POLYMERS 101 – GLASS 101

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Rome
01 – 02 March, 2018

Dr. Piet Christiaens

CONTENT

Content

1. What is a Polymer?
2. Classification of Polymers
3. Types of Polymers – Examples in Medical Use
4. Properties of polymers
5. Understanding the Composition of Polymers

WHAT IS A POLYMER?

Polymers 101

1. What is a "Polymer"?

*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")

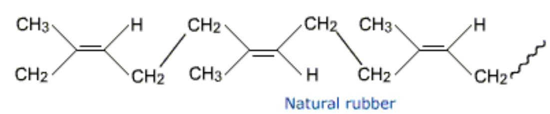
Refers to a molecule

- whose structure is composed of **multiple repeating units**
- As a consequence:
  - *a characteristic of high relative molecular mass and*
  - *associated properties*.

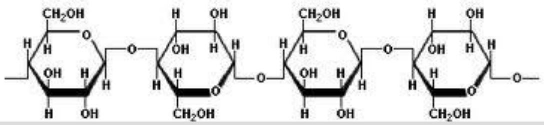
NATURAL VS SYNTHETIC POLYMERS

Classification of Polymers

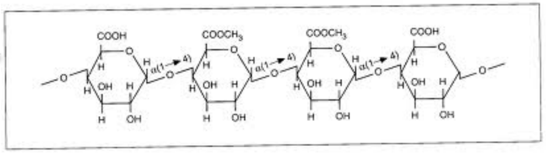
- Polymers also exist in Nature: **NATURAL POLYMERS**
  - Latex / Natural Rubber
  - Starch
  - Cellulose
  - Pectin
  - DNA
  - Silk / Wool
  - ....



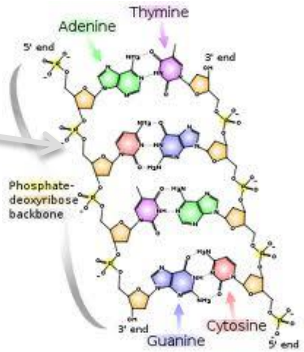
Repeating Isoprene units



Repeating D-Glucose units



Repeating Galacturonic acid units

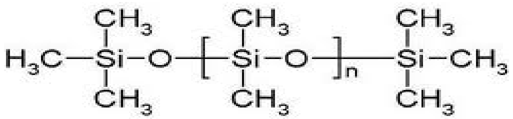


- However, most of the Pharmaceutical Applications are with **SYNTHETIC POLYMERS**

SYNTHETIC Polymers

a small fraction are ***INORGANIC POLYMERS***

Example: Siloxanes (PolyDiMethylSiloxanes; PDMS) *(SILICONE)*

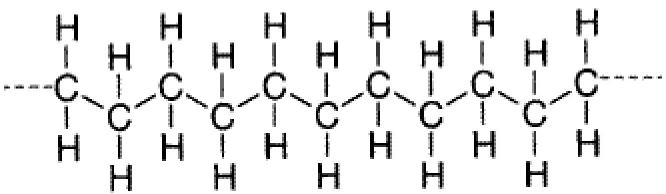


However, most of the Polymers are ***ORGANIC POLYMERS***

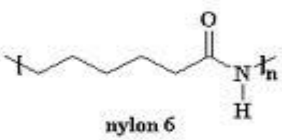
Examples: **see next slide**

SYNTHETIC Polymers

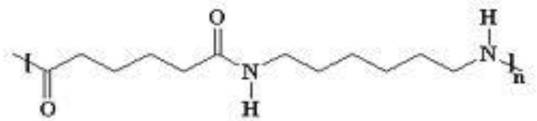
Some Examples of ***ORGANIC POLYMERS***



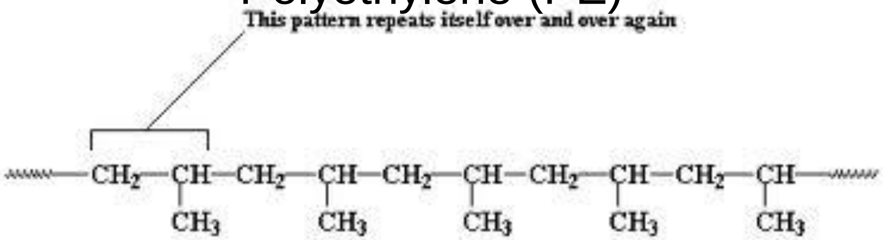
Polyethylene (PE)



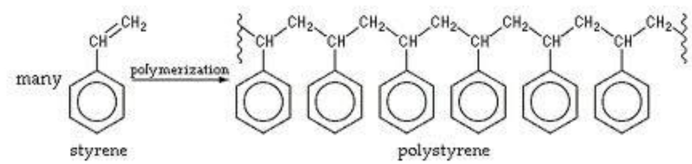
nylon 6

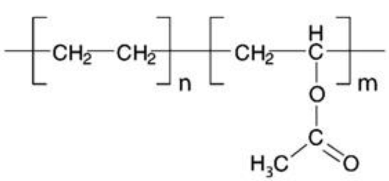


nylon 6,6

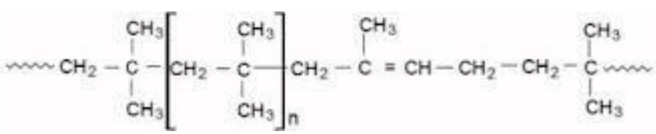


Polypropylene



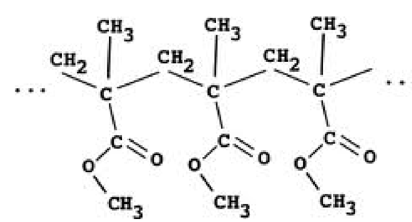


Ethylene Vinyl Acetate

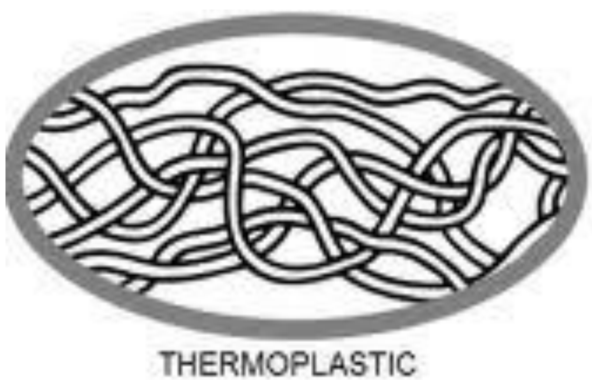


IIR Rubber

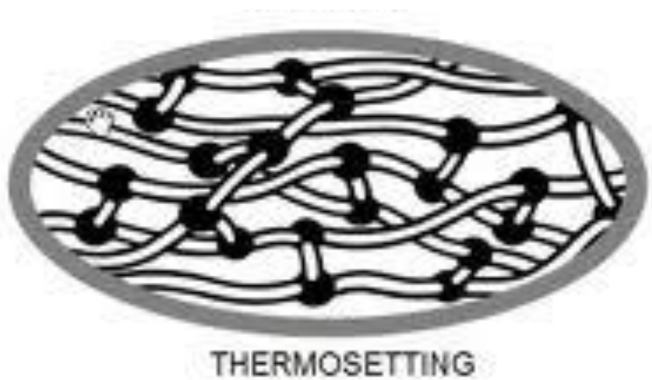
Isobutyl **I**sopropenyl **R**ubber



THERMOPLASTIC VS THERMOSET POLYMERS



“Entangled” Polymer Chains



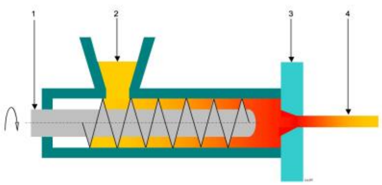
Crosslinked Polymer Chains

THERMOPLAST VERSUS THERMOSET

THERMOPLAST :

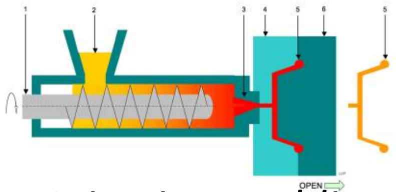
Polymers that soften when heated and become firm again when cooled

Giving the **final form to a container/component** is based upon this principle: Molding, Extrusion...



Extrusion

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



Injection Molding

THERMOPLAST VERSUS THERMOSET

THERMOSET :

Polymers that soften when heated and molded subsequently

BUT

Decompose when Reheated

Thermoset polymers are typically "**cross linked**"

Example: Bakelite

Fenol Formaldehyde Resin

Rubbers

Silicone tubings

TYPES OF POLYMERS

TYPES OF POLYMERS - **HOMOPOLYMERS**

A-A-A-A-A-A-A-A-A-A-A-A-A-A-A-A

A homopolymer is a **polymer** built from a **sequence of identical monomers**

EXAMPLES:

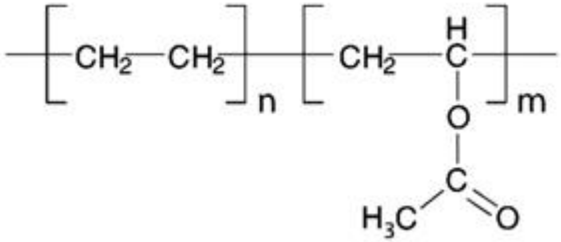
- Polyethylene
- Polypropylene
- PVC

TYPES OF POLYMERS – **COPOLYMERS**

When *two or more different monomers* unite together to polymerize, their result is called a **copolymer**

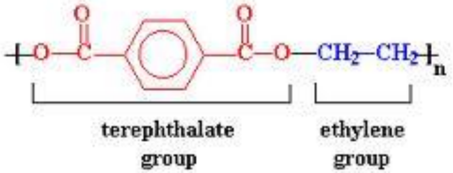
Random Copolymer A-B-A-A-B-B-B-A-B-A-A-A-B-A-B-B-A-B-A

Examples: Poly EVA



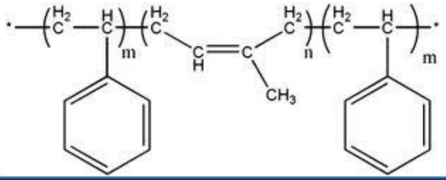
Regular Copolymer A-B-A-B-A-B-A-B-A-B-A-B-A-B-A-B-A-B-A

