POLYMERS 101 – GLASS 101

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
Sevilla
29 – 30 November 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")

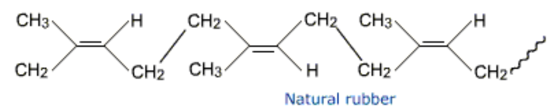
Refers to a molecule

- 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

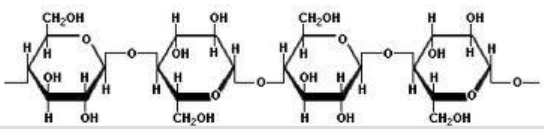
Classification of Polymers

- Polymers also exist in Nature: **NATURAL POLYMERS**
  - Latex / Natural Rubber



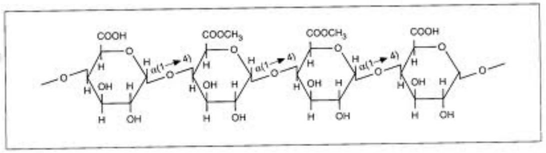
Repeating Isoprene units

  - Starch
  - Cellulose



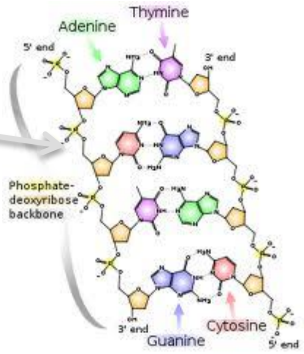
Repeating D-Glucose units

  - Pectin



Repeating Galacturonic acid units

  - DNA



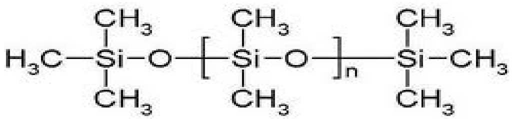
  - Silk / Wool
  - ....

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

SYNTHETIC Polymers

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

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

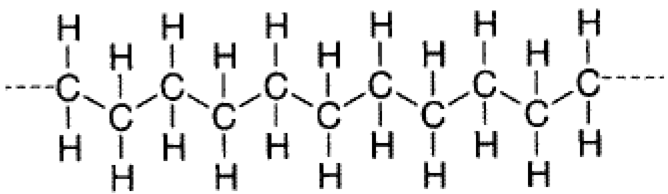


However, most of the Polymers are ***ORGANIC POLYMERS***

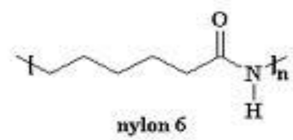
Examples: **see next slide**

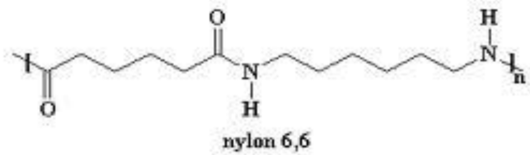
SYNTHETIC Polymers

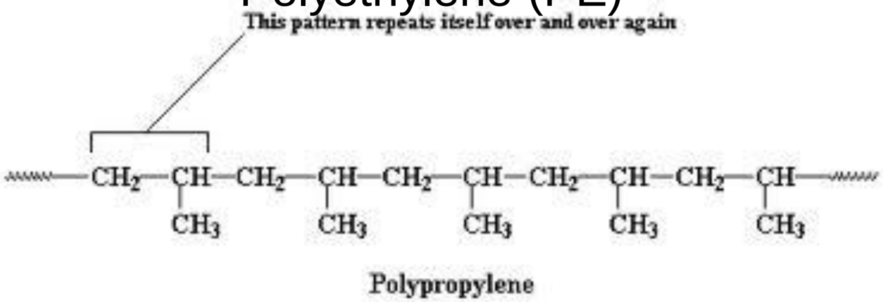
Some Examples of ***ORGANIC POLYMERS***

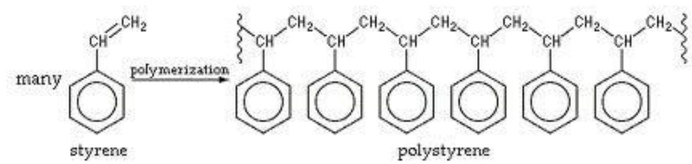


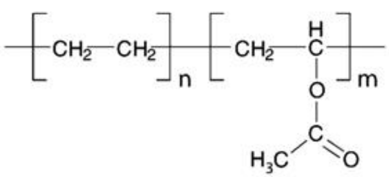
Polyethylene (PE)



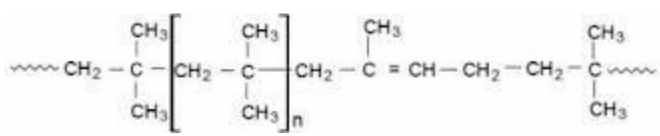






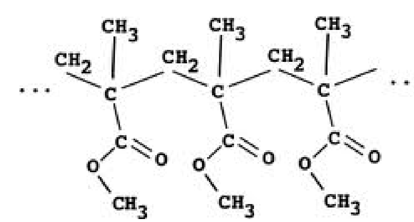


Ethylene Vinyl Acetate

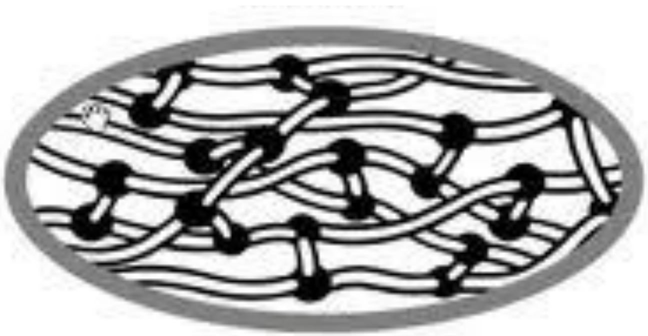


IIR Rubber

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



THERMOPLASTIC VS THERMOSET POLYMERS



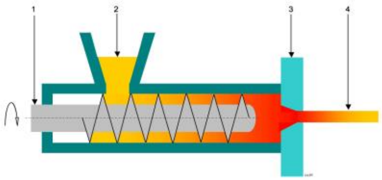
"Entangled" Polymer Chains

Crosslinked Polymer Chains

THERMOPLAST VERSUS THERMOSET

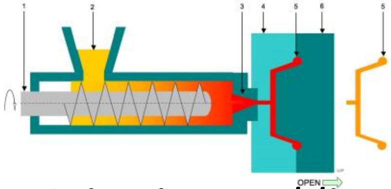
THERMOPLAST :
Polymers that soften when heated and become firm again when cooled

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

Parenteral Drug Association

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:

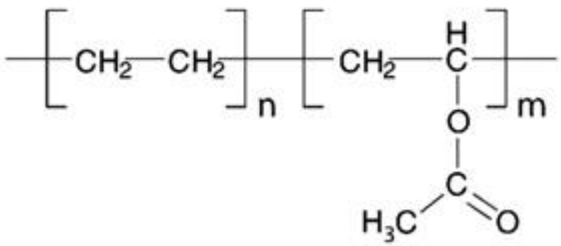
- Polyethylene
- Polypropylene
- PVC

TYPES OF POLYMERS – **COPOLYMERS**

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

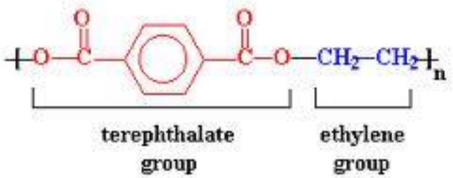
Random Copolymer A-B-A-A-B-B-B-A-B-A-A-A-B-A-B-B-A-B-A

Examples: Poly EVA



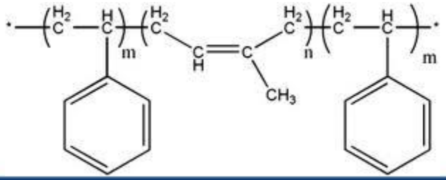
Regular Copolymer A-B-A-B-A-B-A-B-A-B-A-B-A-B-A-B-A-B-A

Examples:PET



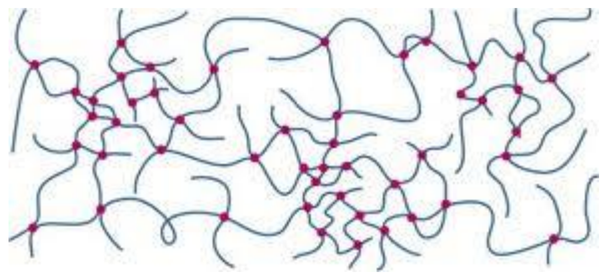
Block Copolymer A-A-A-A-B-B-B-B-B-B-B-B-B-B-B-A-A-A-A

Examples

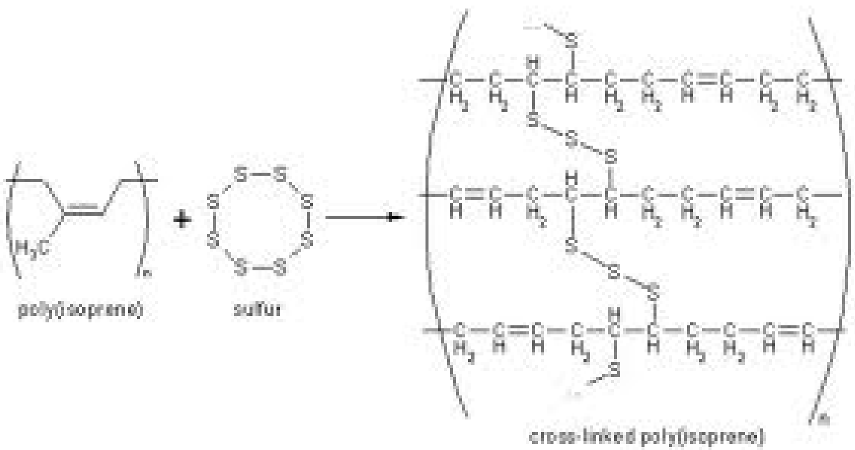


SIS Elastomer

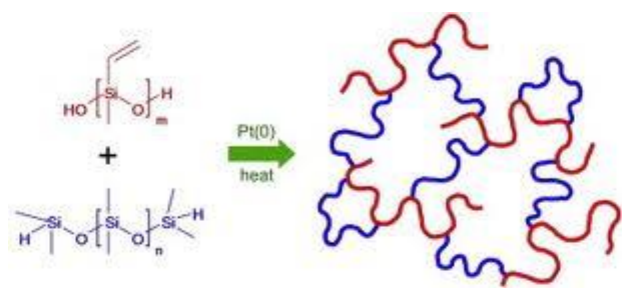
TYPES OF POLYMERS – **CROSS-LINKED Polymers**



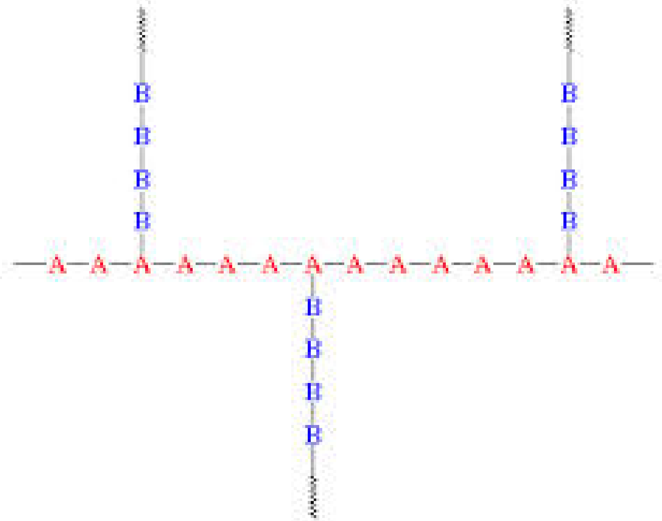
Isoprene/ Butadiene RUBBERS



Silicone rubbers (Pt-cured)



