PDA Training Course Extractables & Leachables

31 May 2022

POLYMERS 101

Koen Smets, Senior E&L expert

OVERVIEW

1. Definition and classification
2. Types of polymers
3. Properties of polymers
4. On the origin of extractables species

OVERVIEW

1. **Definition and classification**
2. Types of polymers
3. Properties of polymers
4. On the origin of extractables species

1. DEFINITION AND CLASSIFICATION

A **POLYMER** is a chemical compound or mixture of compounds consisting of repeating structural units created through a process of polymerization

Greek words:
πολύς (polus, meaning "many, much")
μέρος (meros, meaning "parts")

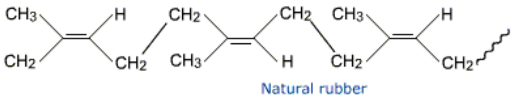
Refers to a molecule whose structure is composed of **multiple repeating units**

→ High relative molecular mass and associated properties

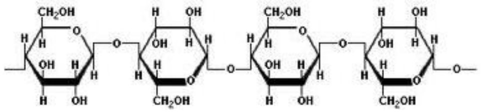
1. DEFINITION AND CLASSIFICATION

Origin of polymers

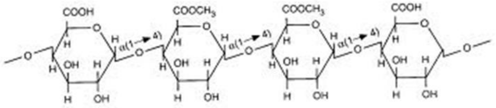
- **NATURAL POLYMERS** also exist in nature
  - *Latex / natural rubber*
  - *Starch*
  - *Cellulose*
  - *Pectine*
  - *Silk / Wool*
  - *DNA,...*



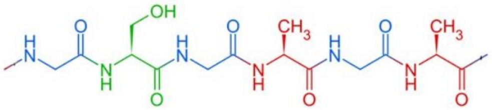
Repeating Isoprene units



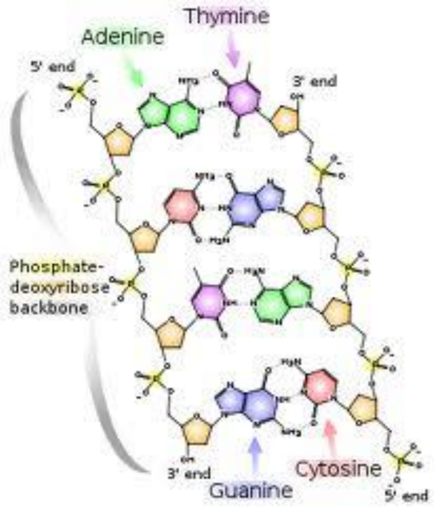
Repeating D-Glucose units



Repeating Galacturonic acid units



Repeating units of amino acids



DNA

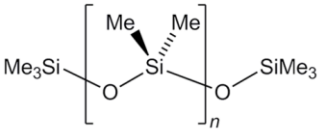
Most pharmaceutical applications are with **SYNTHETIC POLYMERS**

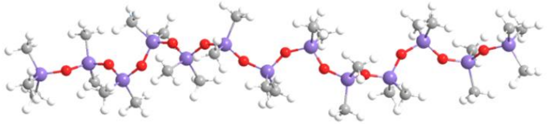
1. DEFINITION AND CLASSIFICATION

Examples of synthetic polymers

A small fraction are **INORGANIC POLYMERS**

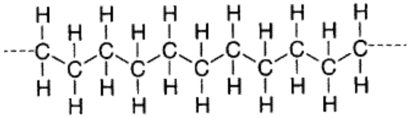
Example: Siloxanes (PolyDiMethylSiloxanes; PDMS) (SILICONE)

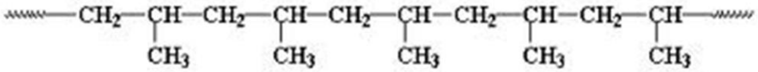


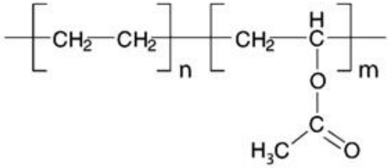


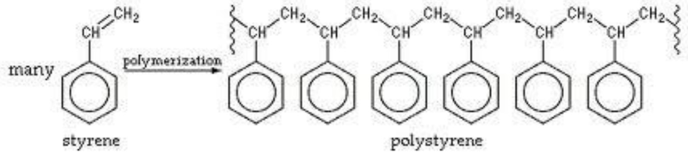
However, most of the polymers are **ORGANIC POLYMERS**

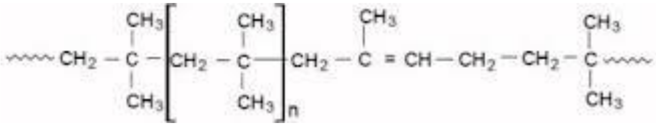
Examples: polyethylene (PE), polypropylene (PP), ethylene vinyl acetate (EVA), polystyrene (PS), Isobutylene Isoprene Rubber (IIR rubber), nylon 6, nylon 6,6,...

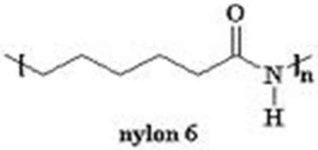


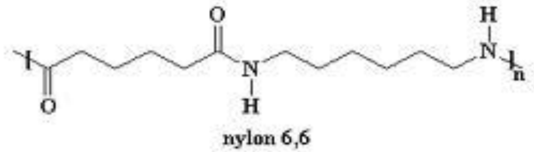










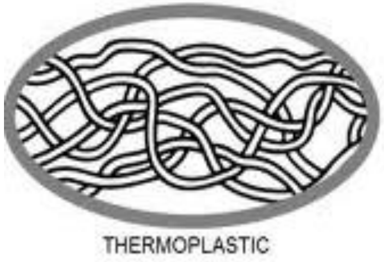


1. DEFINITION AND CLASSIFICATION

THERMOPLASTIC

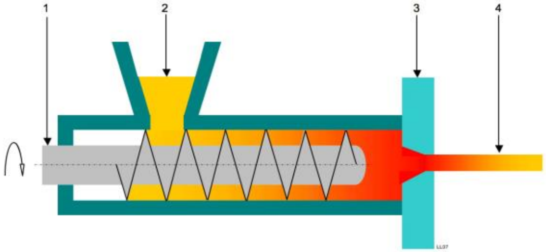
Polymers that soften when heated and become firm again when cooled

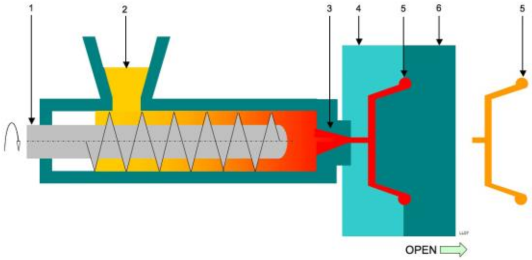
Examples: PS, LDPE, HDPE, PP, EVA, PTFE, PC,...



“Entangled” polymer chains

Giving the **final form to a container/component** is based on these principles:





Extrusion

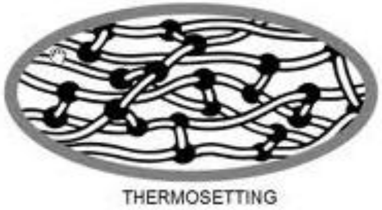
Injection Molding

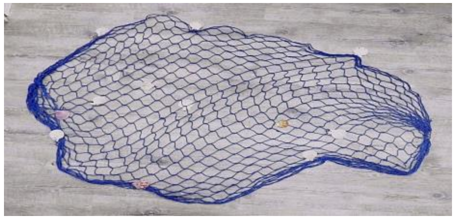
1. DEFINITION AND CLASSIFICATION

THERMOSET

Polymers that soften when heated and molded subsequently BUT decompose when reheated (i.e. cannot be reformed after cooling)

Examples: Fenol formaldehyde resins, epoxy resins





Crosslinked polymer chains

Thermoset polymers are **typically "cross linked"** (irreversible chemical bonds formed during **curing** process)

Bakelite

1. DEFINITION AND CLASSIFICATION

ELASTOMER

Material with low degree of irreversible chemical cross-linking

Examples: rubbers and silicones

THERMOPLASTIC ELASTOMER (TPE)

Thermoplastic materials with elastomeric, rubbery-elastic properties generated by physical cross-linking points

TPE materials can be melted down again and thermoplastic processing is possible

Examples: styrene block copolymers (TPE-S: SBS, SEBS), polyolefin mixtures (TPE-O), thermoplastic polyurethanes (TPE-U), thermoplastic co-polyesters (TPE-E or TPC) and thermoplastic polyamides (TPE-A)

OVERVIEW

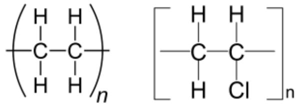
1. Definition and classification
2. **Types of polymers**
3. Properties of polymers
4. On the origin of extractables species

2. TYPES OF POLYMERS

Organization of subunits

HOMOPOLYMER built from a sequence of identical monomers

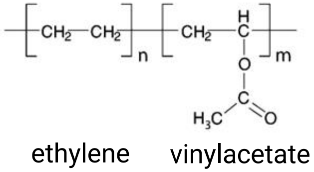
Examples: PE, PP, PVC A-A-A-A-A-A-A-A-A-A-A-A-A-A



COPOLYMER built from a sequence of *two or more different monomers*

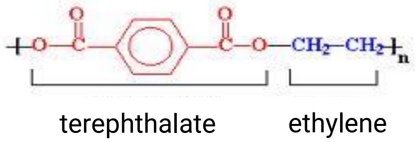
Random copolymer A-B-A-A-B-B-B-A-B-A-A-A-B

Example: Poly EVA



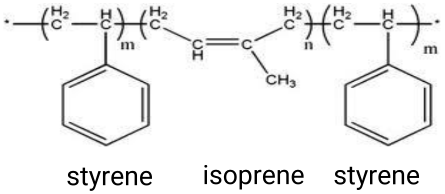
Regular copolymer A-B-A-B-A-B-A-B-A-B-A-B-A

Example: PET



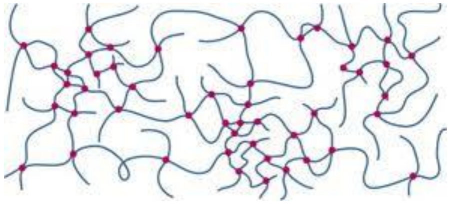
Block copolymer A-A-A-B-B-B-B-B-B-B-B-A-A