Examples:PET



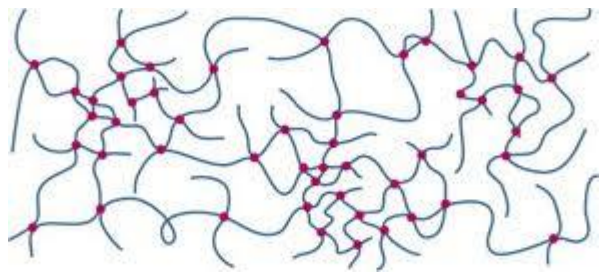
Block Copolymer A-A-A-A-B-B-B-B-B-B-B-B-B-B-B-A-A-A-A

Examples

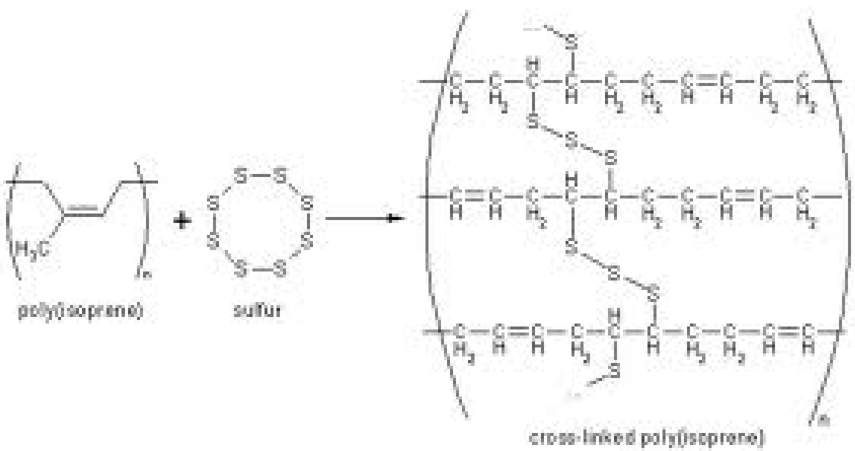


SIS Elastomer

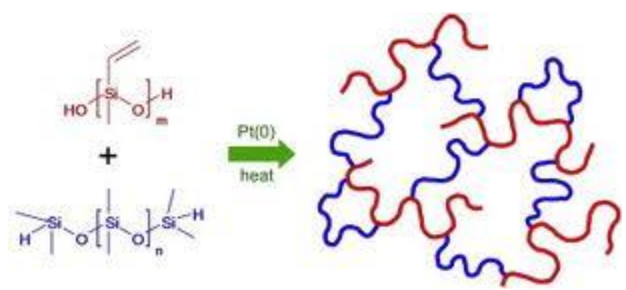
TYPES OF POLYMERS – **CROSS-LINKED Polymers**



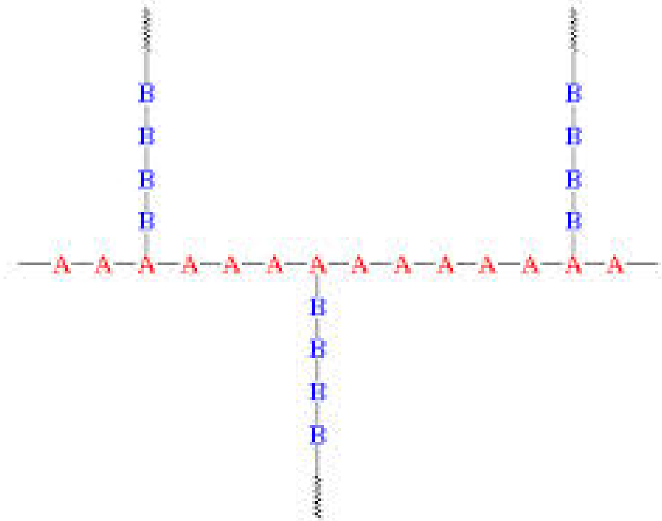
Isoprene/ Butadiene RUBBERS



Silicone rubbers (Pt-cured)



TYPES OF POLYMERS – **GRAFT COPOLYMERS**



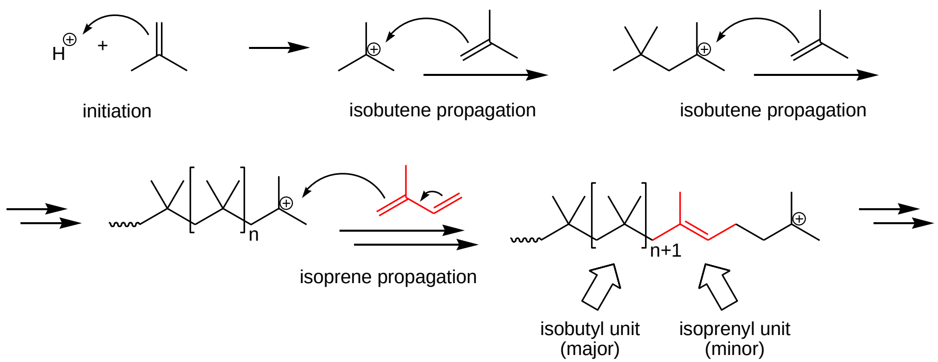
graft copolymer

CLASSIFICATION BASED UPON POLYMERISATION MECHANISM

CHAIN GROWTH

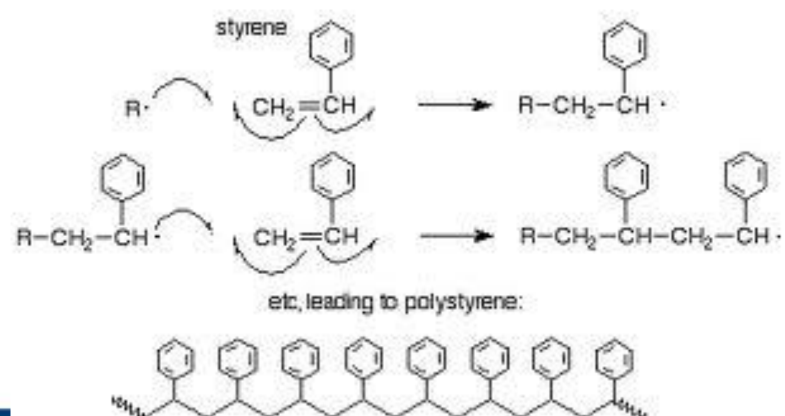
Example 1: Cationic Polymerization of "Butyl Elastomer"

Lewis Acid

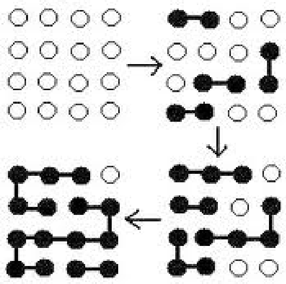


Understanding Polymerization of Butyl Elastomer helps to understand the formation and presence of rubber oligomers (see presentation E/L for Parenterals – Day 2)

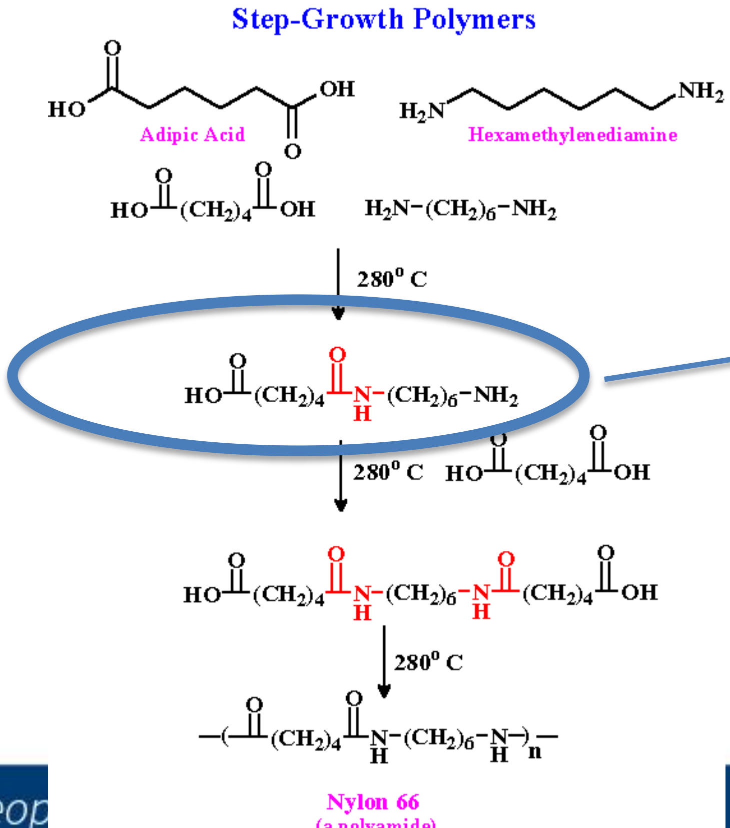
Example 2: Radical Polymerization of Polystyrene



STEP GROWTH (definition)



Examples: Polyaddition, polycondensation – Nylon 6,6

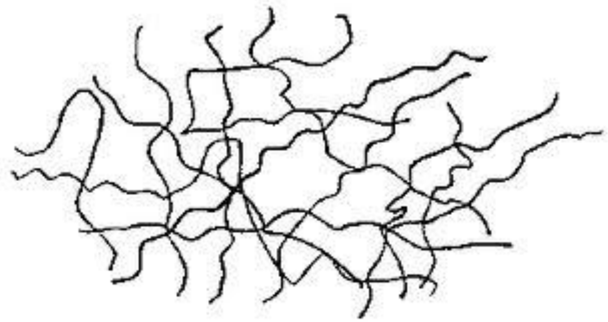


Seen as an Extractable /Leachable

POLYMER PROPERTIES

1. MORPHOLOGY

1. **AMORPHOUS Polymers**

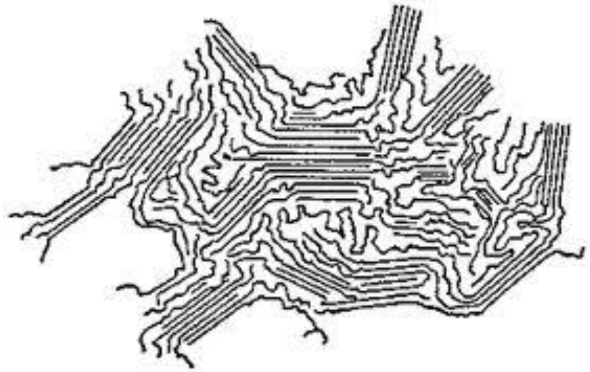


Because of
- Irregularities in Polymer Structure
- The Nature of the Polymer
- Cross-linking (for certain Polymers)