TYPES OF POLYMERS – **GRAFT COPOLYMERS**



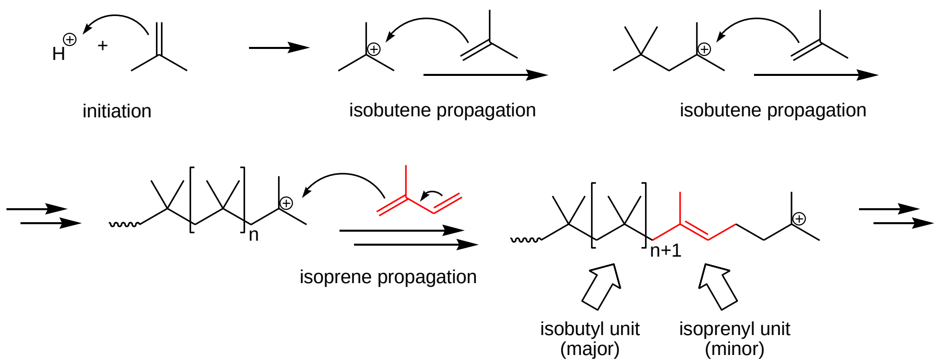
graft copolymer

CLASSIFICATION BASED UPON POLYMERISATION MECHANISM

CHAIN GROWTH

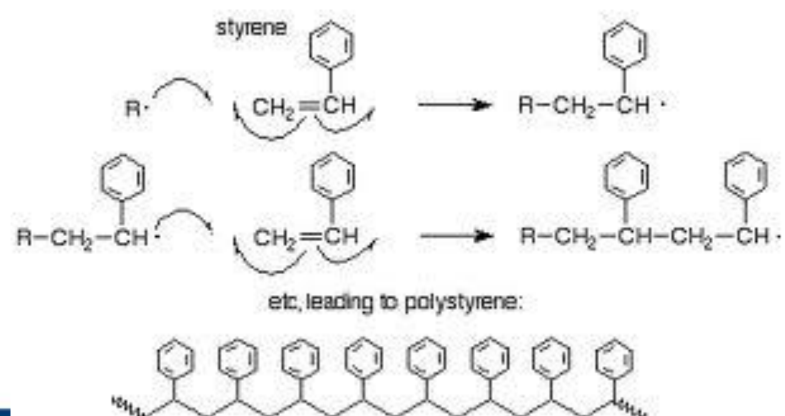
Example 1: Cationic Polymerization of “Butyl Elastomer”

Lewis Acid

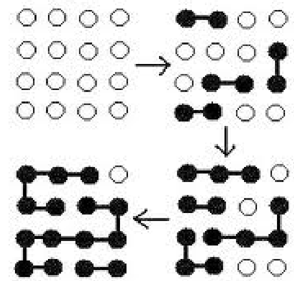


Understanding Polymerization of Butyl Elastomer helps to understand the formation and presence of rubber oligomers (see presentation E/L for Parenterals – Day 2)

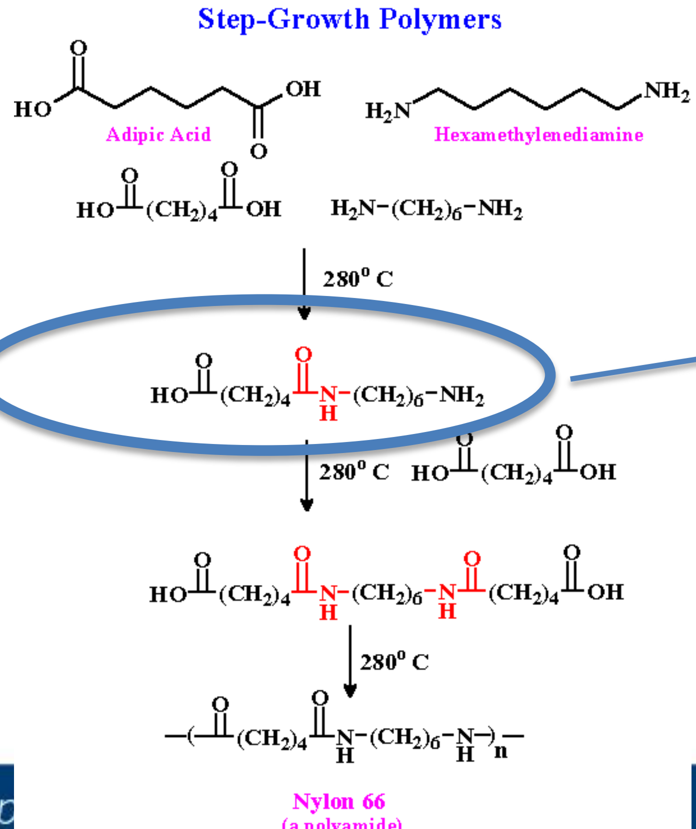
Example 2: Radical Polymerization of Polystyrene



STEP GROWTH (definition)



Examples: Polyaddition, polycondensation – Nylon 6,6

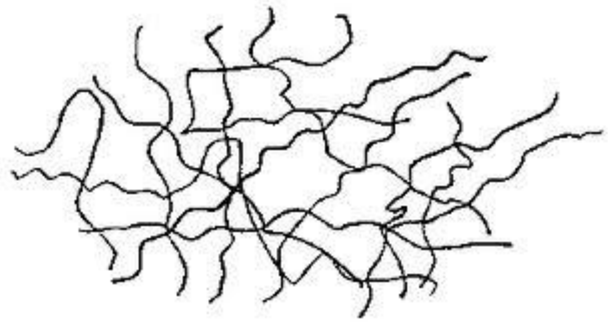


Seen as an Extractable /Leachable

POLYMER PROPERTIES

1. MORPHOLOGY

1. **AMORPHOUS Polymers**



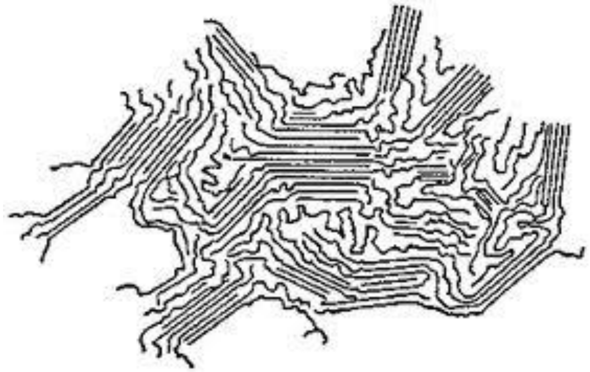
Because of

• 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

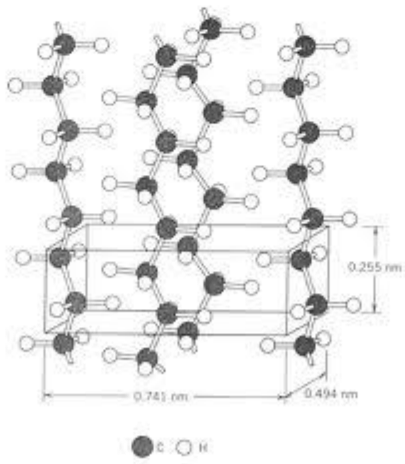
2. (Semi-)CRYSTALLINE POLYMERS

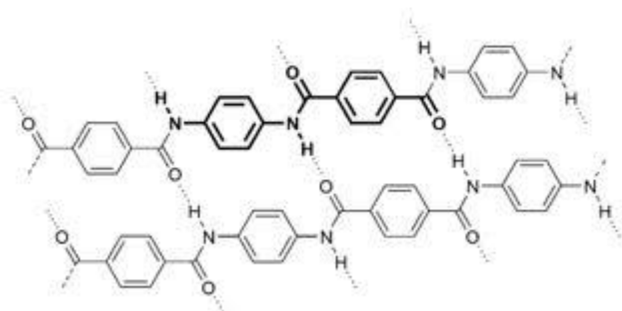


Hydrogen Bonds (e.g. PA)
Van der Waals Forces
(e.g. Polyolefins)