Example: SIS elastomer



2. TYPES OF POLYMERS

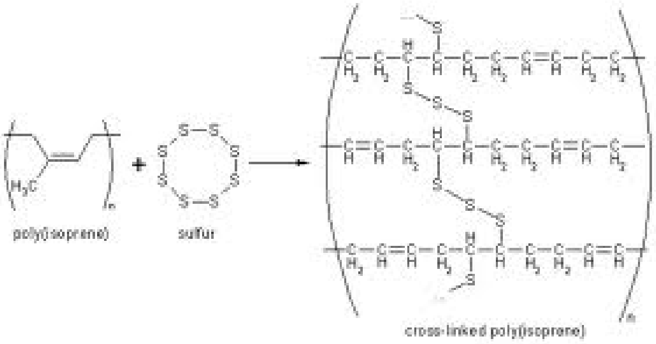
Examples of copolymers

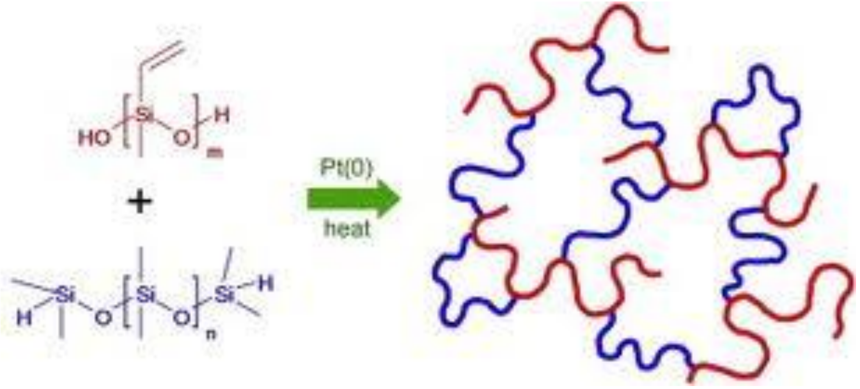


CROSSLINKED POLYMERS

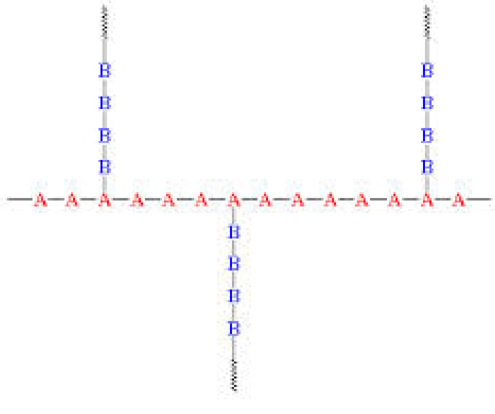
Isobutylene isoprene rubbers

Silicone rubbers (Pt-cured)





GRAFT COPOLYMERS



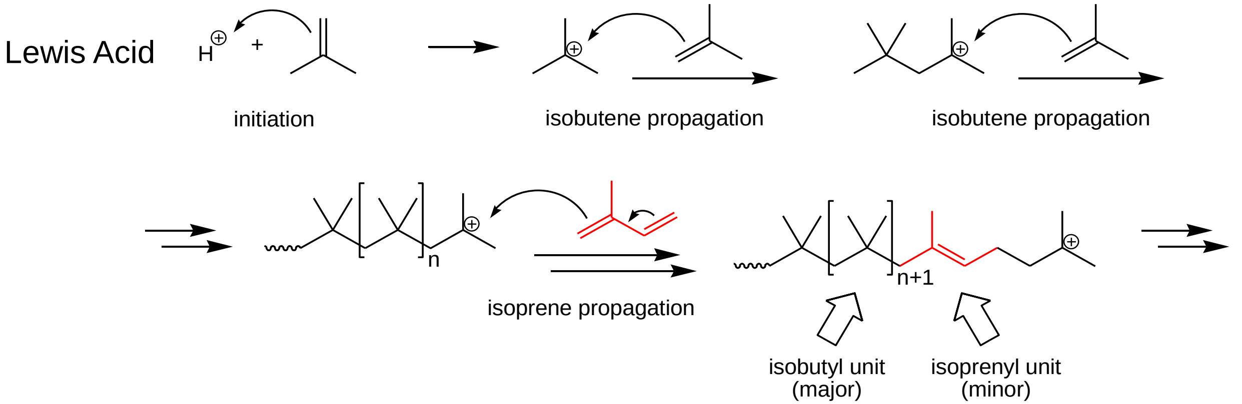
graft copolymer

2. TYPES OF POLYMERS

Polymerisation mechanism

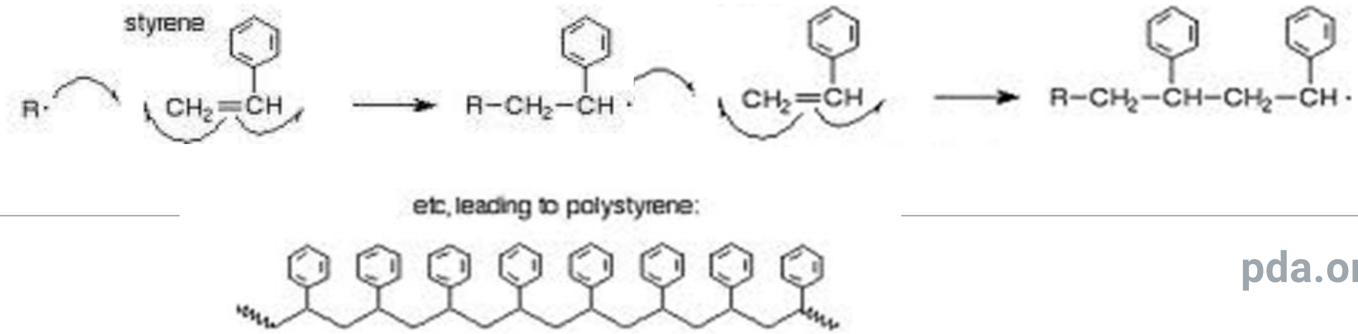
CHAIN GROWTH

Example 1: Cationic polymerisation of "butyl elastomer"



Understanding polymerization of butyl elastomer helps to understand the formation and presence of rubber oligomers

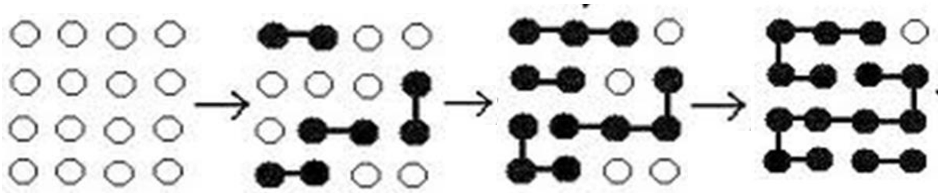
Example 2: Radical polymerisation of polystyrene



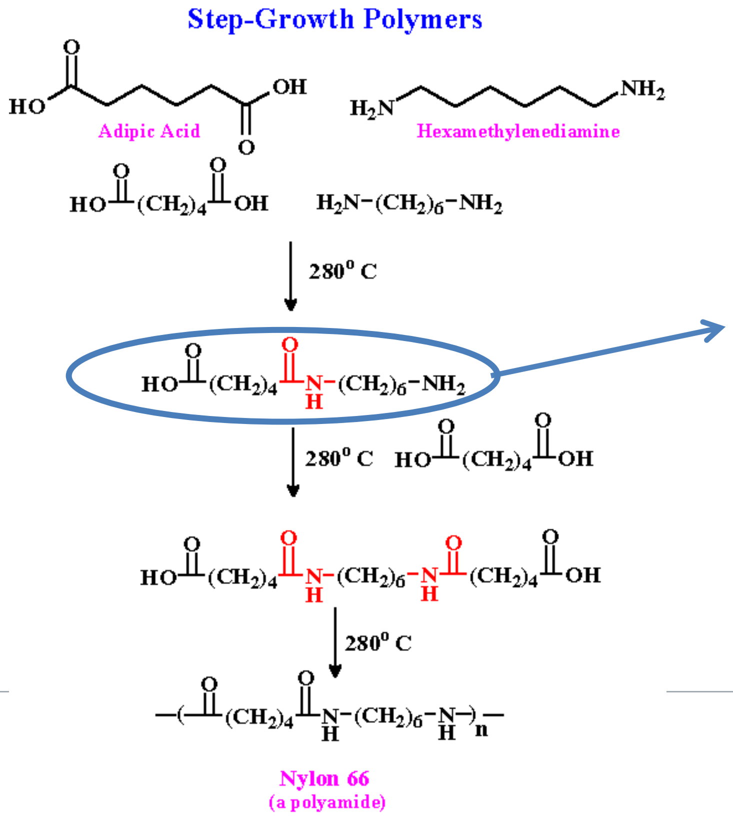
2. TYPES OF POLYMERS

Polymerisation mechanism

STEP GROWTH



Example: Polyaddition, polycondensation of Nylon 6,6



SEEN AS EXTRACTABLE/LEACHABLE

OVERVIEW

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3. **Properties of polymers**
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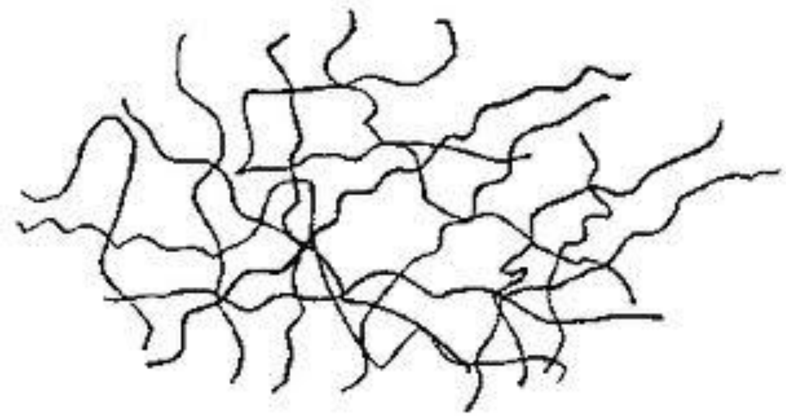
3. PROPERTIES OF POLYMERS

MORPHOLOGY

AMORPHOUS POLYMERS



Because of
- Irregularities in polymer structure
- Nature of the polymer
- Cross-linking (for certain polymers)