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

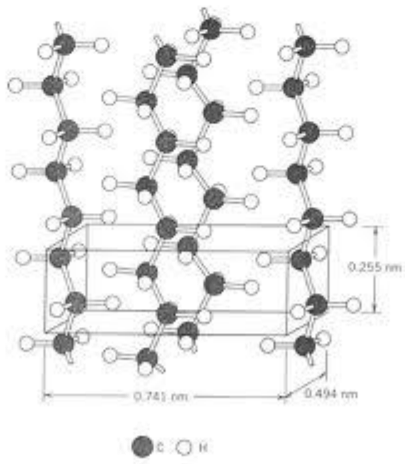
2. (Semi-)CRYSTALLINE POLYMERS

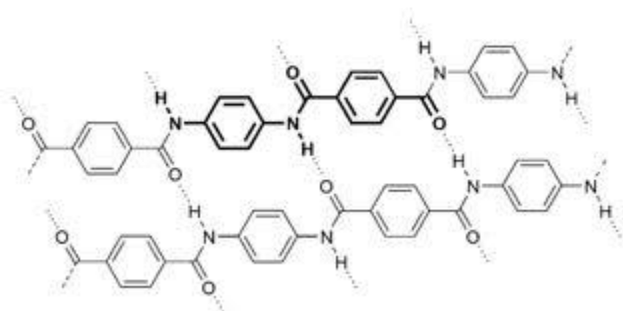


Hydrogen Bonds (e.g. PA)
Van der Waals Forces (e.g. Polyolefins)

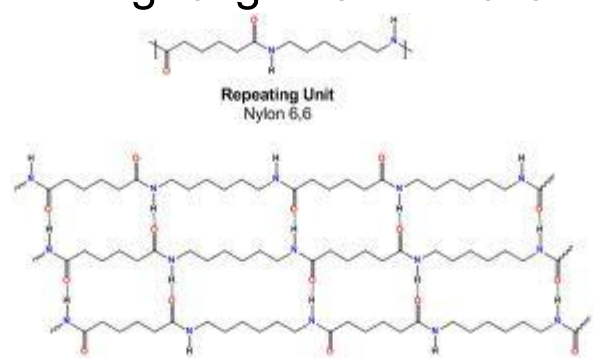
Impact of Stereochemistry of a polymer on physical properties

Bring “alignment” in chains



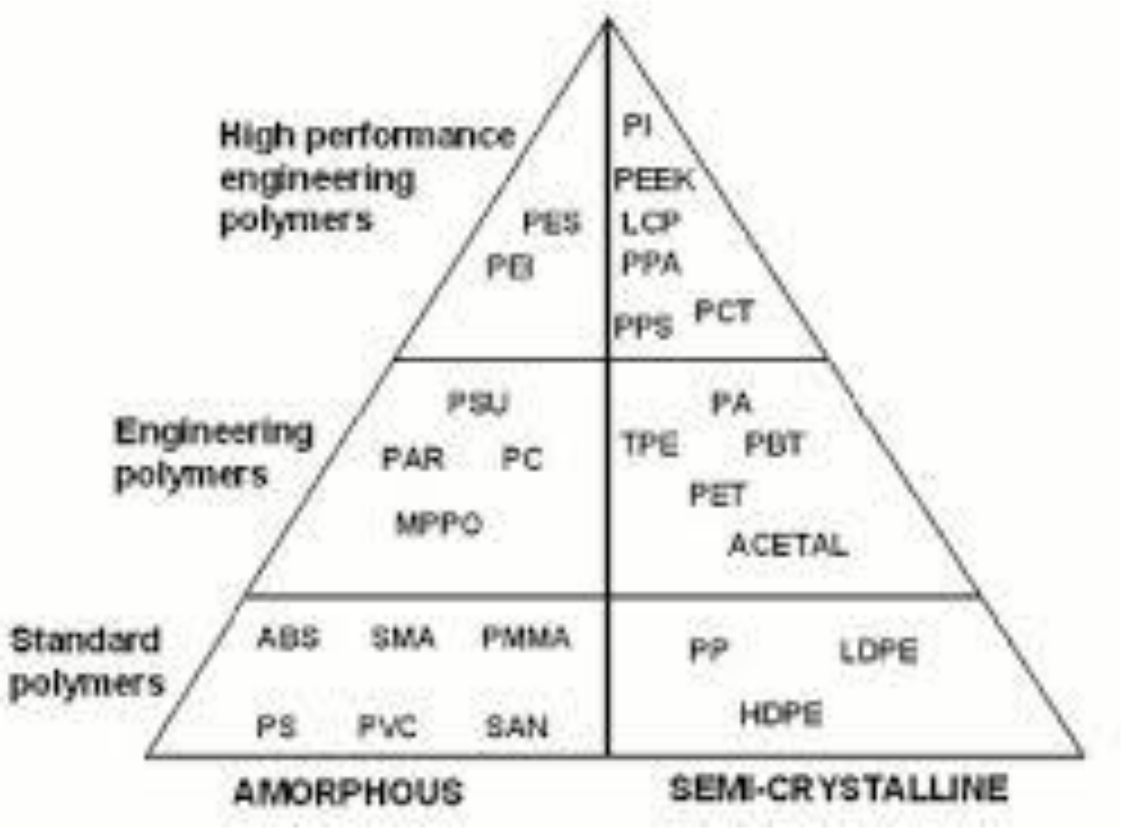


Kevlar



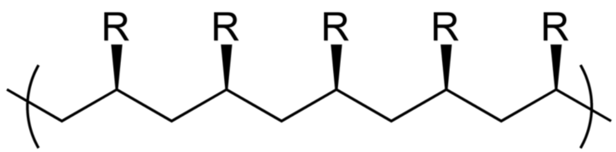
Nylon 6,6

AMORPHOUS versus CRYSTALLINE

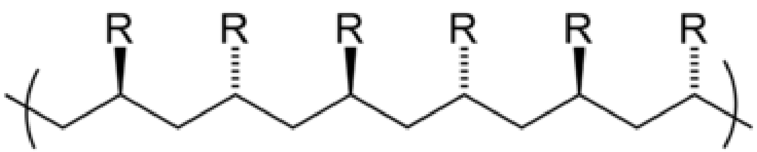


AMORPHOUS versus CRYSTALLINE

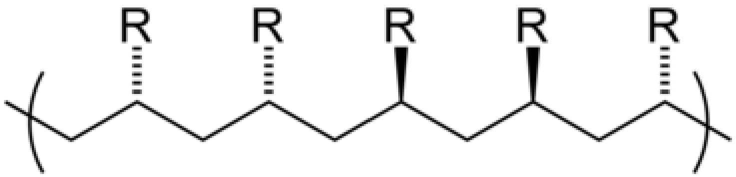
Impact of **StereoChemistry** of a polymer on physical properties



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



Syndiotactic
PS: Syndiotactic PS is semi-crystalline



Atactic
Typically amorphous polymers
PS: Atactic PS is amorphous

TACTICITY MODULATORS, SOMETIMES FOUND AS EXTRACTABLES

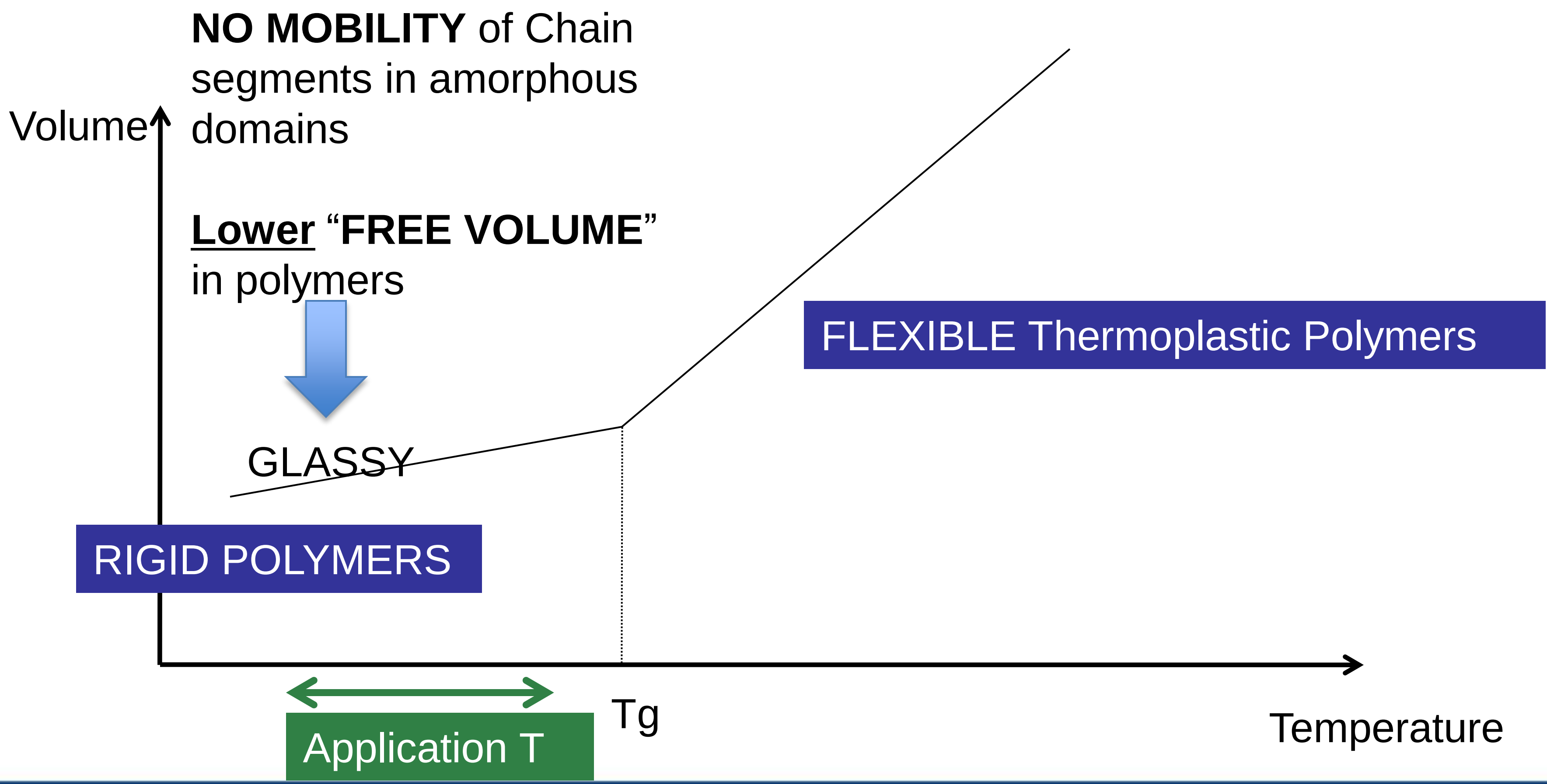
2. GLASS TRANSITION T° (T_g)