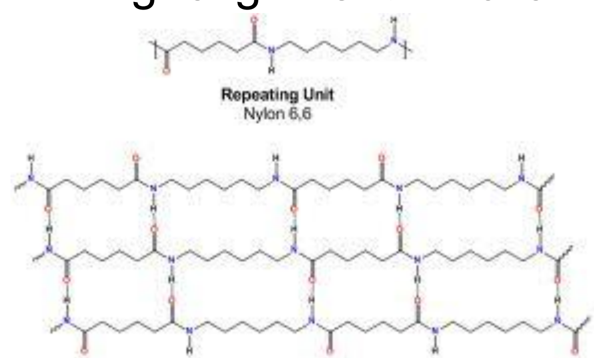
Impact of Stereochemistry of a polymer on physical properties

Bring “alignment” in chains





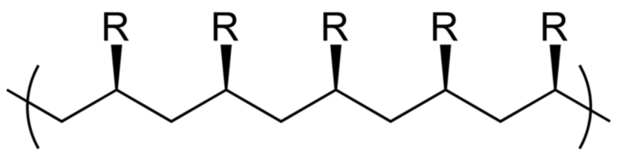
Kevlar



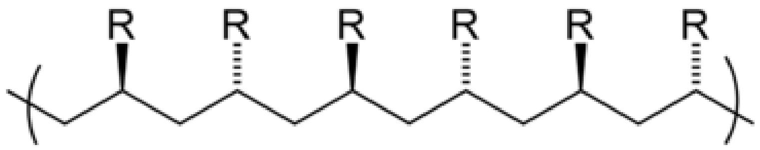
Nylon 6,6

AMORPHOUS versus CRYSTALLINE

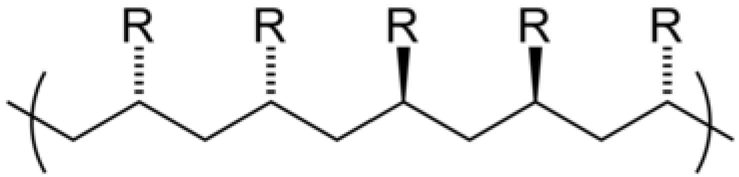
Impact of **StereoChemistry** of a polymer on physical properties



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

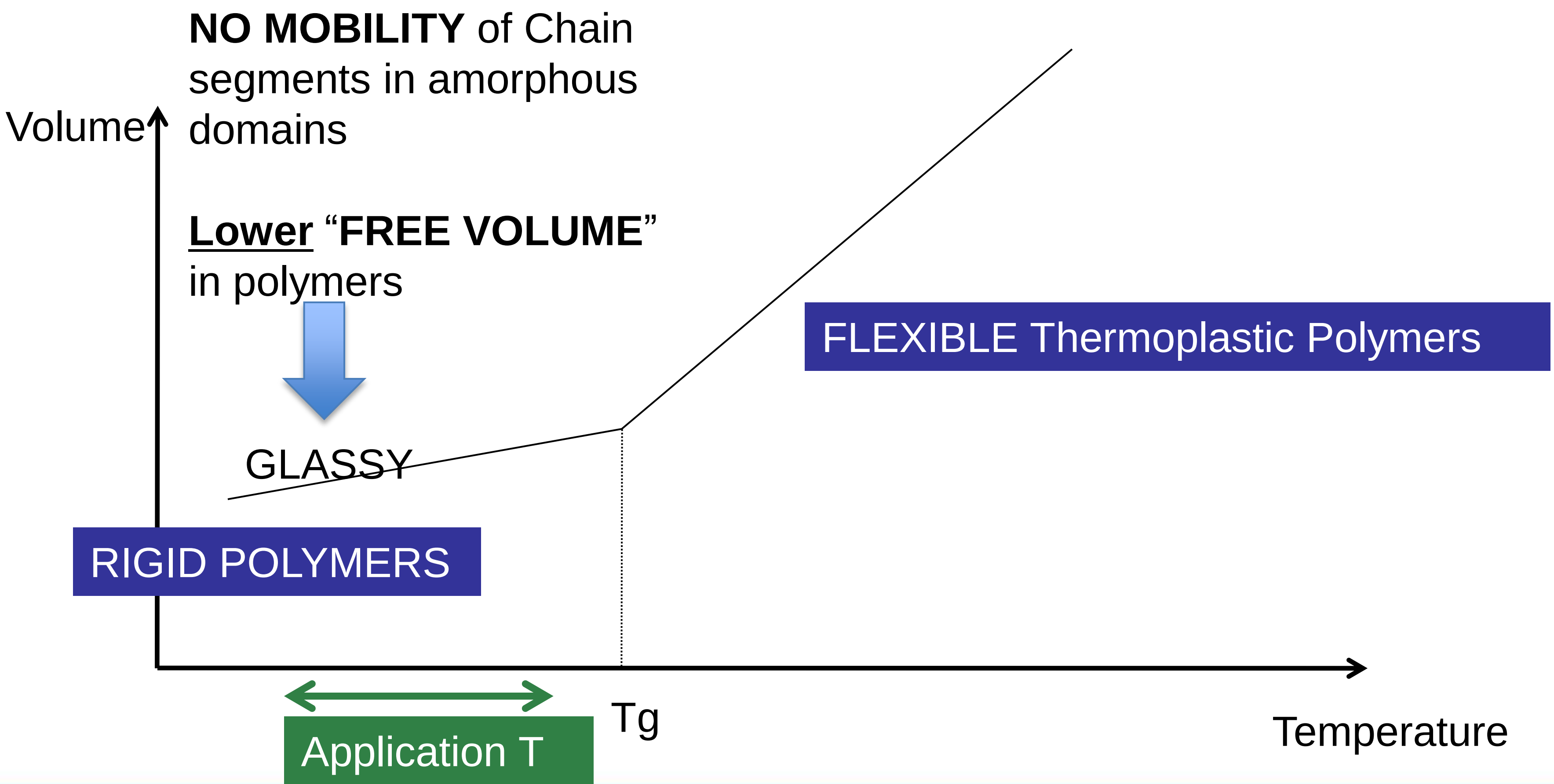
2. GLASS TRANSITION T° (T_g)