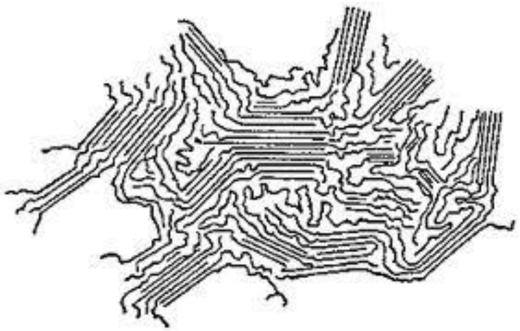
No intermolecular bonds (e.g. Hydrogen bonds, Van der Waals forces) will lead to an alignment of the polymer chains

Examples: PS, PVC, SAN, ABS, PMMA, PC, PES

3. PROPERTIES OF POLYMERS

MORPHOLOGY

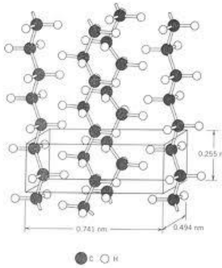
(SEMI-) CRYSTALLINE POLYMERS



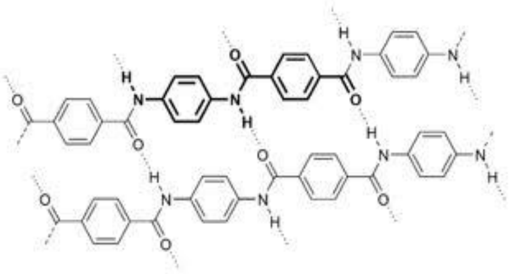
Van der Waals forces (e.g. polyolefins)
Hydrogen bonds (e.g. polyamide)

Bring “alignment” in chains

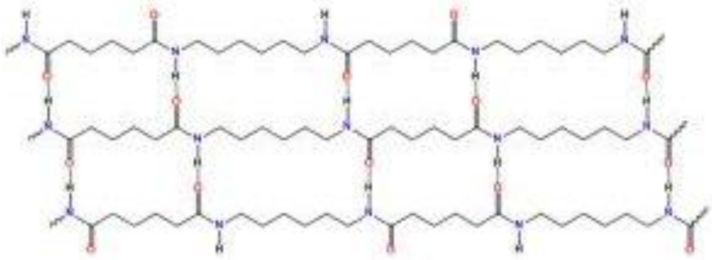
Impact of stereochemistry of a polymer on physical properties



PE



Kevlar (polyamide)

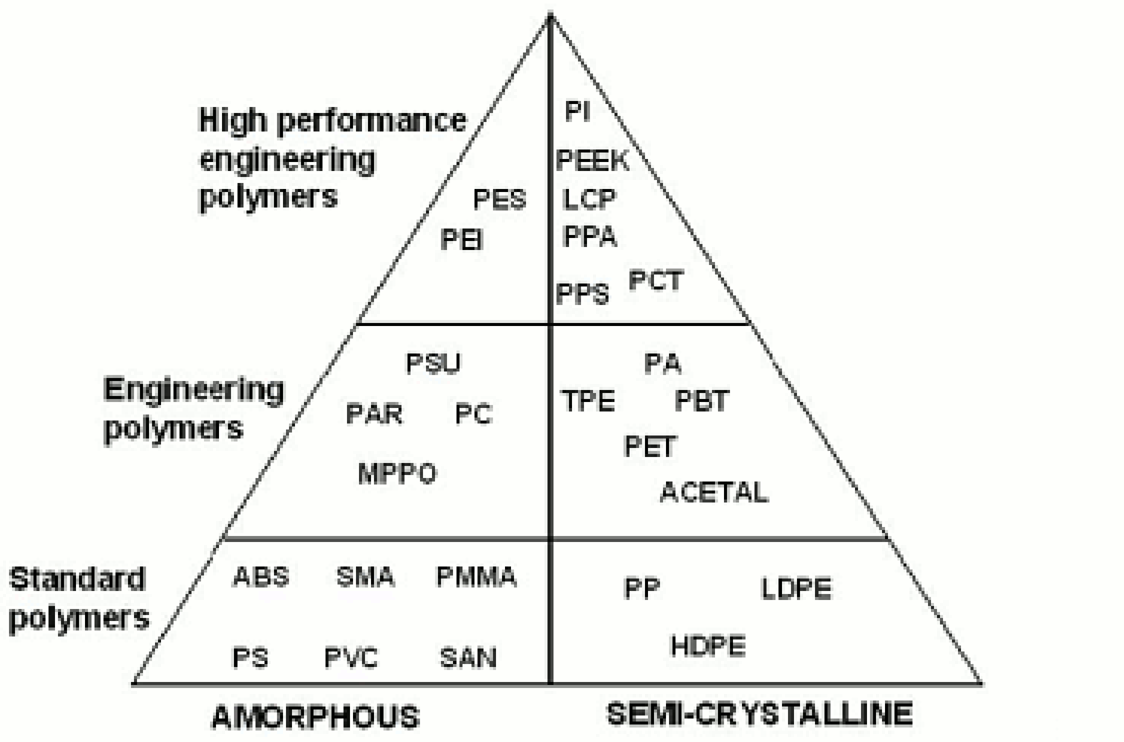


Nylon 6,6 (polyamide)

3. PROPERTIES OF POLYMERS

MORPHOLOGY

AMORPHOUS VS. CRYSTALLINE

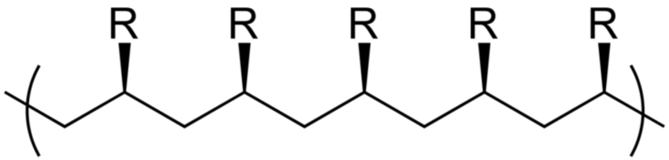


3. PROPERTIES OF POLYMERS

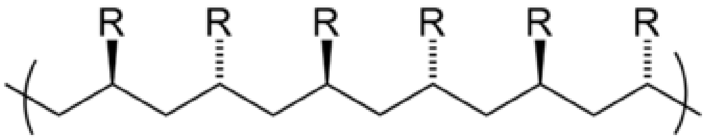
MORPHOLOGY

AMORPHOUS POLYMERS

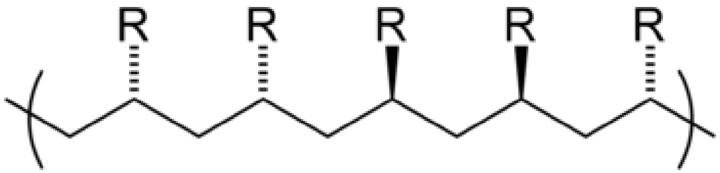
Impact of **stereochemistry** of a polymer on physical properties



Isotactic
Typically semi-crystalline
(e.g. PP via Ziegler-Natta polymerisation)



Syndiotactic
(e.g. syndiotactic PS is semi-crystalline)



Atactic
Typically amorphous polymers
(e.g. atactic PS is amorphous)

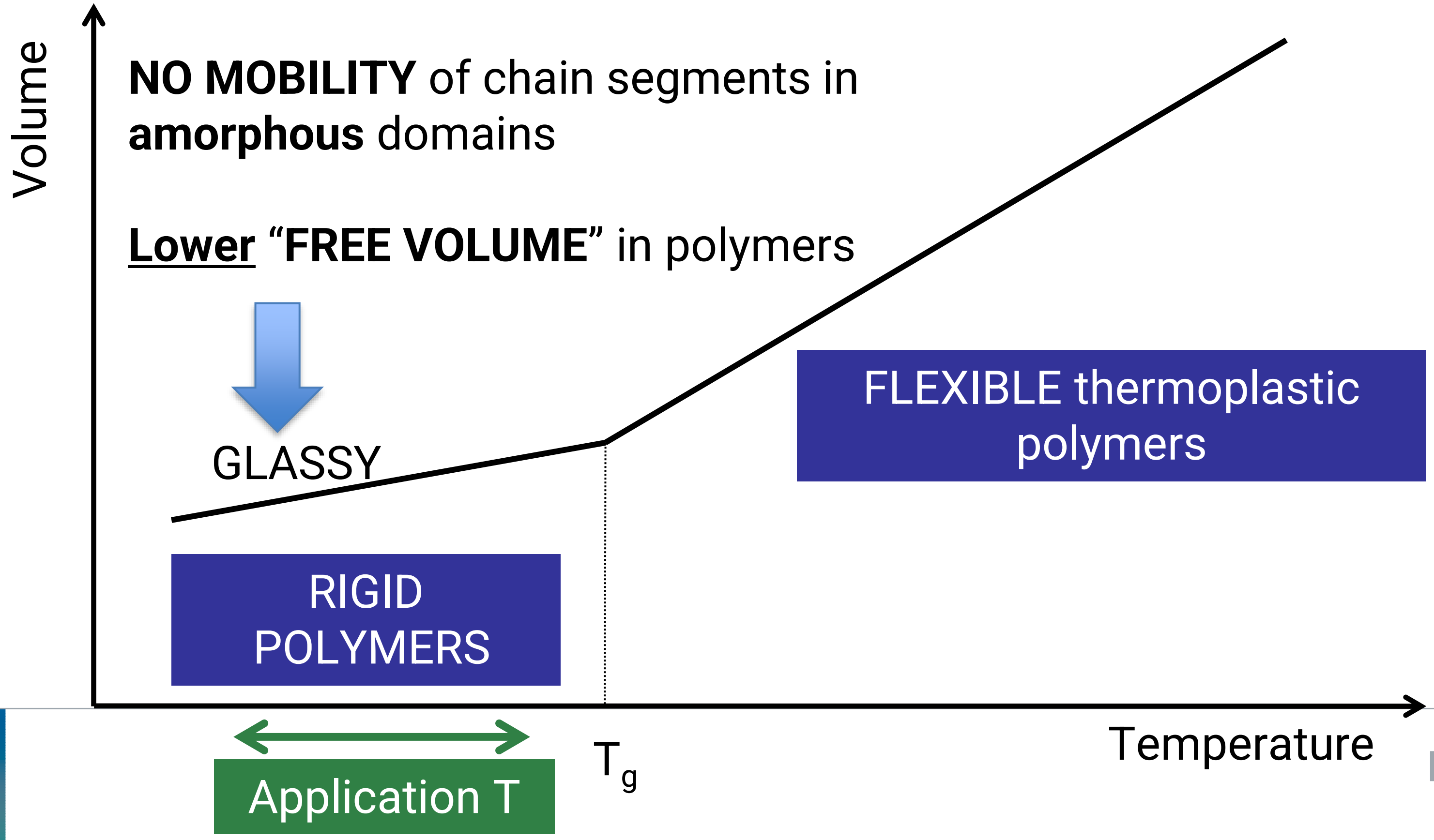
TACTICITY MODULATORS, SOMETIMES FOUND AS EXTRACTABLES

3. PROPERTIES OF POLYMERS

GLASS TRANSITION TEMPERATURE (Tg)

When a polymer goes from a “glassy” state (< Tg) to a “rubber” state (> Tg)

WHAT IS RIGID PACKAGING?