DEFINITION

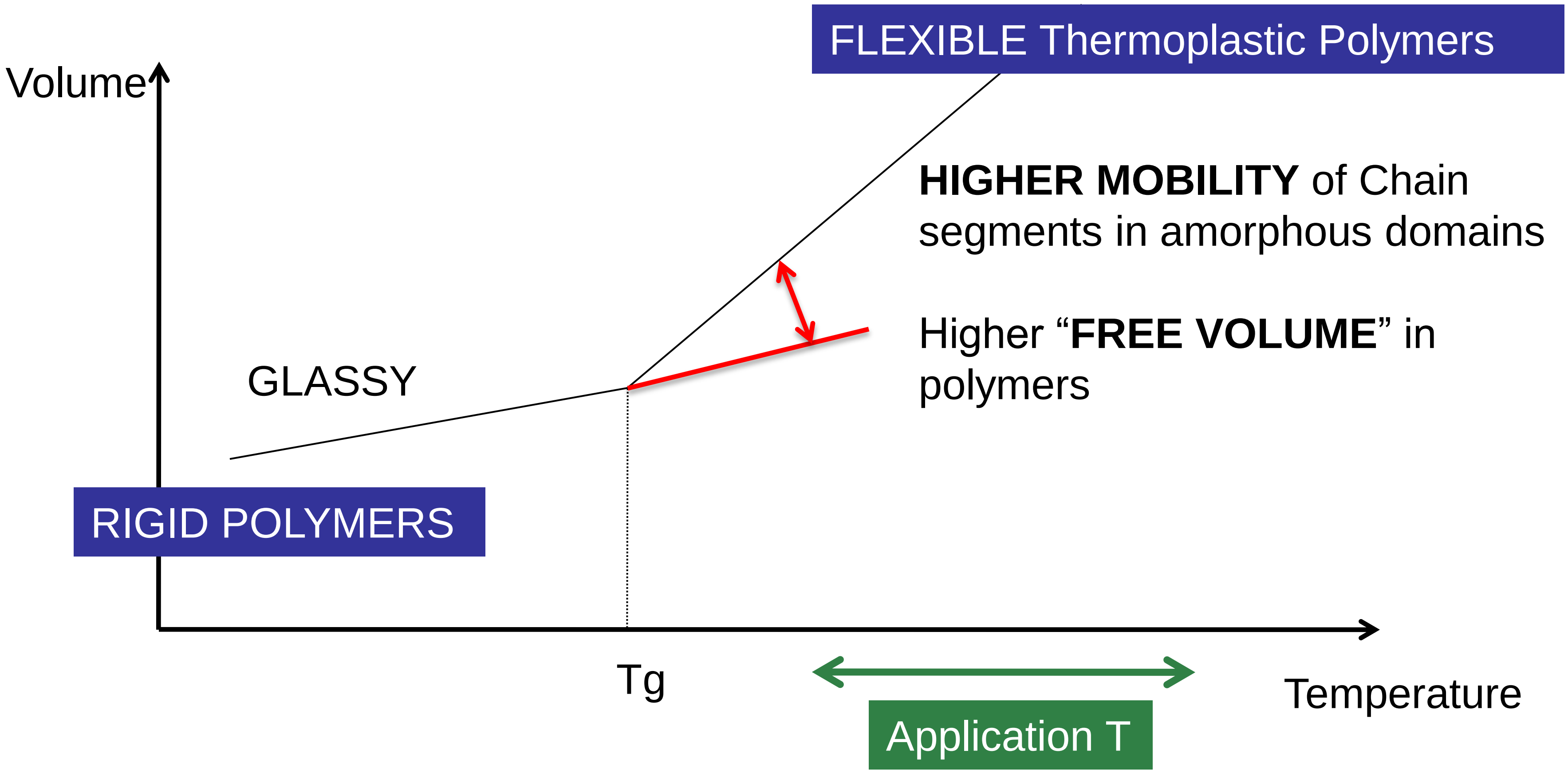
GLASS TRANSITION TEMPERATURE (T_g):

Temperature when a Polymer goes
from a “glassy” state (< T_g) to a “rubber” state (> T_g)

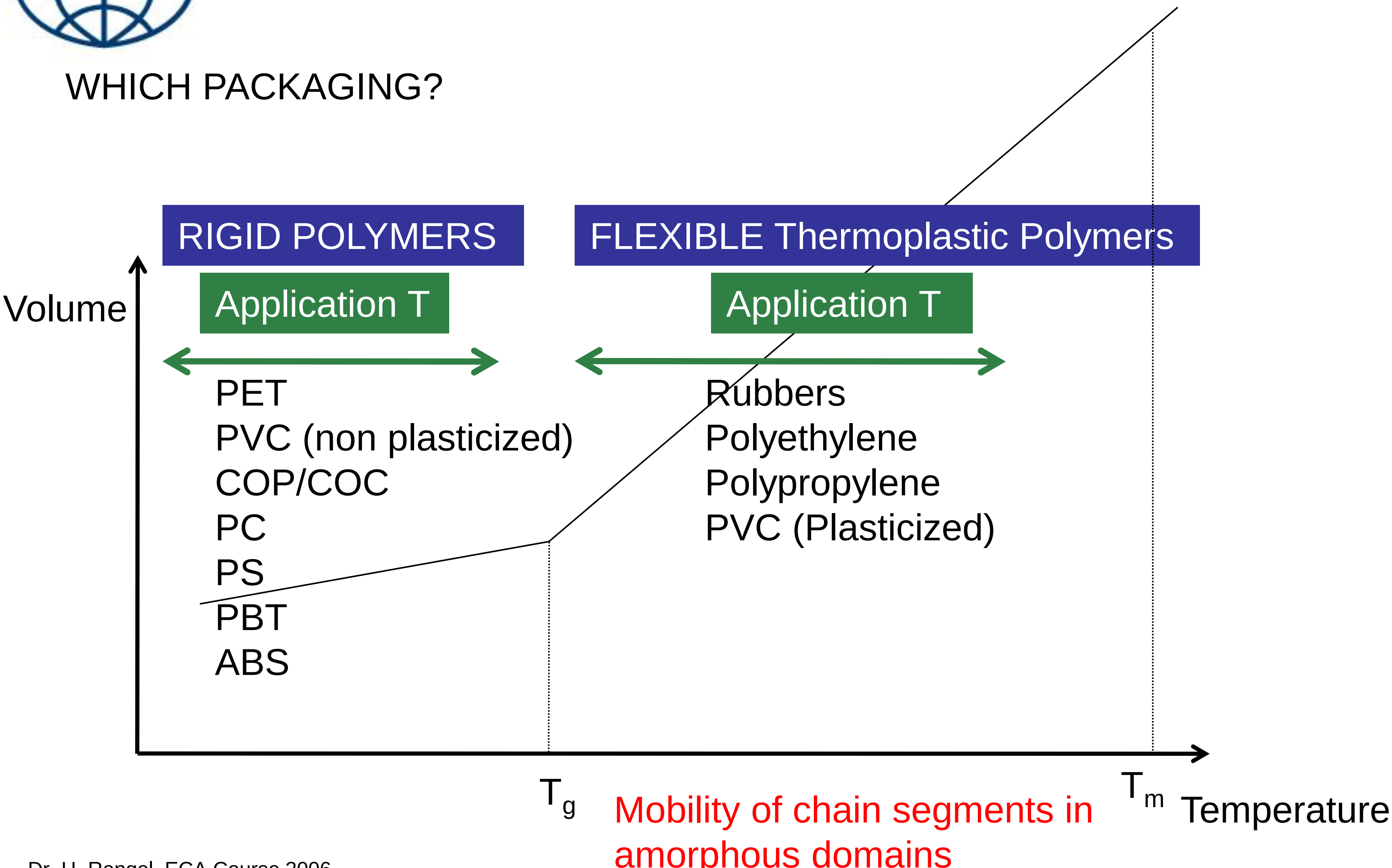
WHAT IS **RIGID** PACKAGING?



WHAT IS **FLEXIBLE** PACKAGING?



WHICH PACKAGING?



Dr. H. Rengel, ECA Course 2006

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!

COMPOSITION OF COMMERCIAL POLYMERS

COMPOSITION OF **COMMERCIAL POLYMERS**

- Additives
- Residues
- Catalysts
- Oligomers
- Degradation Compounds from Polymers
- Degradation Compounds from Polymer Additives

1. ADDITIVES

Anti-Oxidants

Plasticizers

Photostabilizers

Slip Agents

Antiozonants

Coupling Agents

Lubricants

Acid Scavengers

Peroxides / Crosslinkers

Blowing Agents

Pigments/Colorants

Antistatic Agents

Metal Chelators

Adhesives

Catalysts

Clarifying Agents

Antifogging agents

Fillers

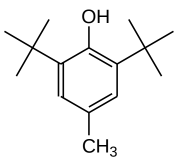
(Red: coming with some examples)

Anti-Oxidants

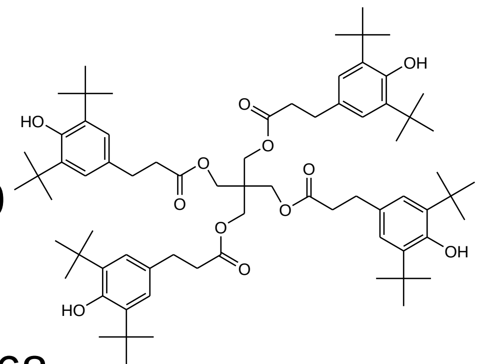
Function: assuring protection against thermal and oxidative degradation during processing and during shelf life of polymer
(*Sterically Hindered Phenols & Organic Phosphites/Phosphonates are mostly used*)

European Pharmacopoeia lists a.o. the following Anti-Oxidants:

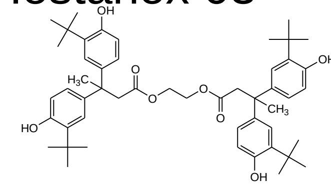
BHT



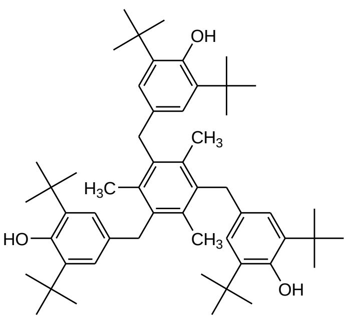
Irganox 1010



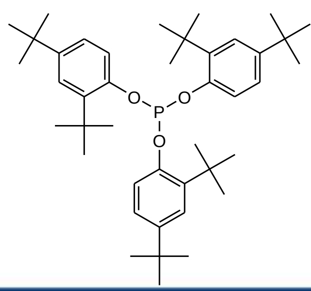
Hostanox 03



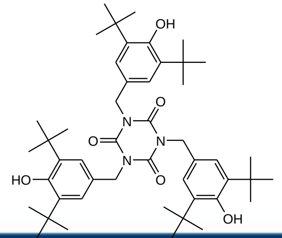
Irganox 1330



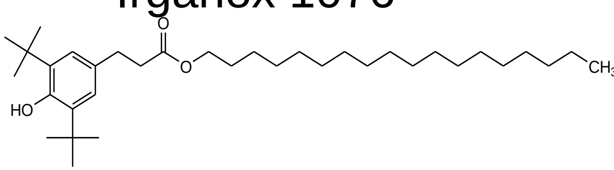
Irgafos 168



Irganox 3114



Irganox 1076



Parenteral Drug Association

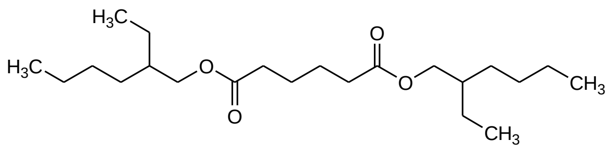
Plasticizers

Function: Gives the plastic flexibility and durability

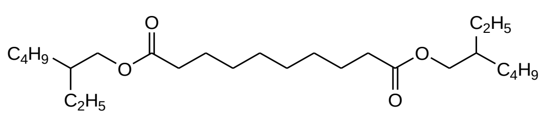
Plasticizer requirements:

- Low Water solubility (low extractibility)
- Stability to heat and light
- Low Odor, taste and toxicity

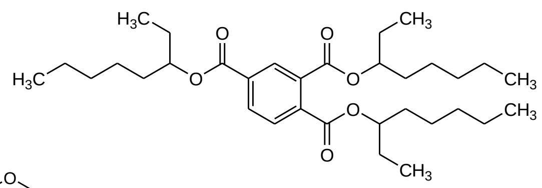
Diethylhexyladipate



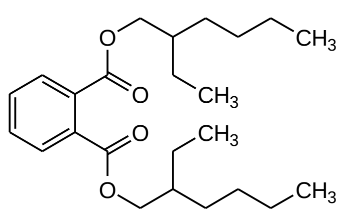
Diethylhexylsebacate



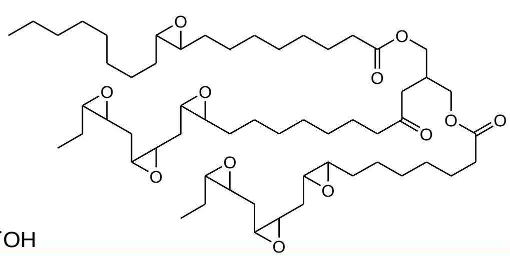
TOTM



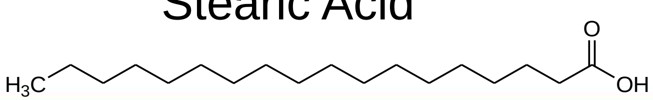
Diethylhexylphthalate (DEHP)



ESBO



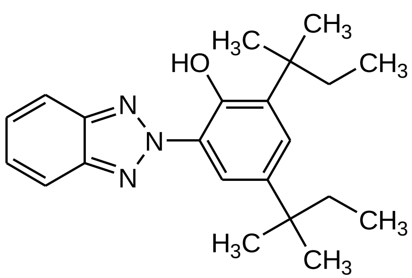
Stearic Acid



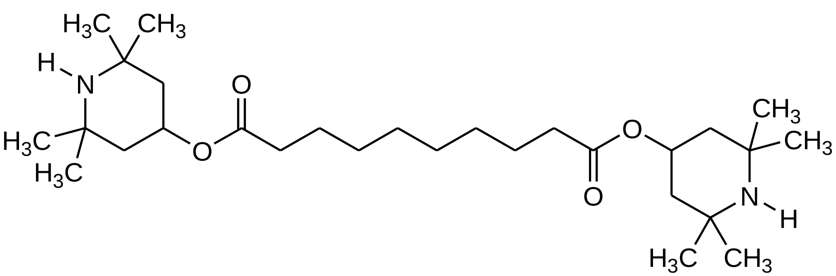
Photostabilizers

Function: Protects the Polymer from UV-Degradation (exposure to sunlight)

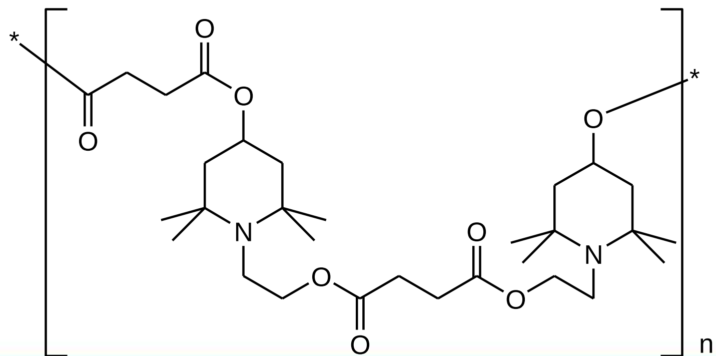
Tinuvin 328



Tinuvin 770



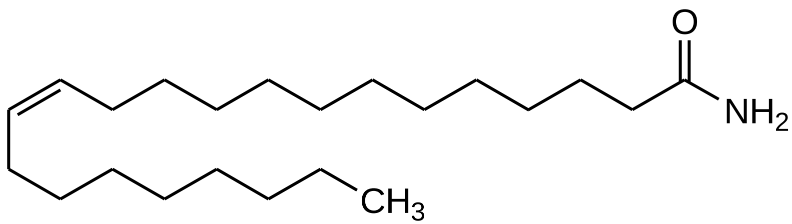
Tinuvin 622



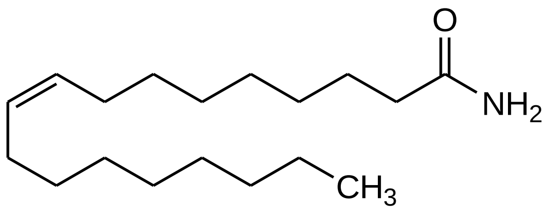
Slip Agents

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

Erucamide



Oleamide



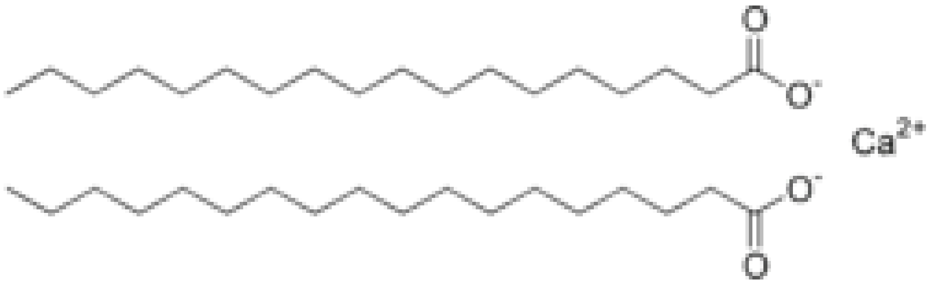
Remark:
because of their specific properties, Slip agents will be widely detected as Leachables!

Acid Scavengers

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

Examples: Ca(Stearate)$_2$ + 2HCl ➔ $CaCl_2$ + Stearic acid

strong acid *weak acid*

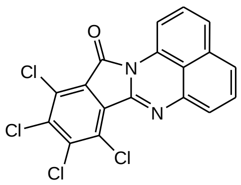


Pigments / Colorants

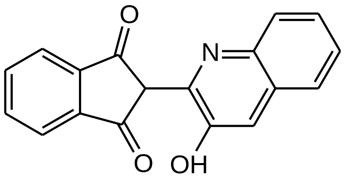
Function: Gives the polymer/rubber the desired color (cosmetic)

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

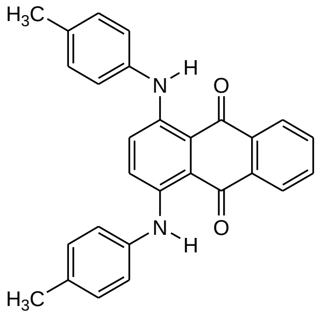
Solvent Red



Solvent yellow 114



Solvent Green 03

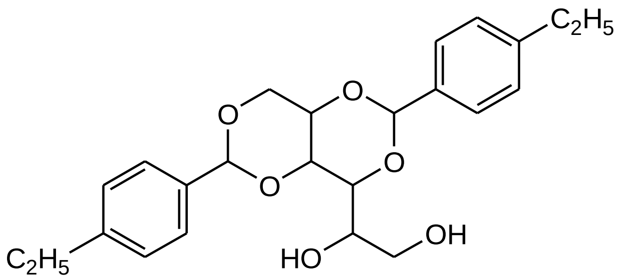


Remarks: beware of the composition of the Masterbatch!

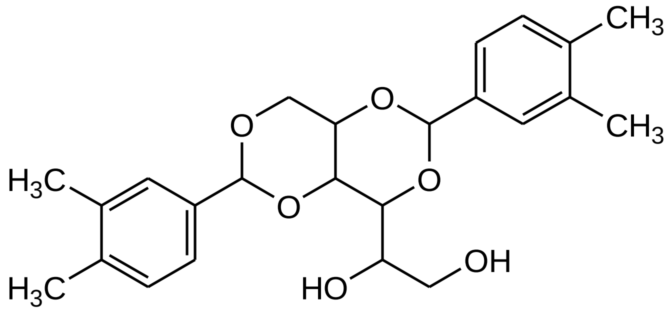
Clarifying Agents (Nucleating Agents)

Function: by controlling the crystallisation (nucleation) when cooling off PP,
it becomes transparent.