DEFINITION

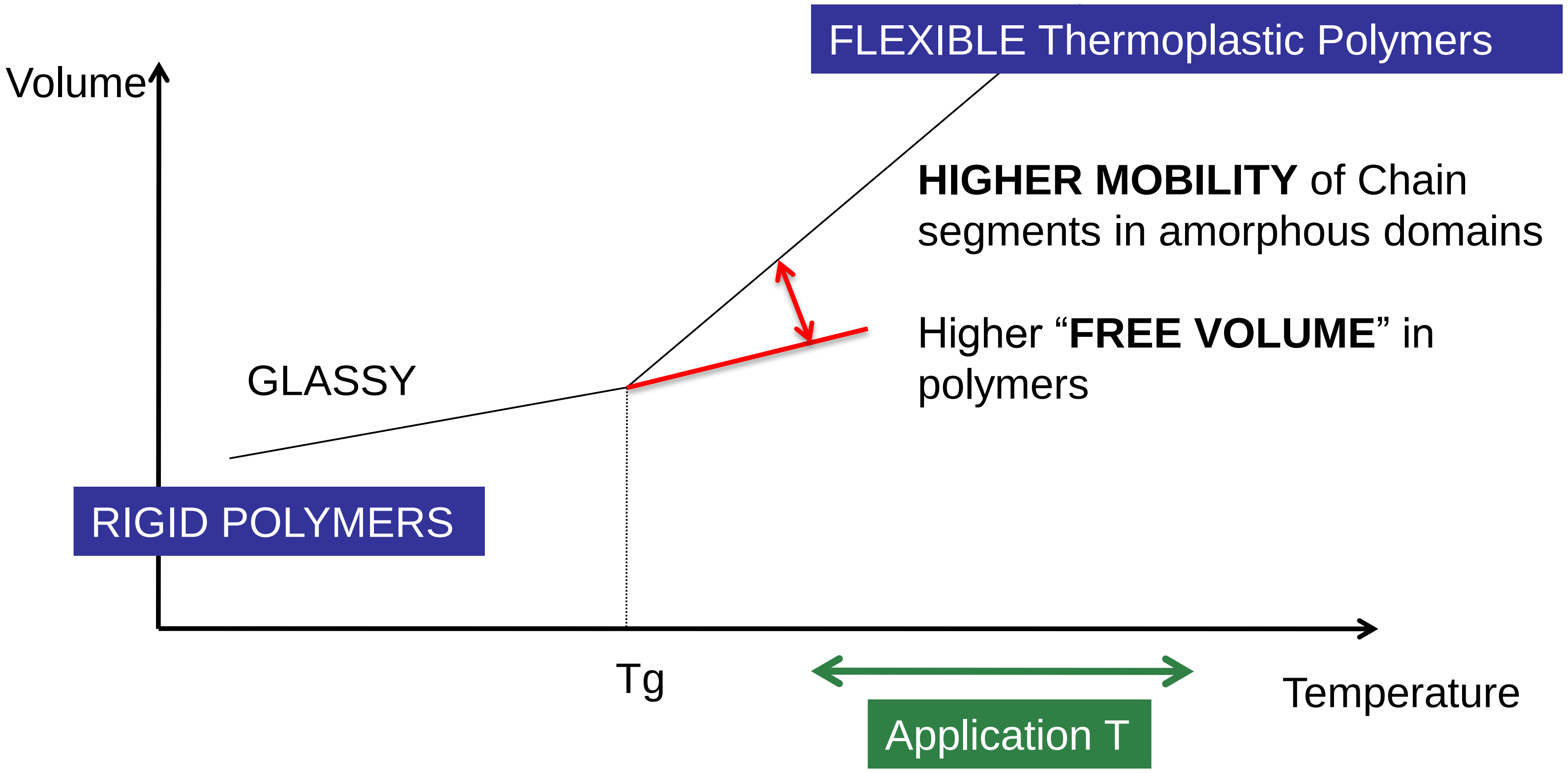
GLASS TRANSITION TEMPERATURE (T_g):

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

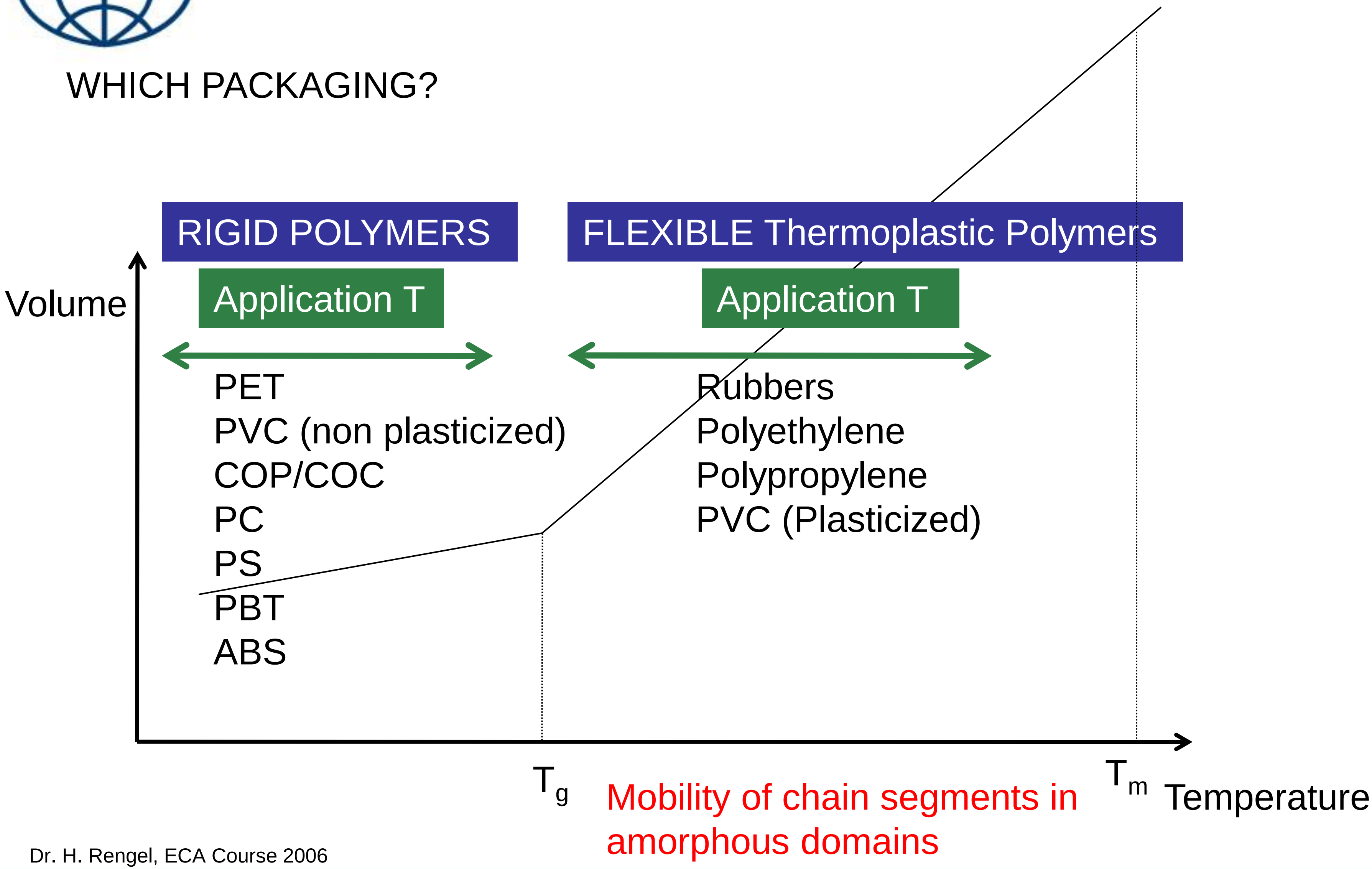
WHAT IS **RIGID** PACKAGING?