NO MOBILITY of chain segments in **amorphous** domains

Lower “**FREE VOLUME**” in polymers

GLASSY

FLEXIBLE thermoplastic polymers

RIGID POLYMERS

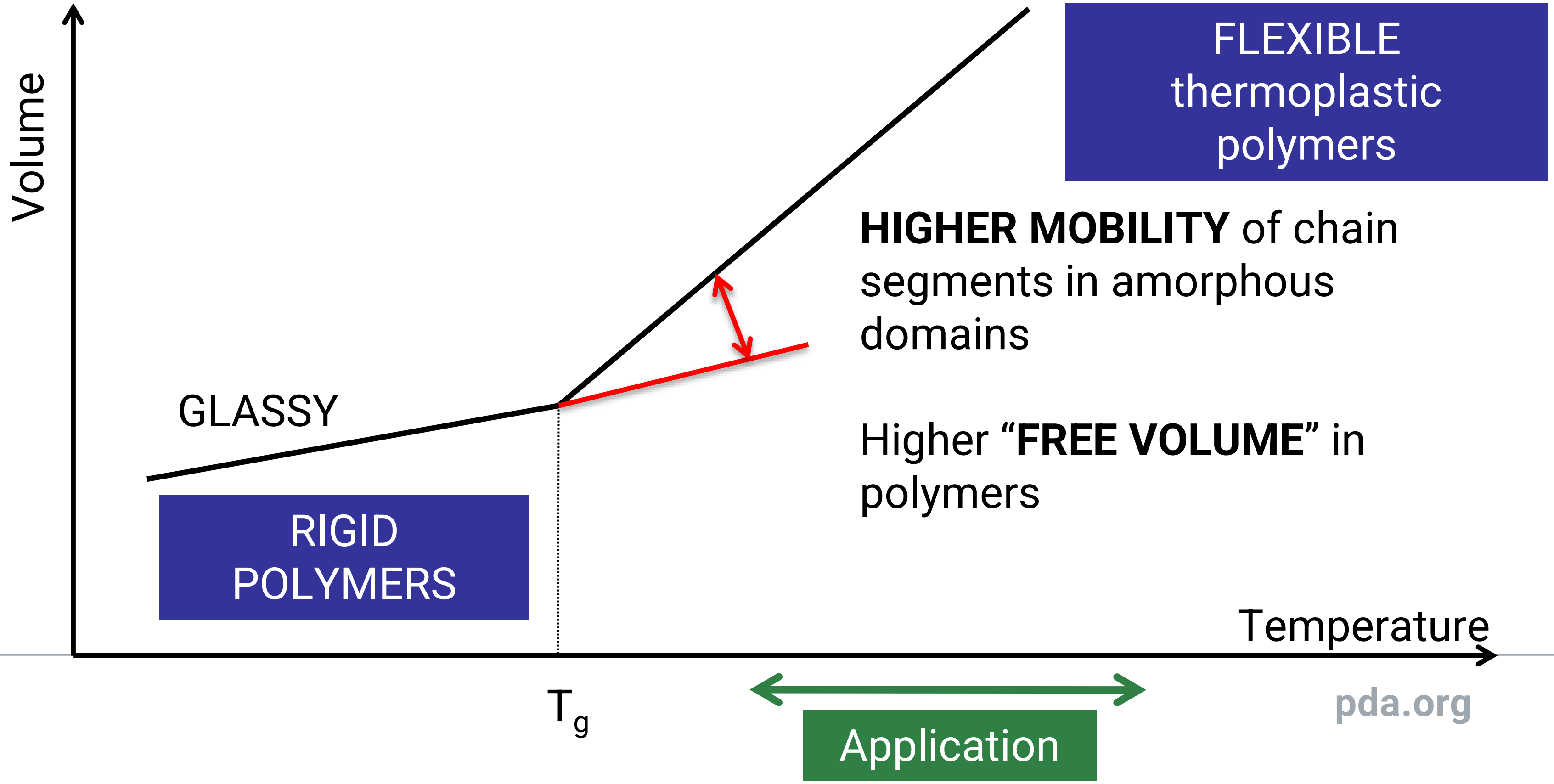
Application T

3. PROPERTIES OF POLYMERS

GLASS TRANSITION TEMPERATURE (Tg)

When a polymer goes from a “glassy” state (< Tg) to a “rubber” state (> Tg)

WHAT IS FLEXIBLE PACKAGING?



FLEXIBLE thermoplastic polymers

HIGHER MOBILITY of chain segments in amorphous domains

Higher “**FREE VOLUME**” in polymers

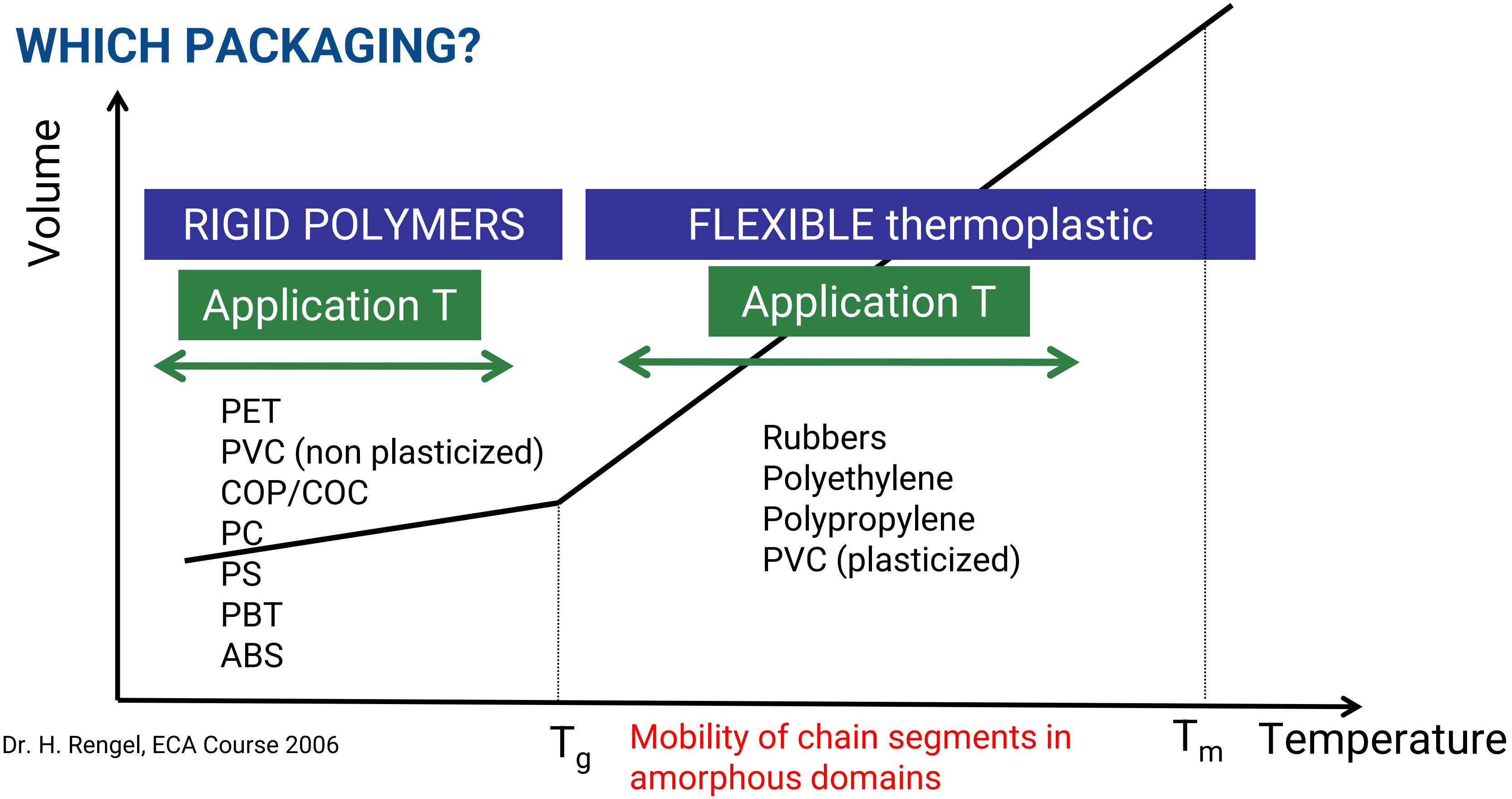
RIGID POLYMERS

Application

3. PROPERTIES OF POLYMERS

GLASS TRANSITION TEMPERATURE (Tg)

WHICH PACKAGING?



RIGID POLYMERS

Application T

PET
PVC (non plasticized)
COP/COC
PC
PS
PBT
ABS

FLEXIBLE thermoplastic

Application T

Rubbers
Polyethylene
Polypropylene
PVC (plasticized)

Mobility of chain segments in amorphous domains

Dr. H. Rengel, ECA Course 2006

3. PROPERTIES OF POLYMERS

GLASS TRANSITION TEMPERATURE (Tg)

Examples of T_g for different materials:

LDPE $T_g = -125°C$

POM $T_g = -50°C$

PP $T_g = -25°C$

PBT $T_g = +70°C$

PVC $T_g = +81°C$ (non plasticized)

ABS $T_g = +110°C$

PC $T_g = +150°C$

The T_g of a material will also have an impact on the migration behavior of a material!

OVERVIEW

1. Definition and classification
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WHAT IS IN A POLYMER?

Most Common Sources of Extractables in Polymeric Materials

Intentionally Added

- Pigments / colorants
- Clarifying agents
- Catalysts and Curing Agents
- Fillers
- Anti-oxidants
- Plasticizers
- Photostabilizers
- Slip agents
- Acid scavengers
- ...