NC-4



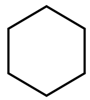
Millad 3988



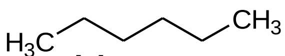
2. RESIDUES

Residues from the production process (non-limitative)

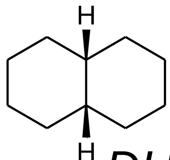
Solvents



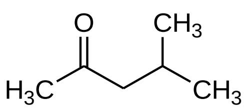
Cyclohexane



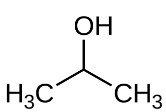
Hexane



DHN

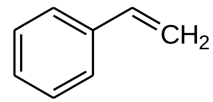


MIBK

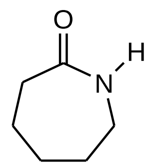


IPA

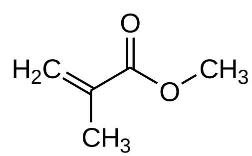
Monomers



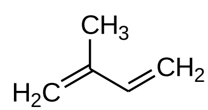
Styrene



Caprolactam



Methyl methacrylate



Isoprene

Catalysts

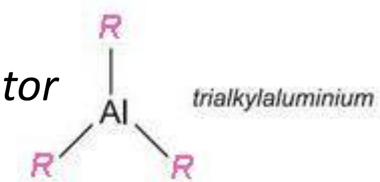
Titanium
Zirkonium
Cobalt
Aluminum
Iron
Hafnium
...

Catalysts

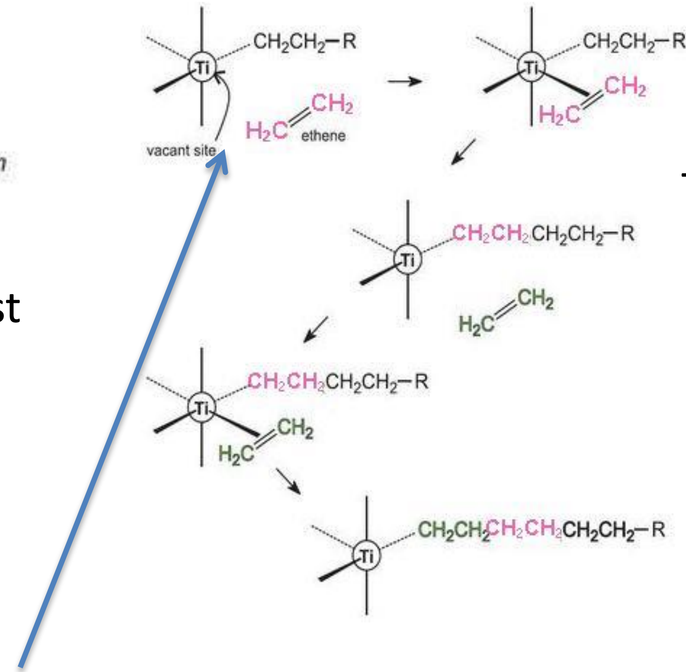
Function: assists in a very efficient polymerization process.

EXAMPLES:

promotor

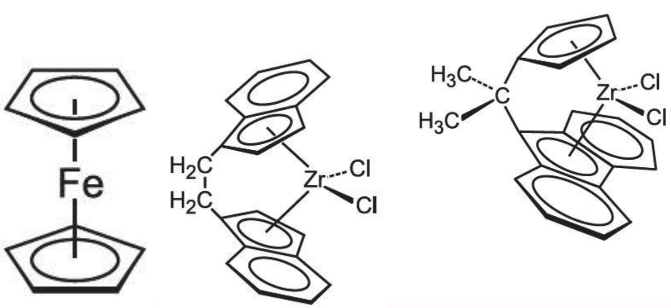


Ziegler-Natta Catalyst



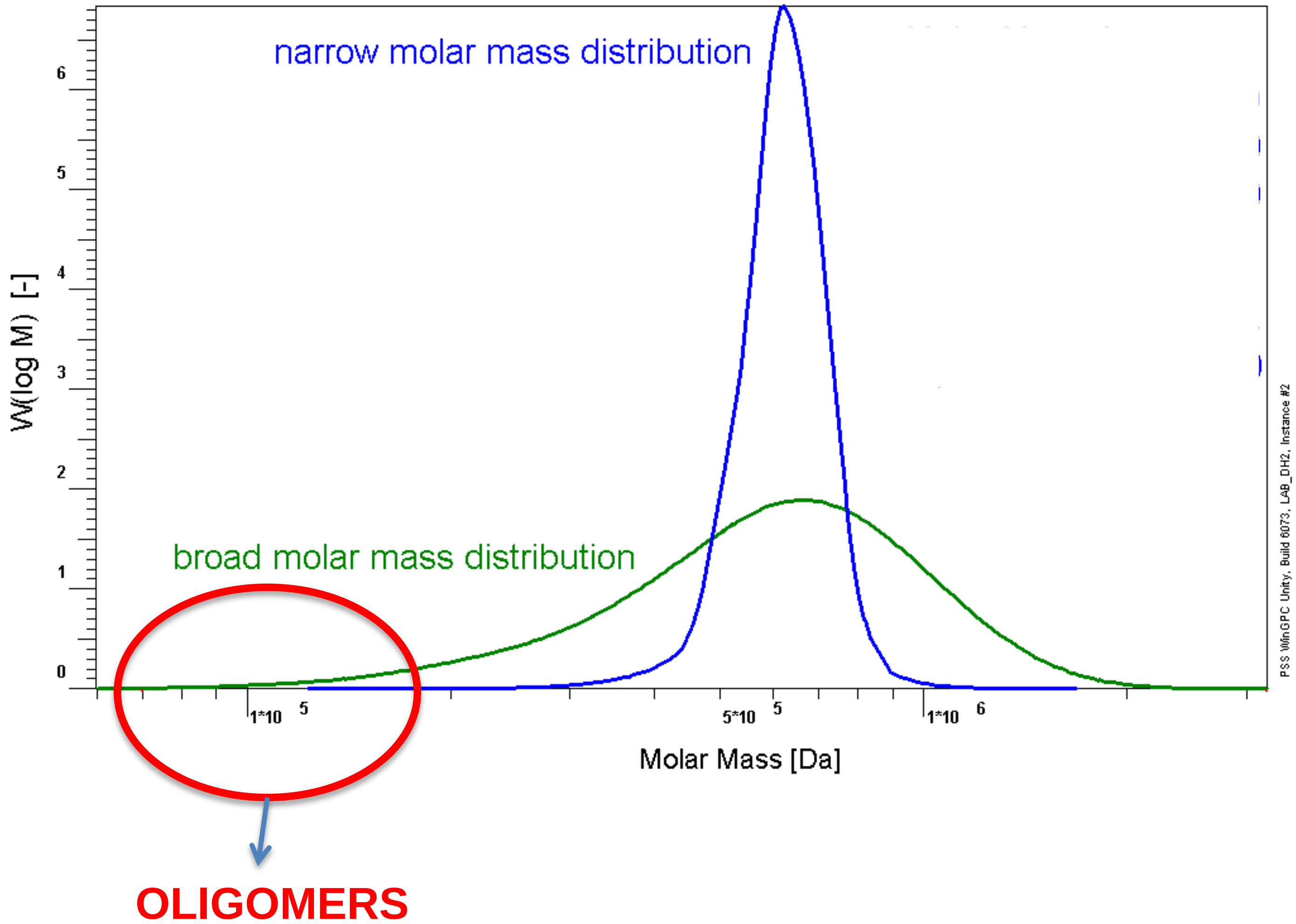
Ti-Catalyst

Metallocenes
(stereospecific catalysts)



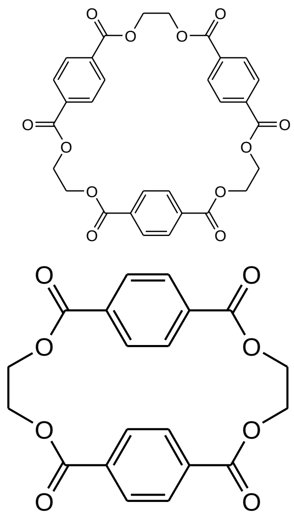
The alkene monomer attaches itself to an empty coordination site on the titanium atom and this alkene molecule then inserts itself into the carbon-titanium bond to extend the alkyl chain. This process then continues, thereby forming a linear polymer

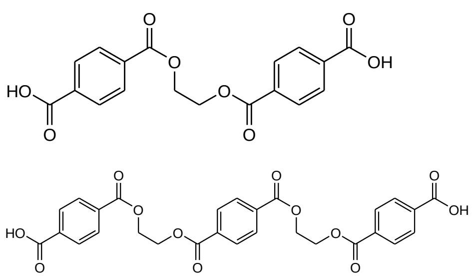
3. OLIGOMERS


narrow molar mass distribution
broad molar mass distribution
W(log M) [-]
0
1
2
3
4
5
6
1*10 5
5*10 5
1*10 6
Molar Mass [Da]
PSS WinGPC Unity, Build 6073, LAB_DH2, Instance #2
OLIGOMERS