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

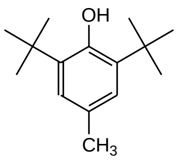
(Red: coming with some examples)

Anti-Oxidants

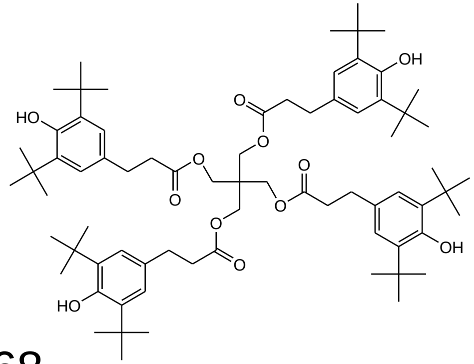
Function: assuring protection against thermal and oxidative degradation during processing and during shelf life of polymer
(*Sterically Hindered Phenols & Organic Phosphites/Phosphonates are mostly used*)

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

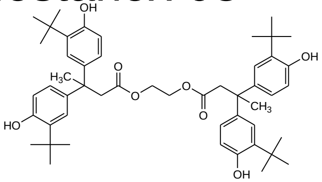
BHT



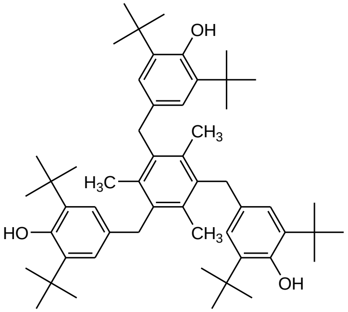
Irganox 1010



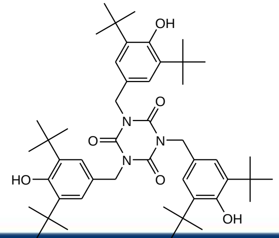
Hostanox 03



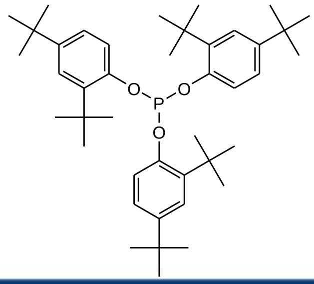
Irganox 1330



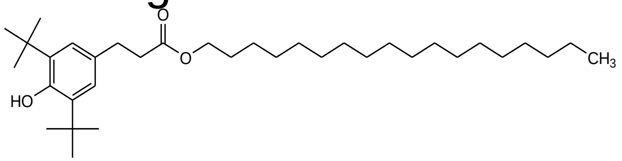
Irganox 3114



Irgafos 168



Irganox 1076



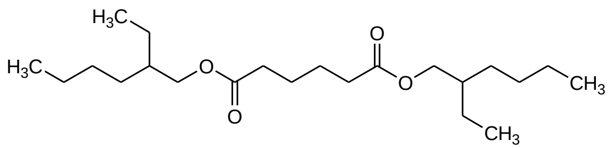
Plasticizers

Function: Gives the plastic flexibility and durability

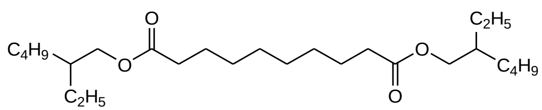
Plasticizer requirements:

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

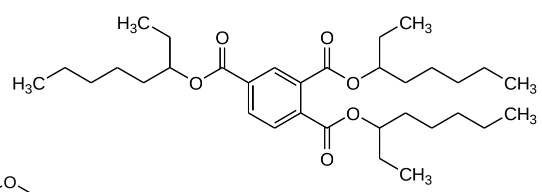
Diethylhexyladipate



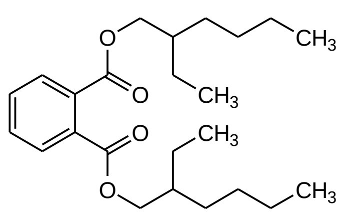
Diethylhexylsebacate



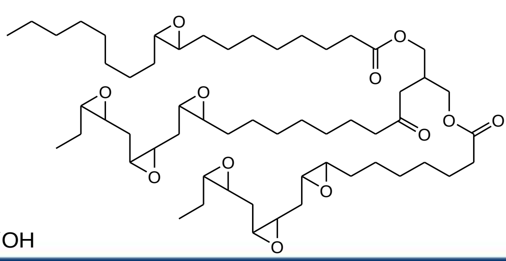
TOTM



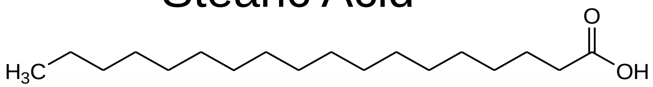
Diethylhexylphthalate (DEHP)