NOT Intentionally Added

- Related to the Polymer
  - ➢Polymer Degradation Compounds
- Related to the Polymerization Process
  - ➢Solvent residues
  - ➢Monomers
  - ➢Catalysts
  - ➢Oligomers
- Related to the additives
  - ➢Additive degradation compounds
- Related to secondary packaging
  - ➢Glue, Labels, Carton/Paper
- Processing Impurities
  - ➢Lubricants, surfactants, solvents
- …

1. INTENTIONALLY ADDED SUBSTANCES

Functionality, performance, protection, processability, cosmetic…

Blowing agents
Pigments / colorants
Antistatic agents
Metal chelators
Adhesives
Clarifying agents
Catalysts and Curing Agents
Antifogging agents
Fillers

Anti-oxidants
Plasticizers
Photostabilizers
Slip agents
Antiozonants
Coupling agents
Lubricants
Acid scavengers
Peroxides / crosslinkers

*(**blue**: coming with some examples)*

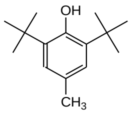
1. INTENTIONALLY ADDED SUBSTANCES

Anti-Oxidants

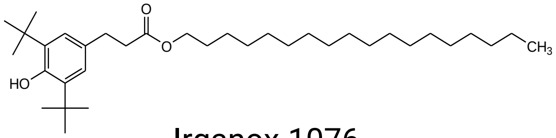
Function: assuring protection against thermal and oxidative degradation during processing and during shelf life of polymer

(Sterically Hindered Phenols (Primary AO) & Organic Phosphites/Phosphonates (Secondary AO) are most used)

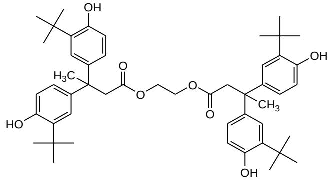
European Pharmacopoeia lists a.o. the following anti-oxidants:



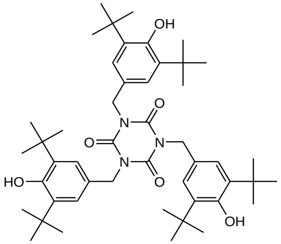
BHT



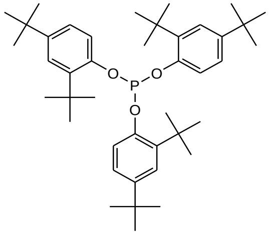
Irganox 1076



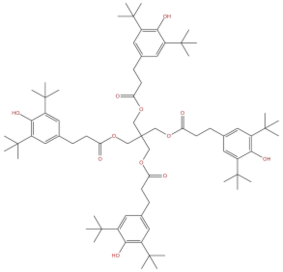
Hostanox 03



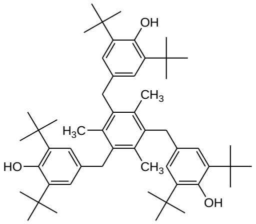
Irganox 3114



Irgafos 168



Irganox 1010



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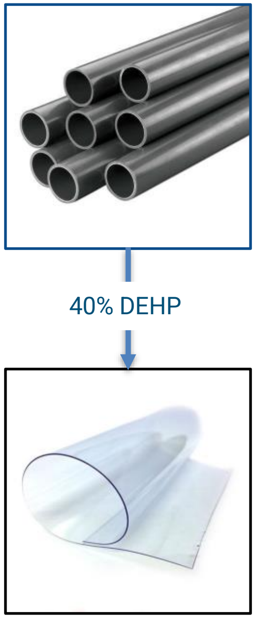
1. INTENTIONALLY ADDED SUBSTANCES

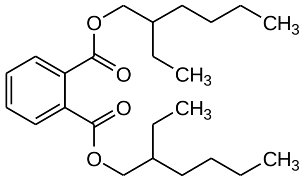
Plasticizers



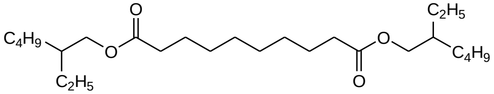
Function: gives the plastic flexibility and durability

Plasticizer requirements:

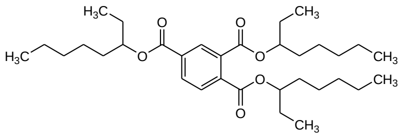
- *Low water solubility (low extractibility)*
- *Stability to heat and light*
- *Low odor, taste and toxicity*



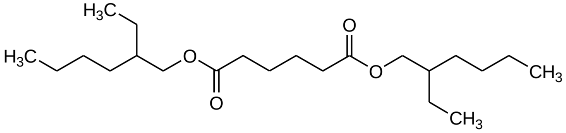
Diethylhexylphthalate (DEHP)



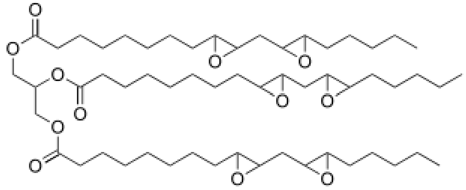
Diethylhexylsebacate



TOTM



Diethylhexyladipate

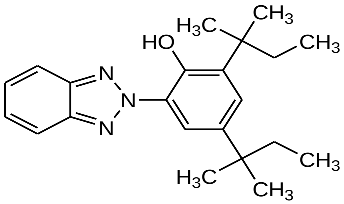


ESBO

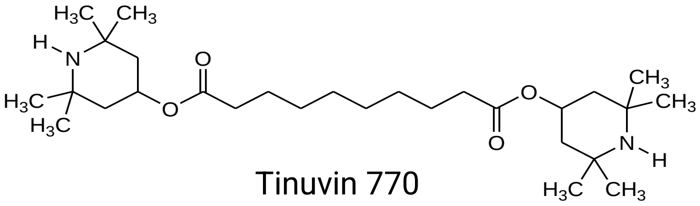
1. INTENTIONALLY ADDED SUBSTANCES

Photo Stabilizers

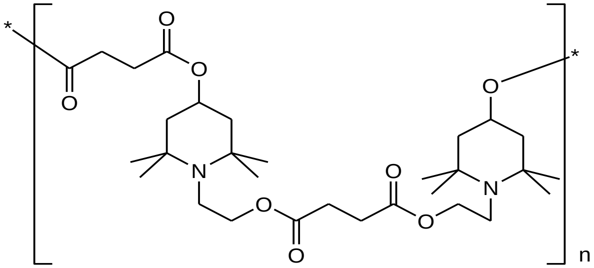
<u>Function</u>: protects the polymer from UV-Degradation (exposure to sunlight)



Tinuvin 328



Tinuvin 770



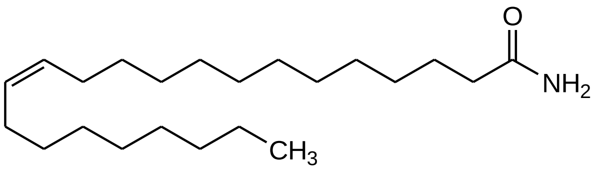
Tinuvin 622

1. INTENTIONALLY ADDED SUBSTANCES

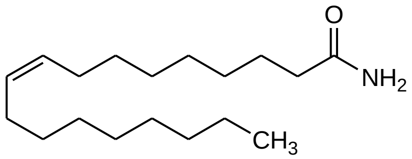
Slip Agents

Function: reduce the “friction” or “film adherence”, important when producing bags from films

Low solubility in e.g. polyolefins will push slip agents to the polymer surface



Erucamide (C22)



Oleamide (C18)

Remark:

because of their specific properties, slip agents will be widely detected as Leachables!

1. INTENTIONALLY ADDED SUBSTANCES

Acid Scavengers

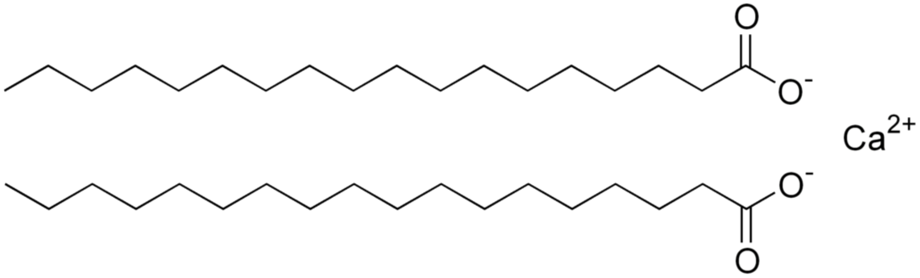
Function: Protects the polymer from “acid attacks” through conversion of strong acids (high degradation impact) to weak acids (low degradation impact)

Example: $Ca(Stearate)_2 + 2HCl \rightarrow CaCl_2 +$ stearic acid

strong acid

weak acid

E.g. in a Chlorobutyl rubber after curing

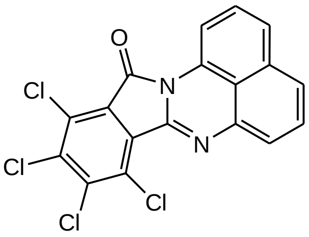


1. INTENTIONALLY ADDED SUBSTANCES

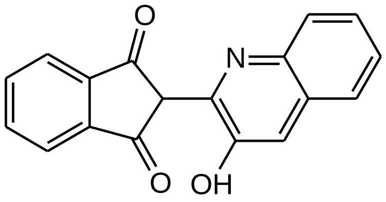
Pigments and Colorants

Function: Gives the polymer / rubber the desired color (cosmetic)

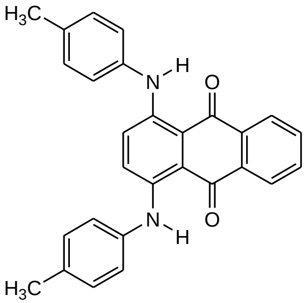
Examples: Carbon Black (PNA's!), TiO_2 (white), Fe_2O_3 (red), Pigment Green 07



Solvent Red



Solvent yellow 114



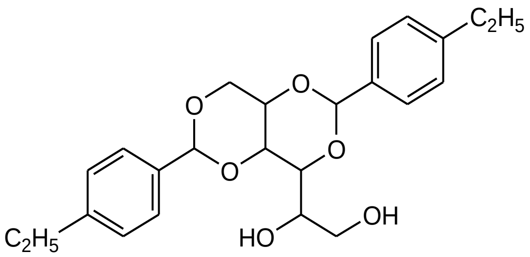
Solvent Green 03

***Remark*: beware of the composition of the masterbatch!**

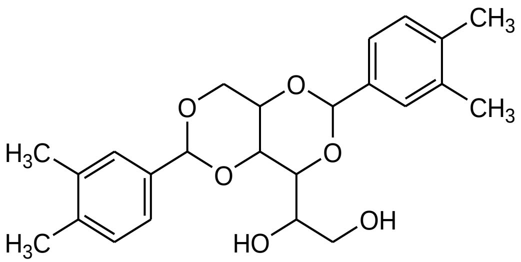
1. INTENTIONALLY ADDED SUBSTANCES

Clarifying / Nucleating Agents

Function: by controlling the crystallisation (nucleation) when cooling off polypropylene, PP becomes transparent instead of opaque



NC-4



Millad 3988

1. INTENTIONALLY ADDED SUBSTANCES

Fillers

- Function (e.g. Rubbers):

  Fillers give **mechanical strength** (**stiffness**) to a rubber
  More filler is an advantage for the gliding force for plungers, but makes stopper piercing (coring!) worse

  - Aluminum silicate (clay)
  - Magnesium silicate (talc)
  - Silicates
  - Calcium carbonate
  - Carbon Black (rubbers)
  - …

1. INTENTIONALLY ADDED SUBSTANCES

Catalysts and Curing Agents

Catalyst Function: Creates the "onset" of the polymerization reaction (i.e. for addition *(cationic, anionic, radical)* polymerization)

Curing Agent Function: chemical employed in polymer chemistry that produces the toughening or hardening of polymer material by cross-linking of polymer chains via covalent bonds (thermo-setting)

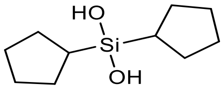
Inorganic Catalysts

(Salts, oxides, complexes...)