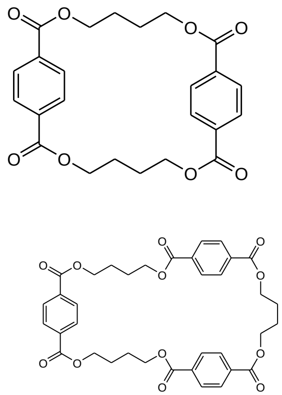
OLIGOMERS: Examples

PET

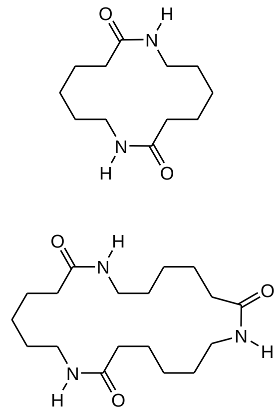




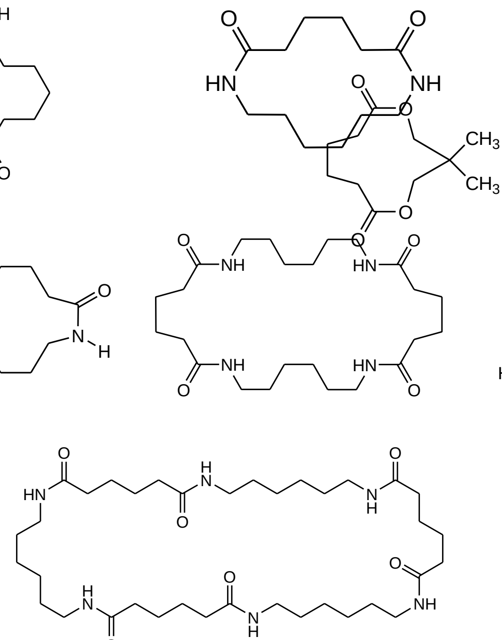
PBT



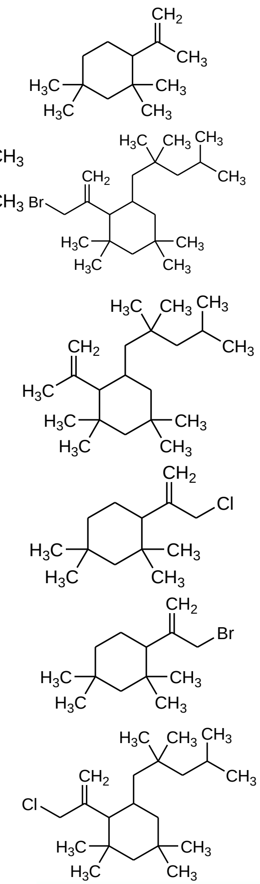
Nylon 6



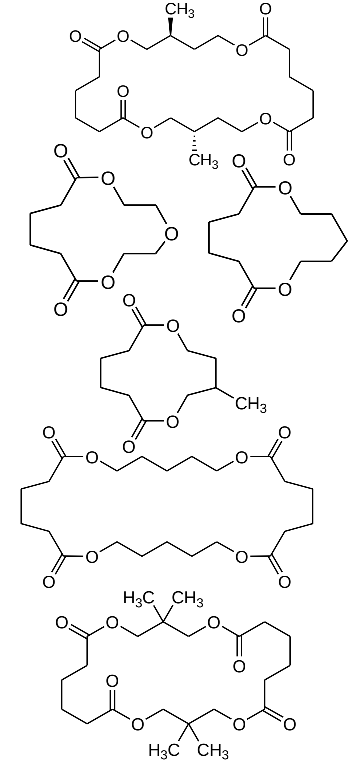
Nylon 6.6



Butyl Rubber



Polyester adhesive



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

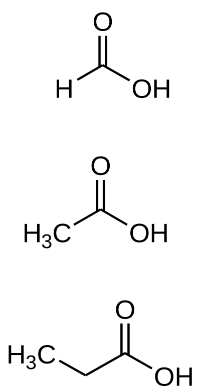
4. POLYMER DEGRADATION COMPOUNDS

Polymer degradation Compounds

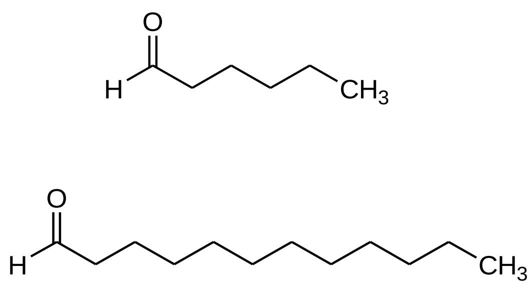
Origin: Oxidative degradation of the polymers

(when the polymer is not properly stabilized via anti-oxidants)

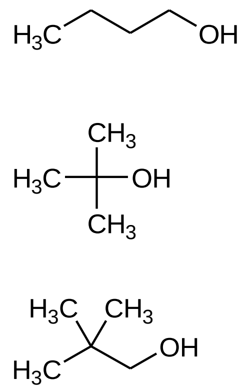
Example of Polymer Degradation Compounds from **Polypropylene**



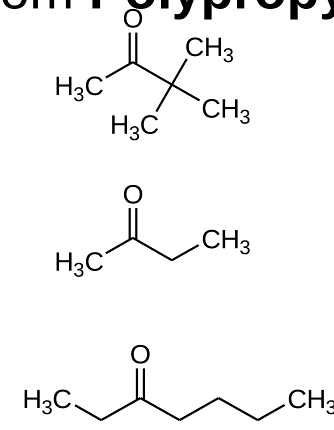
Acids



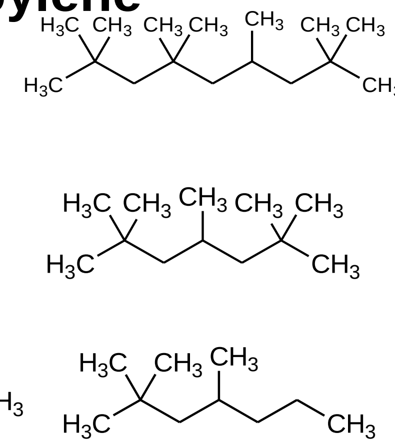
Aldehydes



Alcohols



Ketones

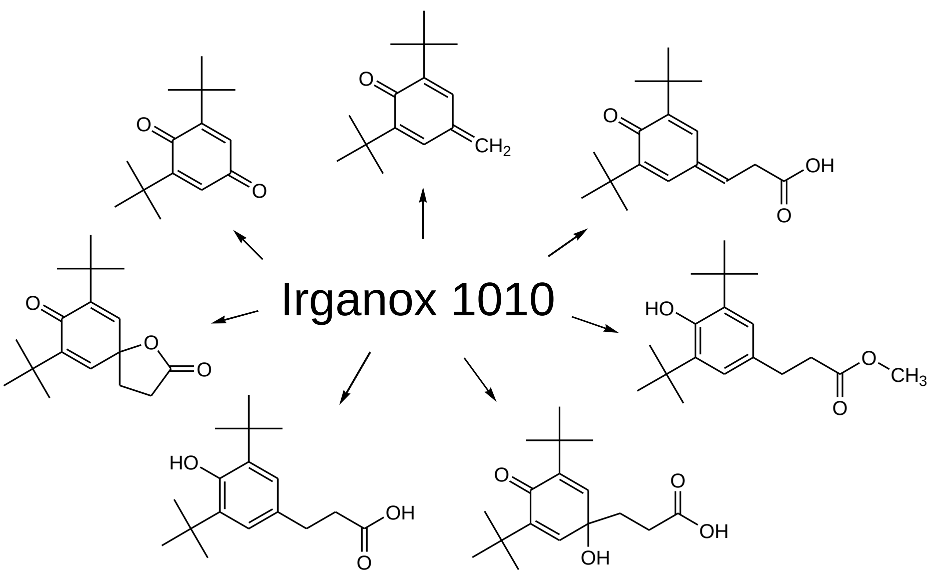


Polymer Fragments

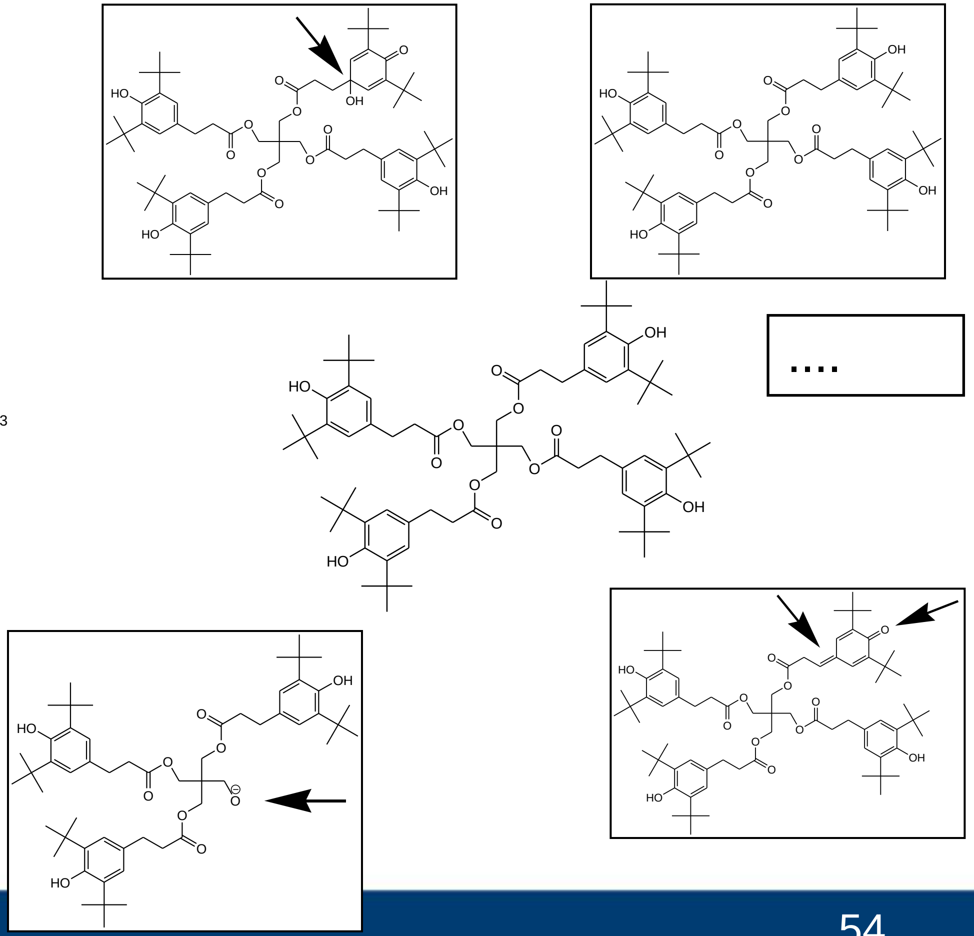
5. POLYMER ADDITIVE DEGRADATION COMPOUNDS

Example Degradation of **Irganox 1010**

SMALL degradation Compounds

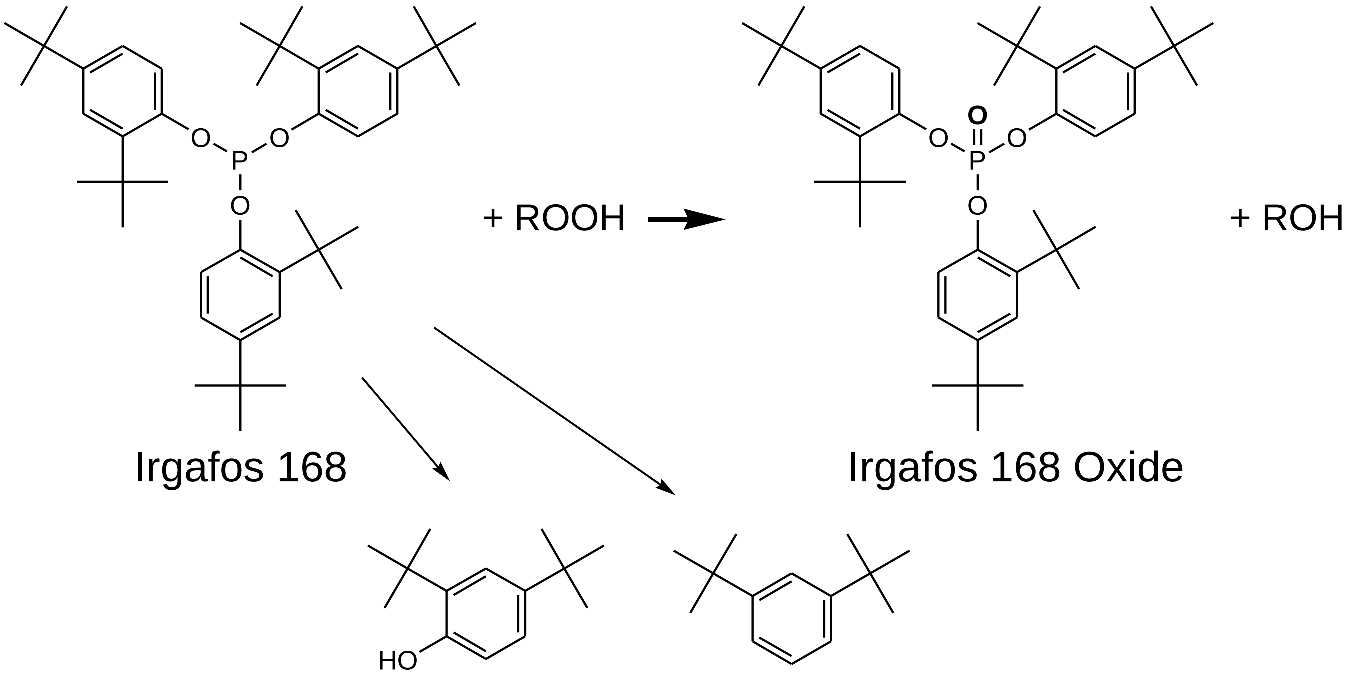


LARGE degradation Compounds



EXAMPLE: Degradation of Irgafos 168

(also other degradation compounds for Irgafos 168 are known)