ESBO



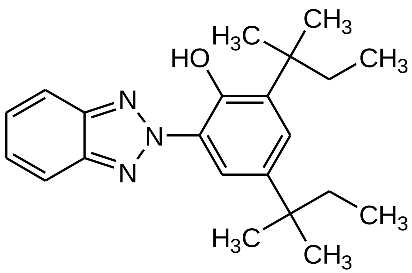
Stearic Acid



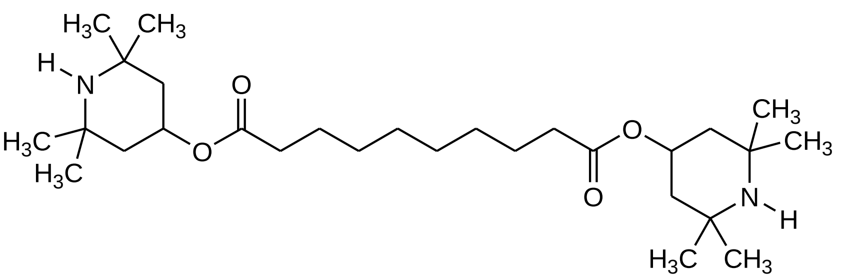
Photostabilizers

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

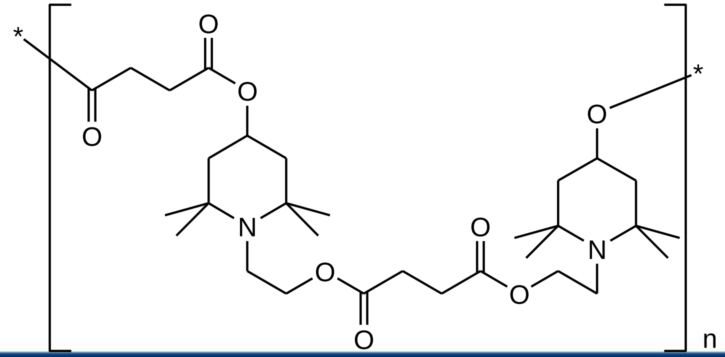
Tinuvin 328



Tinuvin 770



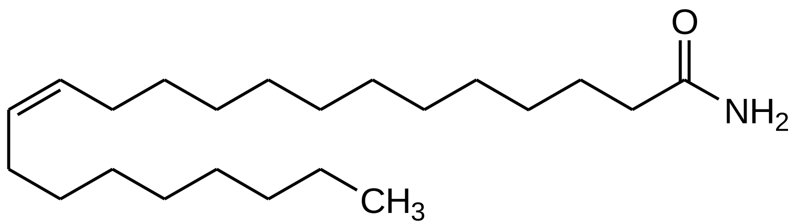
Tinuvin 622



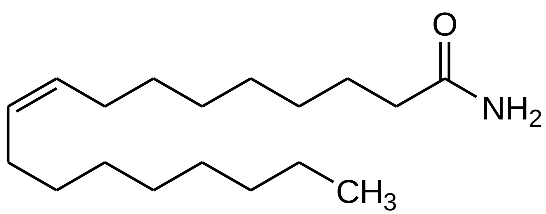
Slip Agents

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

Erucamide



Oleamide



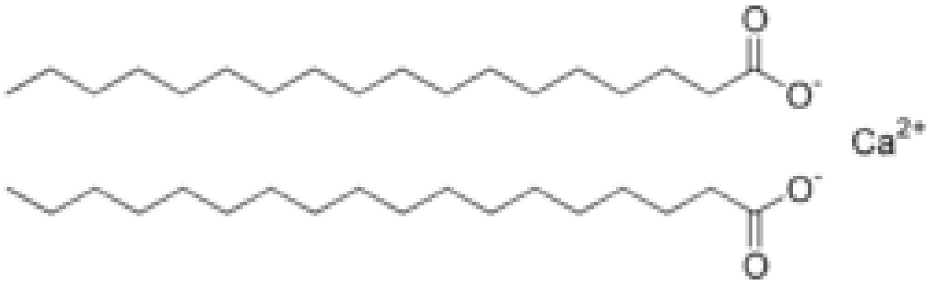
Remark:
because of their specific properties, Slip agents will be widely detected as Leachables!

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*

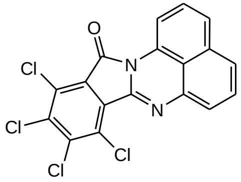


Pigments / Colorants

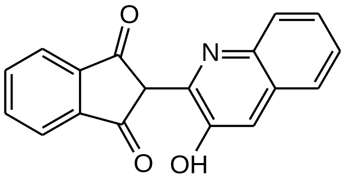
Function: Gives the polymer/rubber the desired color (cosmetic)

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

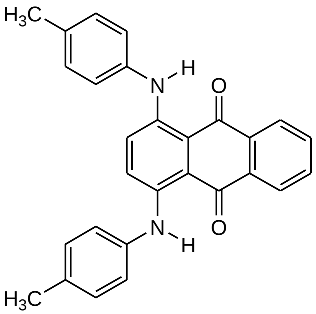
Solvent Red



Solvent yellow 114



Solvent Green 03

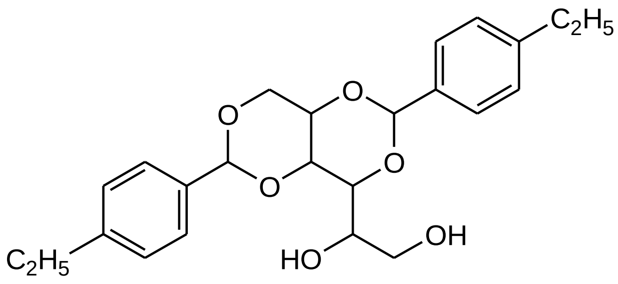


Remarks: beware of the composition of the Masterbatch!

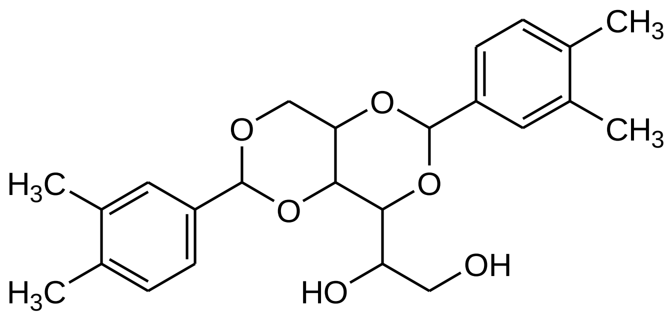
Clarifying Agents (Nucleating Agents)

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

NC-4



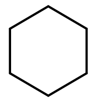
Millad 3988



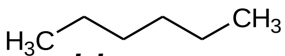
2. RESIDUES

Residues from the production process (non-limitative)