- Titanium
- Zirkonium
- Cobalt
- Aluminum
- Iron
- Hafnium
- Platinum
- ...

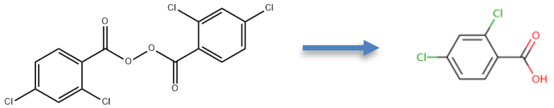
Tacticity modulator

Dicyclopentylsilanediol

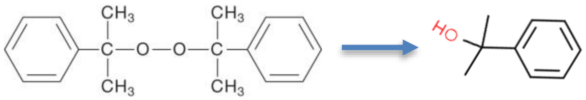


Example for Peroxide Curing Silicone

2,4-Dichlorobenzoyl peroxide



Dicumyl peroxide



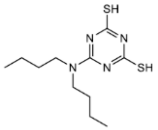
1. INTENTIONALLY ADDED SUBSTANCES

Catalysts and Curing Agents

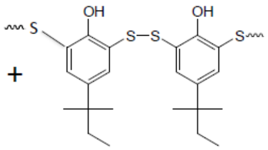
Catalyst Function: Creates the “onset” of the polymerization reaction (i.e. for addition *(cationic, anionic, radical)* polymerization)

Curing Agent Function: chemical employed in polymer chemistry that produces the toughening or hardening of polymer material by cross-linking of polymer chains via covalent bonds (thermo-setting)

Rubber Curing Agents

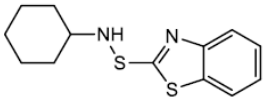


6-(Dibutylamino)-1,3,5-triazine-2,4-dithiol

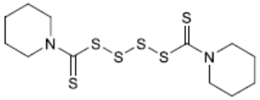


Vultac

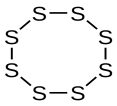
ZnO



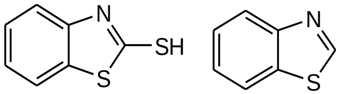
N-cyclohexyl-2-benzothiazole sulfenamide



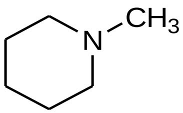
Dipentamethylene thiuram tetrasulfiude (DPTS)



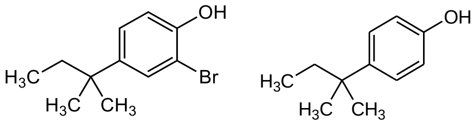
Curing Degradation & Reaction Products



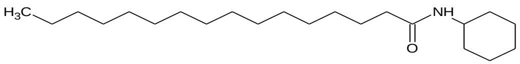
(Mercapto)Benzothiazole



Methyl piperidine



(Bromo)Amylphenols

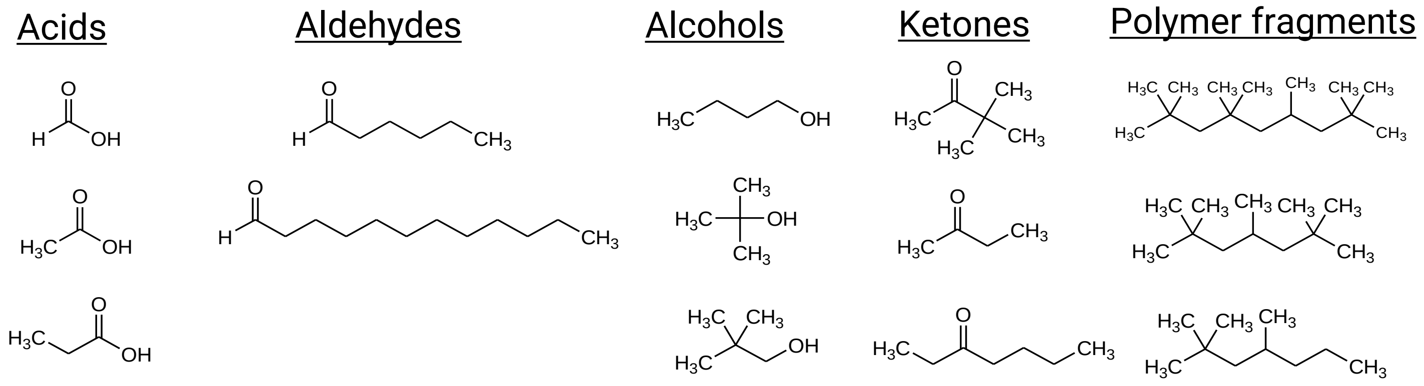


2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Polymer Degradation Compounds

Origin: Oxidative degradation of the polymers
(e.g. when the polymer is not properly stabilized via anti-oxidants;
e.g. “virgin” grades)

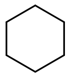
Example of polymer degradation compounds from polypropylene:



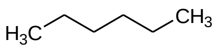
2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Solvents and monomers