PROCESSING OF POLYMERS

Name(s)	Formula	Monomer	Examples of Uses
Polyethylene low density (LDPE)	$–(CH_2\text{-}CH_2)_n–$	ethylene $CH_2=CH_2$	Films for bags, multilayer contact film
Polyethylene high density (HDPE)	$–(CH_2\text{-}CH_2)_n–$	ethylene $CH_2=CH_2$	Bottles, Caps
Polypropylene (PP) different grades	$–[CH_2\text{-}CH(CH_3)]_n–$	propylene $CH_2=CHCH_3$	Bottles, Caps
Poly(vinyl chloride) (PVC)	$–(CH_2\text{-}CHCl)_n–$	vinyl chloride $CH_2=CHCl$	Bags, tubings
Polystyrene (PS)	$–[CH_2\text{-}CH(C_6H_5)]_n–$	styrene $CH_2=CHC_6H_5$	Secondary Packaging (Tubs)
Polytetrafluoroethylene (PTFE, Teflon)	$–(CF_2\text{-}CF_2)_n–$	tetrafluoroethylene $CF_2=CF_2$	Containers, seals, tubes, tubings, "inert"coatings…
Poly(methyl methacrylate) (PMMA)	$–[CH_2\text{-}C(CH_3)CO_2CH_3]_n–$	methyl methacrylate $CH_2=C(CH_3)CO_2CH_3$	Implantable Lenses (IOL)
Poly(vinyl acetate) (PVAc)	$–(CH_2\text{-}CHOCOCH_3)_n–$	vinyl acetate $CH_2=CHOCOCH_3$	Multilayer films
cis-Polyisoprene natural rubber	$–[CH_2\text{-}CH=C(CH_3)\text{-}CH_2]_n–$	isoprene $CH_2=CH\text{-}C(CH_3)=CH_2$	rubbers

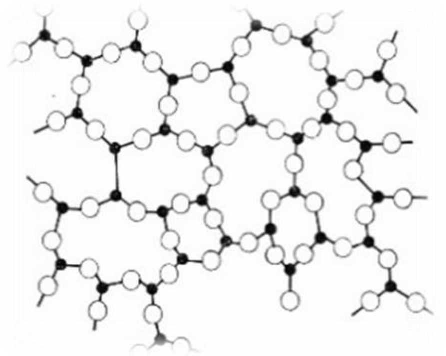
GLASS 101

WORKSHOP
EXTRACTABLES - LEACHABLES

Dr. Piet Christiaens

What is Glass?

An inorganic fused substance that has been cooled to a rigid condition without crystallization (e.g. Supercooled amorphous substance)



Why Glass as packaging material?

- Well-known material
- Transparent
- Heat resistant
- Good barrier properties: gas & vapour tight
- Chemically and physically (quite) inert.

J. Zuercher, ECA Course E/L, Prague 2010

Glass in Pharmaceutical Packaging

- Ampoules
- Injection Vials
- Infusion Bottles
- Syringes
- Carpules
- Bottles for oral drug products
- Bottles for solid preparations

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Composition of Glass – Function of Ingredients

- SiO_2 : Backbone structure
- CaO : Increasing hardness & Chemical resistance
- Al_2O_3 : Increasing Chemical Resistance
- Na_2O & B_2O_3 : Lowering the melting point
- Fe_2O_3, TiO_2 : Amber Glass
- CuO : Blue Glass
- Mn^{3+} : Violet Glass

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Glass Types

Glass Type	General Description	Uses
I	High resistant Borosilicate	Parenteral Preparations
II	Treated Soda-Lime	Acidic and Neutral Parenteral Preparations
III	Soda Lime	Not for Parenteral Preparations
NP	Soda-Lime	Oral / Topical

Glass Composition for different Glass Types:

Component	Type I (Borosilicate)	Type II, III, NP (Soda-Lime)
SiO_2	70 - 73%	69 - 73%
B_2O_3	10%	0 - 1%
Na_2O	2 - 9%	13 - 14%
Al_2O_3	6 - 7%	2 - 4%
BaO	0,1 - 2,0%	0 - 2%
K_2O	1 - 2%	0 - 3%
CaO	0,7 - 1,0%	5 - 7%
MgO	0 - 0,5%	3 - 4%
ZnO	0 - 0,5%	-

Metal Profile of a Type I - Clear Glass Vial (ICP-MS)

Main Metals	Amount (%)	**Trace Metals (> 1µg/g)**	Amount (µg/g)
Si	>30%	Mg	61
Al	2%	Ba	21
Na	2,40%	Ce	8,8
B	5,50%	Ti	6,7
K	0,1%	Hf	6
Ca	0,036%	Mo	4,8
Fe	0,7 - 1,0%	Y	2,8
Zr	0 - 0,5%	La	2,5
		Sr	1,7
		Pd	1,6
		Ga	1,2
		Pb	1

Zuccarello et. Al., PDA, J Parm Sci technol 63, 339-352, 2009

GLASS 101

Examples for Extractables / Leachables

○**High heating** during molding process leads to an **increasing release of alkali ions** from the glass surface => Delamination

○During the process, **components of the heated glass vaporize and deposit** on the surface

○**Heating promotes migration of alkali oxides** within the silica matrix to the glass surface

○Relevant for **glass containers** made from **tubular glass**

○**Small volume** containers are **more impacted** than larger containers

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GLASS 101

Parameters, impacting the Glass Leachables

- **Filling Volume**: *smaller filling volumes show higher leachable concentrations*
- **Storage time**: *leachable concentrations increase over time*
- **Sterilization / Sterilization time**: *longer autoclaving cycles, higher concentrations*
- **Sterilization Temperature**: *higher temperatures, higher concentrations*
- **Type of contact solution**:

  [Si]: Lactic acid < acetic acid < ascorbic acid < malic acid < tartaric acid < oxalic acid < citric acid

  ***Complexing agents**, such as EDTA may also impact the metal release from Glass*

- **Impact of pH**: *higher pH, higher [Si] release.*

  In general, more metals are leaching out of glass at pH>9

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GLASS 101

Risk of Glass Leachables

○**Most observed Metal Leachables from Glass:**
Si and **Na** as MAJOR leachables, **K, B, Ca & Al** as MINOR LEA, **Fe**: traces

○**Alkali release:** pH shift of unbuffered solutions

○**Silicon (Si) release**:increased particle load, delamination!

○**Aluminum release**:
Aluminum can accumulate in patients with reduced renal function, causing e.g. neurological diseases

○Potential **Arsenic (As) release**:
glass can contain arsenic oxide (III) as a fining agent to improve glass tranparency. Arsenic is toxic!

○**Release of metals**, causing precipitation with some salts, present in the DP
Ba => $BaSO_4$, Al => $Al(OH)_3$

GLASS 101

How to (try to) prevent Glass Leaching

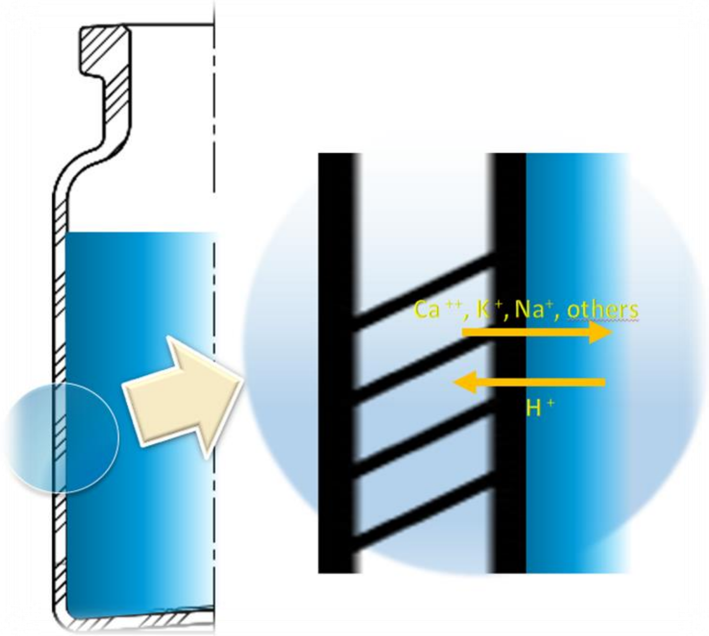
1. Chemical surface treatment

$(NH_4)SO_4$ is injected before annealing

$(NH_4)SO_4 \rightarrow (NH_4)HSO_4 + NH_3$

$2Na^+ + (NH_4)HSO_4 \rightarrow Na_2SO_4 + NH_3 + 2H^+$

Afterwards, rinsing with Water to remove soluble $NaSO_4$



Result: lower pH shift because lower amounts of Na will leach

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GLASS 101

How to (try to) prevent Glass Leaching

2. Put a Coating on the Glass

Deposition of SiO_x layer as an inert glass layer

e.g. Schott Type I Plus

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GLASS 101

How to (try to) prevent Glass Leaching

3. Siliconization

Siliconized surfaces are hydrophobic, **reducing the wettability** of the container surface

Thus siliconized glass surfaces are **reducing the potential of interactions** with aqueous fillings

The **release of alkali ions is reduced**, compared to non-siliconized containers

> *However, Siliconized surface may then release organic compounds!*
> *(e.g. Siloxanes)*

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Questions?