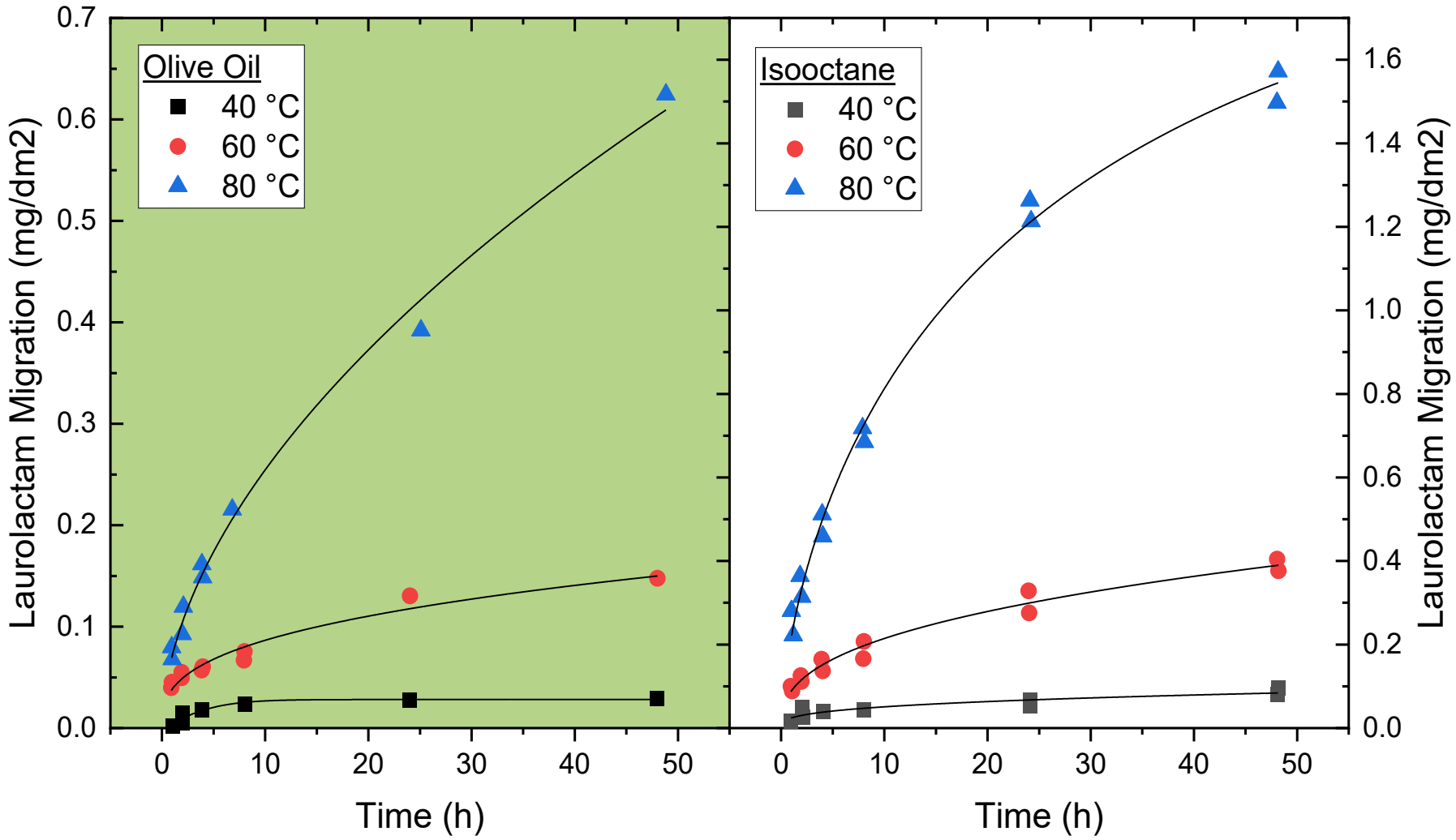
Effect of Temperature on Amount Extracted



Extracted amounts at different temperature on PVC

Yuan, Hui, et al. "Migration of phthalates from polyvinyl chloride film to fatty food simulants: experimental studies and model application: H. Yuan et al." *Journal of Consumer Protection and Food Safety* 15.2 (2020): 135-143.

Effect of Temperature on Amount Extracted



Extracted amounts at different temperature on Nylon

Stoffers, N. H., et al. "Alternative fatty food simulants and diffusion kinetics of nylon 12 food packaging." *Food additives and contaminants* 20.10 (2003): 949-959.