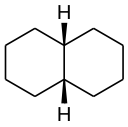
Examples of Solvents



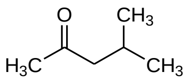
Cyclohexane



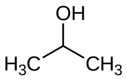
Hexane



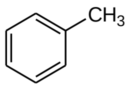
DHN



MIBK

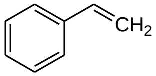


IPA

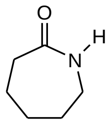


Toluene

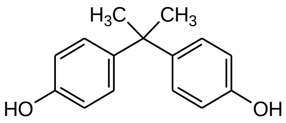
Examples of Monomers



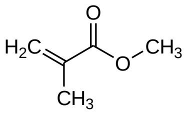
Styrene



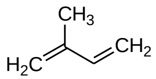
Caprolactam



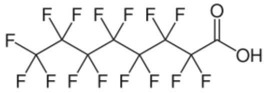
Bisphenol A



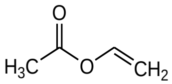
Methyl methacrylate



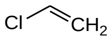
Isoprene



PFOA



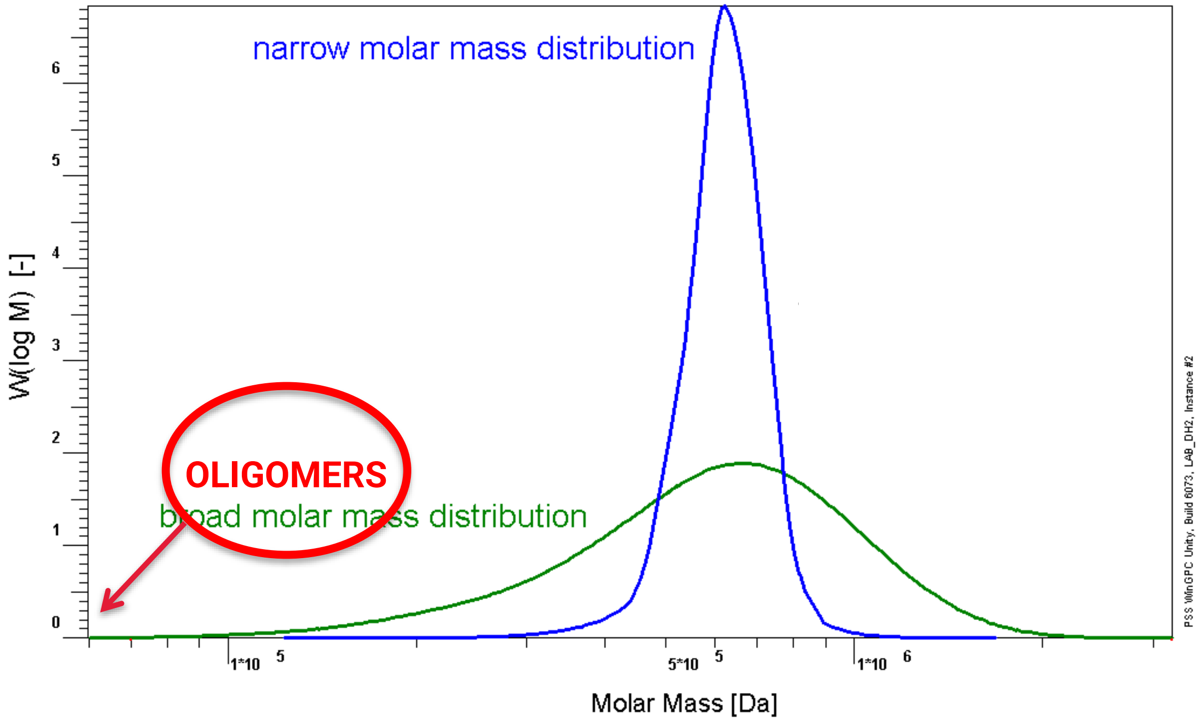
Vinyl Acetate



Vinyl Chloride

2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

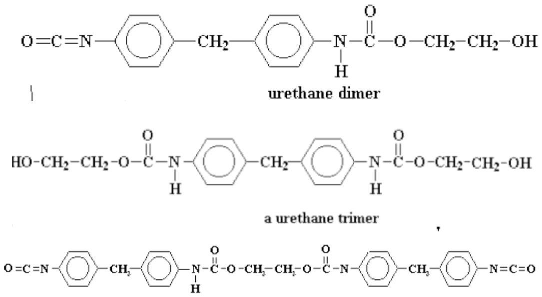
Oligomers



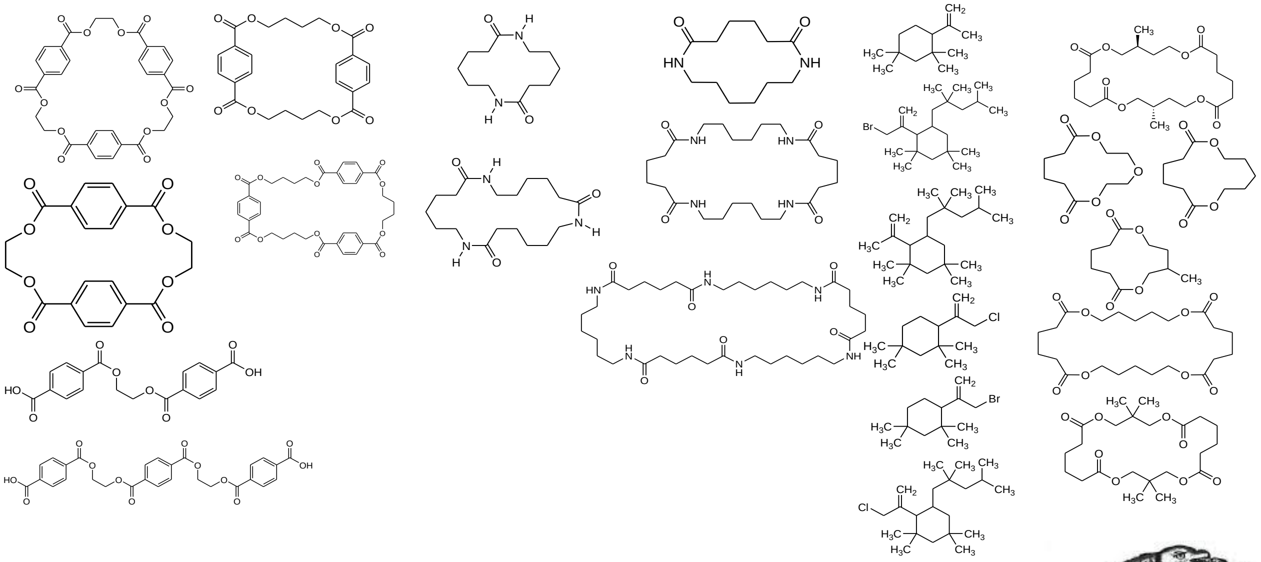
2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Oligomers

Polyurethane



PET PBT Nylon 6 Nylon 6,6 Butyl Rubber Polyester adhesive



+ oxidation, hydrolysis and degradation compounds of oligomers

Other typical oligomers from Silicone, PP, PE, adhesives,...

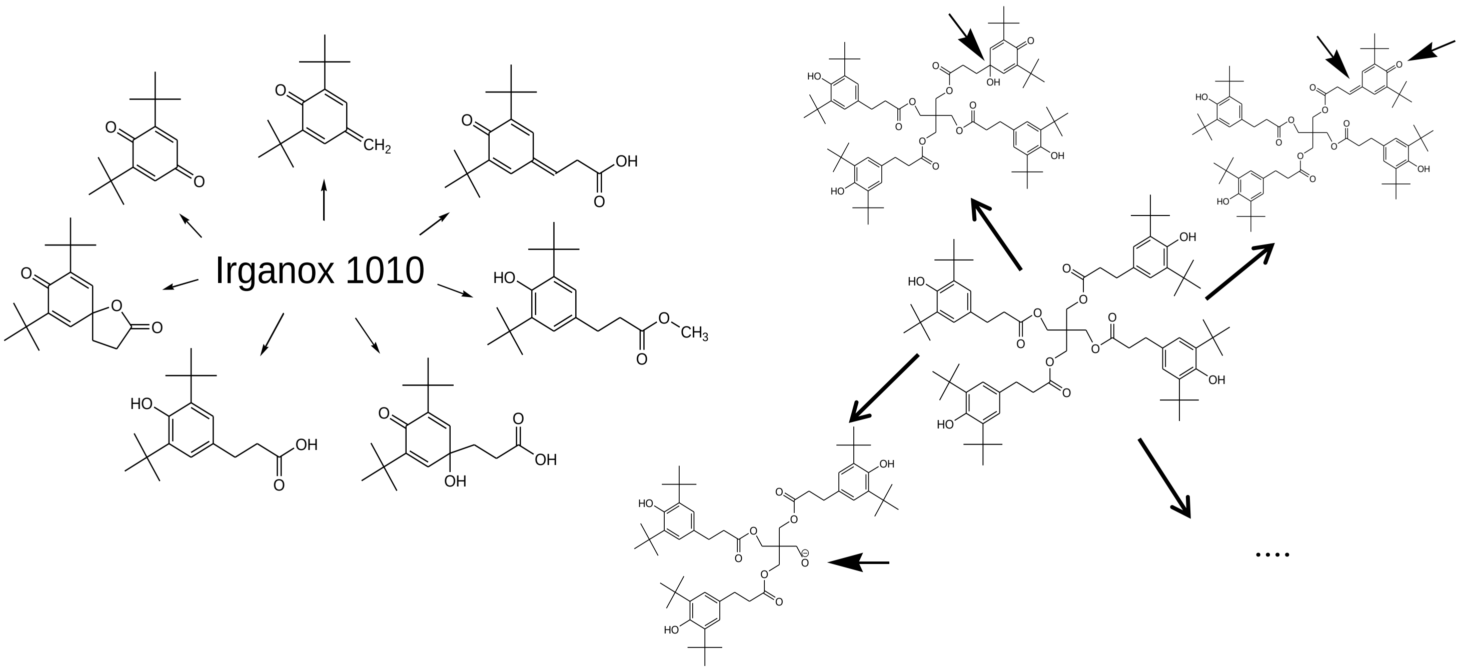
2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Polymer additive degradation compounds

Example of polymer additive degradation compounds from **Irganox 1010**:

SMALL degradation compounds

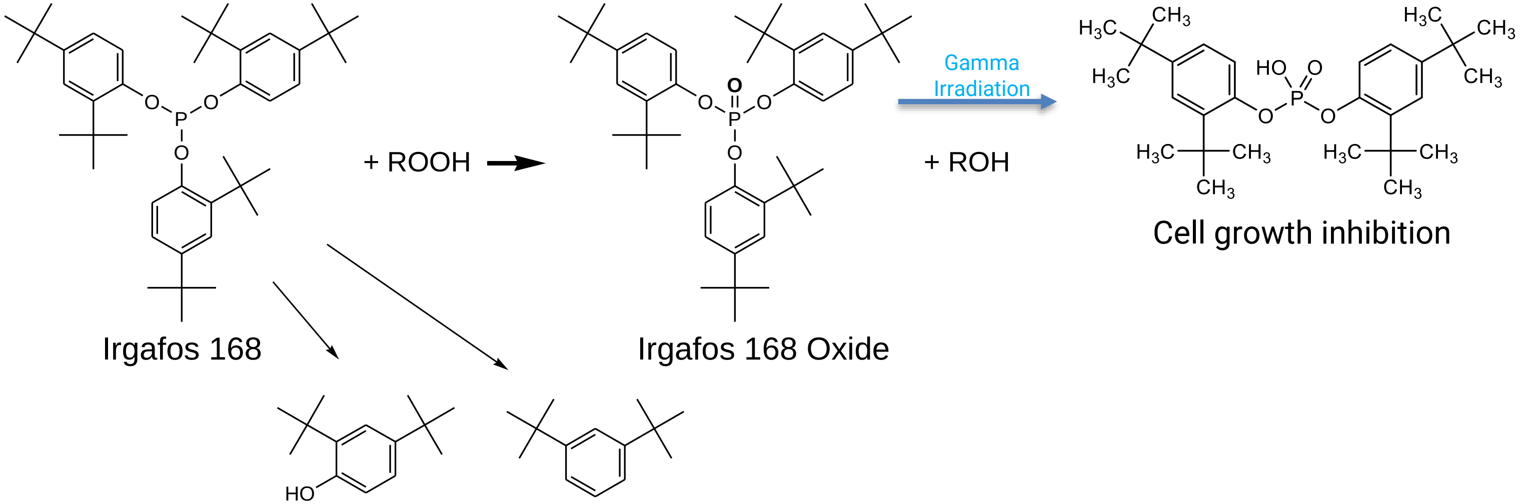
LARGE degradation compounds



2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Polymer additive degradation compounds

Example of polymer additive degradation compounds from **Irgafos 168**:



Remark: also, many other degradation compounds for Irgafos 168 are known

2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

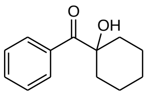
Secondary packaging for semi-permeable primary packaging

Label

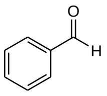
- Adhesive
- Paper
- Ink
- Varnish

Typical extractable compounds:

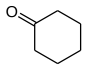
Curing agents (e.g. Benzophenone, Irgacure 184,...)



Irgacure 184



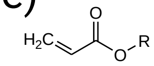
Benzaldehyde



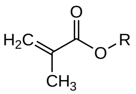
Cyclohexanone

Solvent residues (e.g.Toluene, acetone)

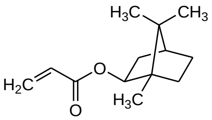
Adhesive residues (e.g. Acrylates)



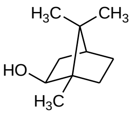
Acrylate



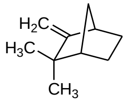
Methacrylate



Isobornyl acrylate



Isoborneol



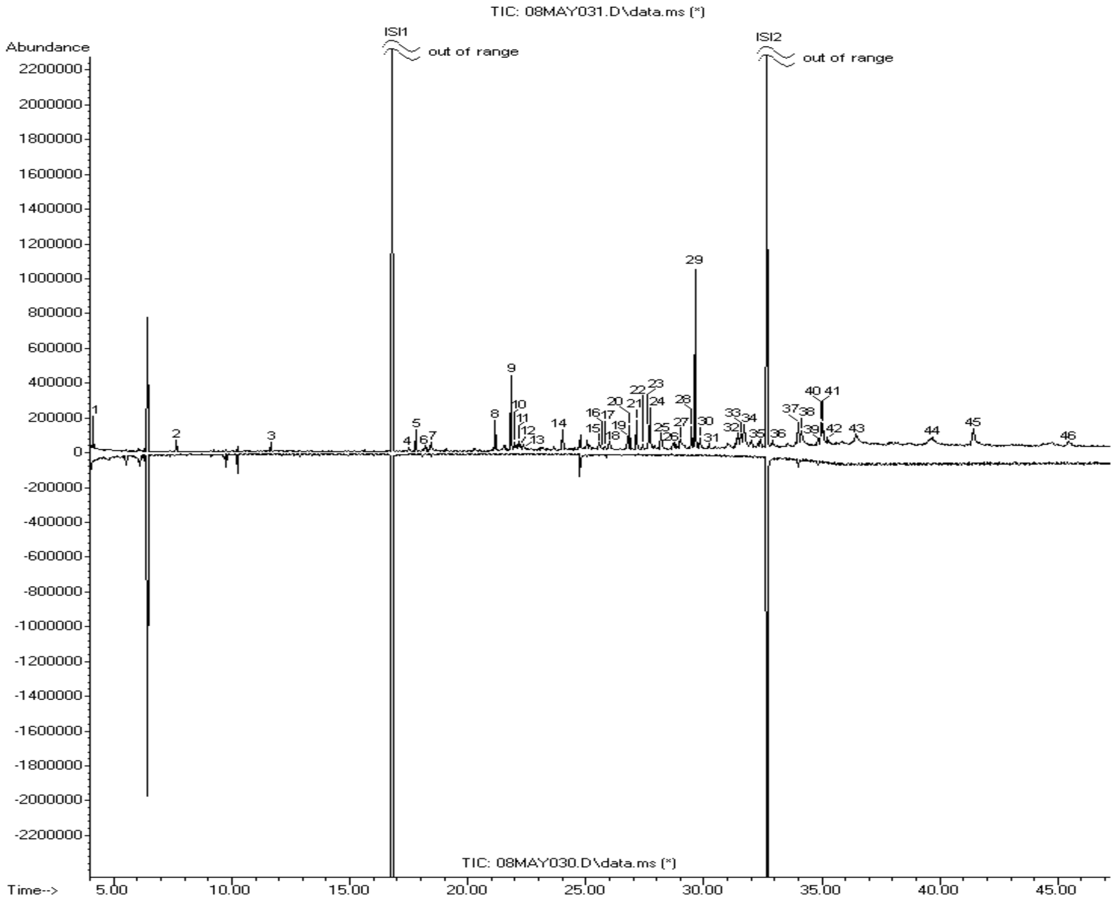
Camphene

Paper residues (e.g. (dehydro)abietic acids, abietates, see later)

2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

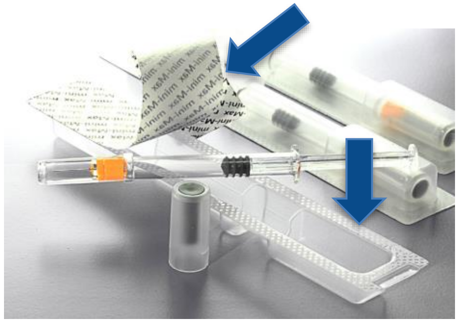
Secondary packaging for semi-permeable primary packaging

Example GC/MS Chromatogram of a Label Extract (IPA)



2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Secondary packaging for semi-permeable primary packaging



Overwrap/Overpouch/Blister

(to compensate for potential lower barrier properties of the polymer)

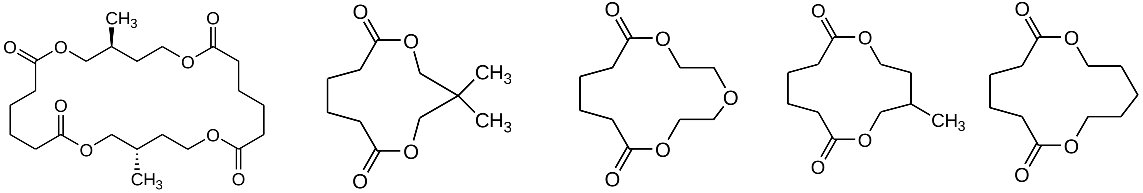
- Multilayer system
- Aluminum as barrier layer
- Tie-layers to keep the different layers together

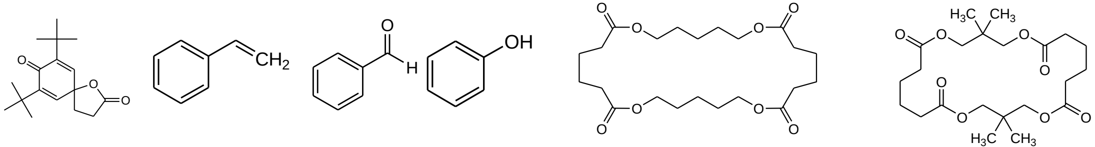
Typical extractable compounds:

Bislactone Compounds from Tie-layer

Residues from other layers
(depends largely on selected materials of the multilayer!!)

Bislactones:





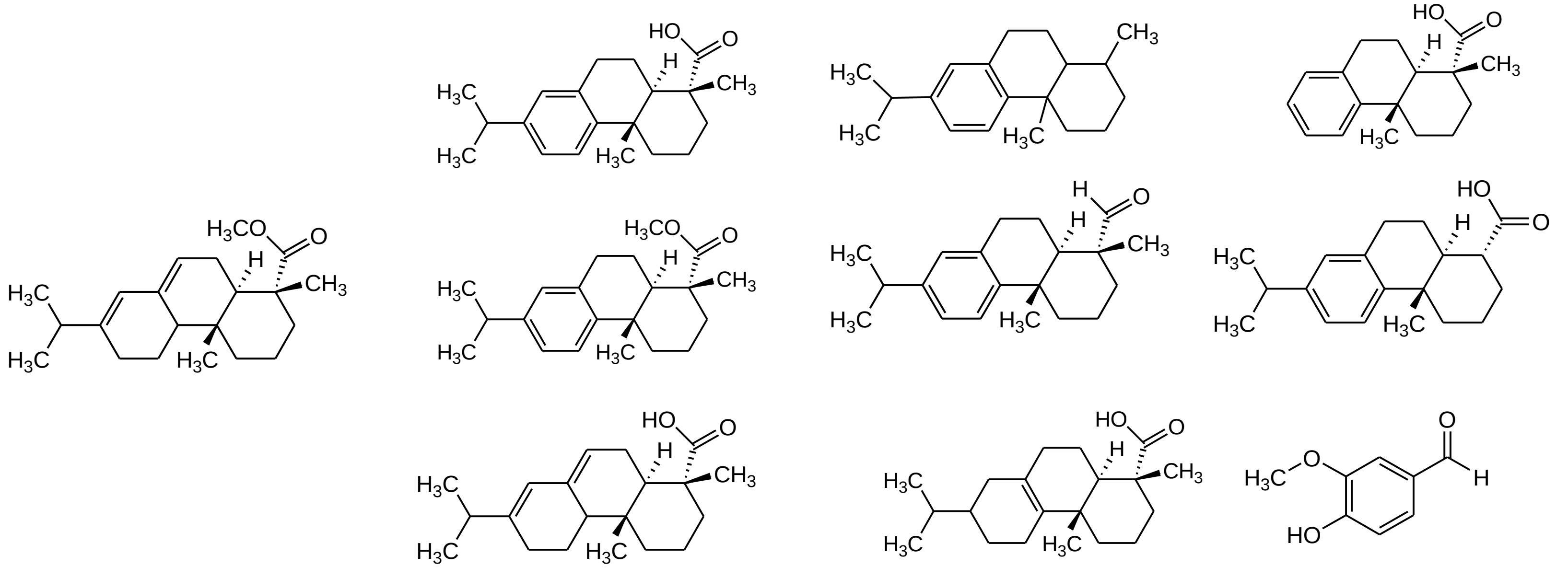
2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Secondary packaging for semi-permeable primary packaging

Carton / paper

(may also come from label)

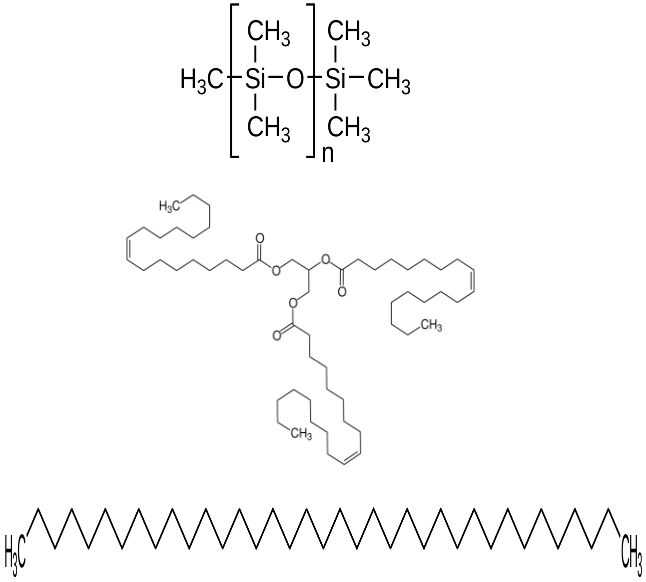
Example structures of abietic acids / abietates (& vanillin)



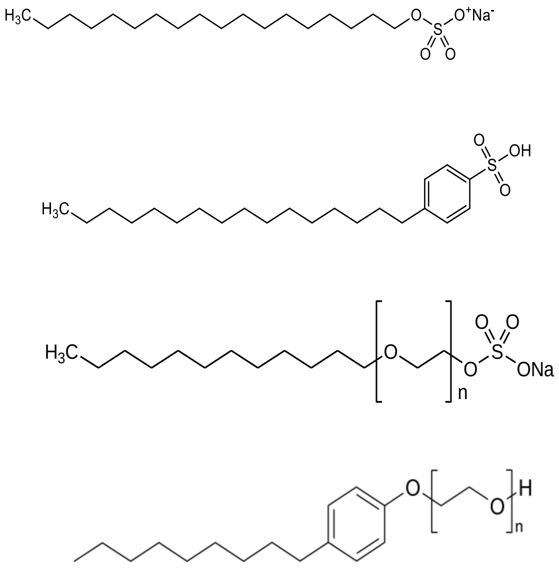
2. NOT INTENTIONALLY ADDED SUBSTANCES (NIAS)

Processing impurities

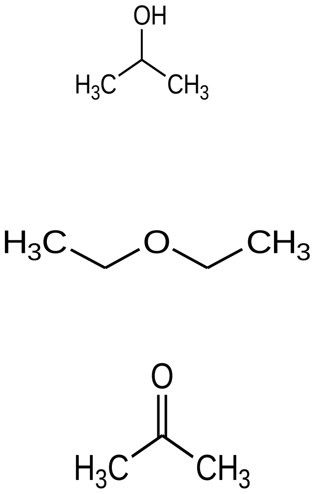
lubricants



detergents



solvent residues



CONCLUSION

- Know Your materials, it's composition and chemistry
- What you put in is not what will come out
- *"A polyethylene is a polyethylene"?* **NO!**
- Some of the compounds are reactive and toxic
- The complex diversity of the universe of extractables requires a broad chemical screening with a combination of techniques
- Knowledge of materials allow to broaden the analytical scope of an E/L study
- Often degradation compounds are difficult to identify
- Database assisted identification is almost a requisite for a successful screening

QUESTIONS?