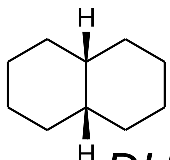
Solvents



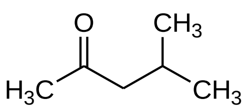
Cyclohexane



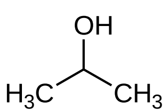
Hexane



DHN

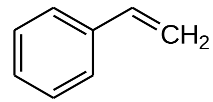


MIBK

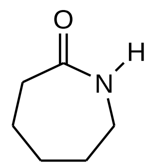


IPA

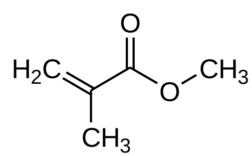
Monomers



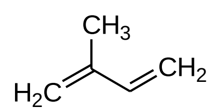
Styrene



Caprolactam



Methyl methacrylate

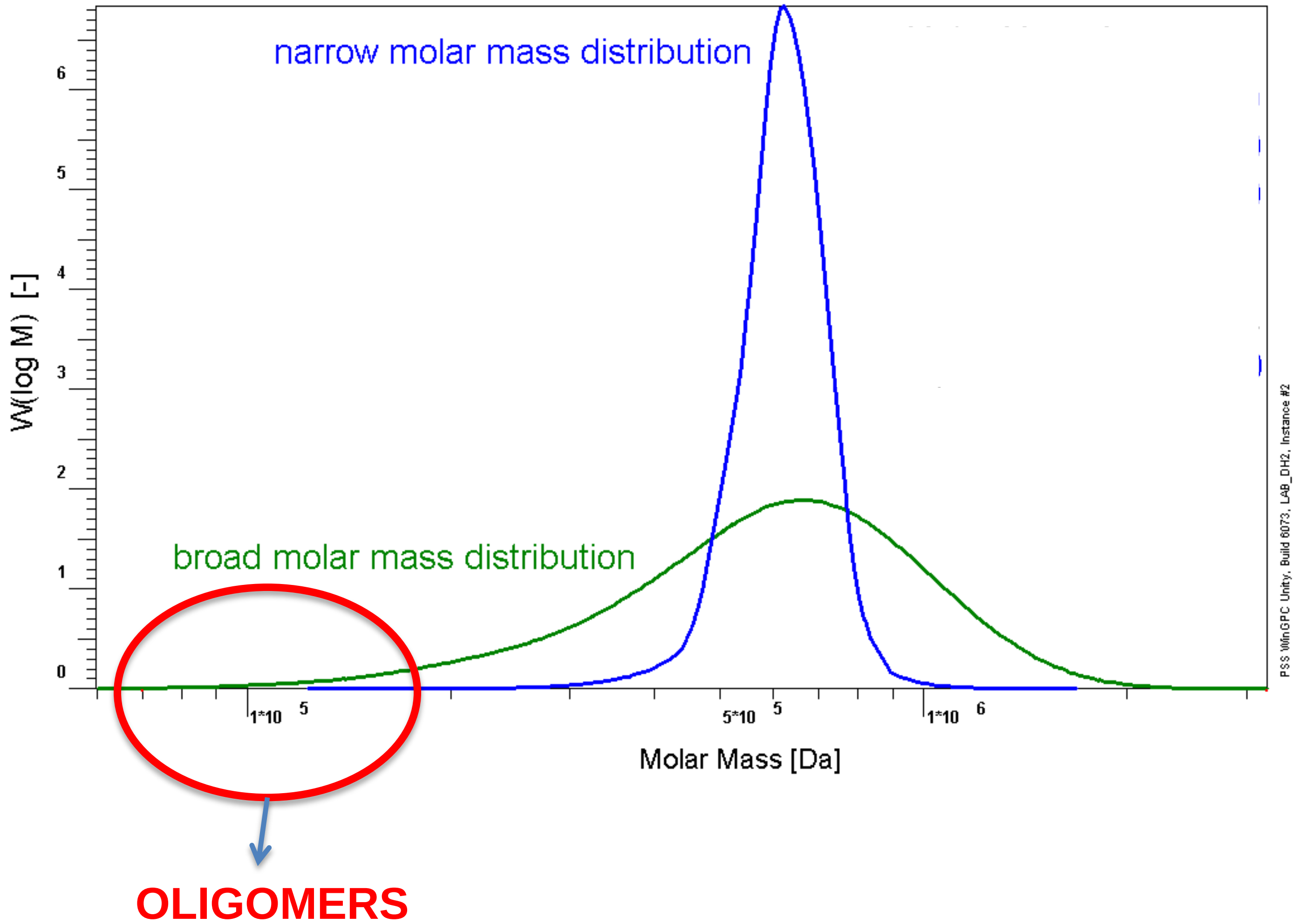


Isoprene

Catalysts

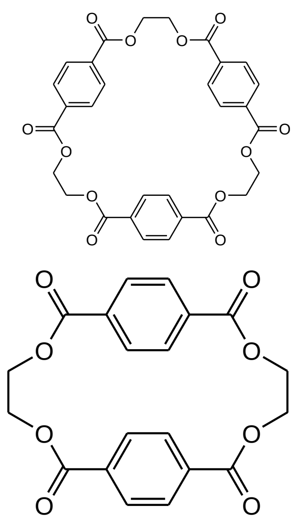
Titanium
Zirkonium
Cobalt
Aluminum
Iron
Hafnium
...

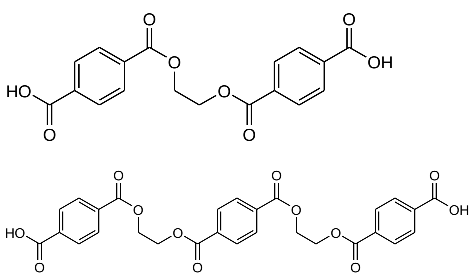
3. OLIGOMERS


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

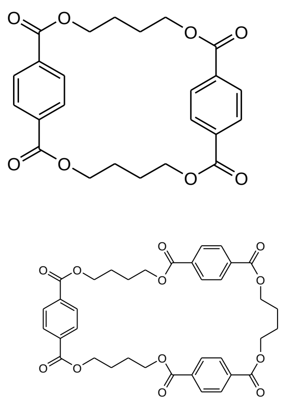
OLIGOMERS: Examples

PET

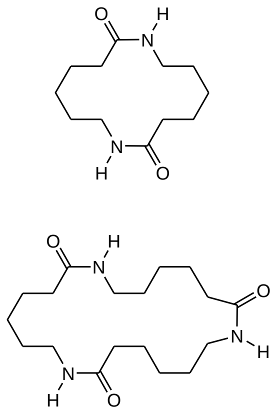




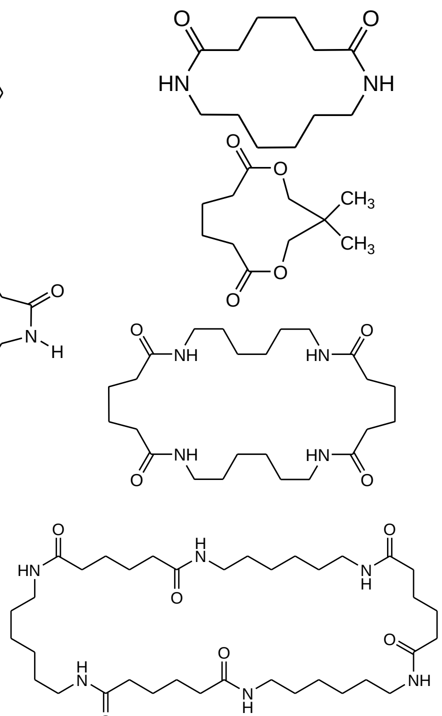
PBT



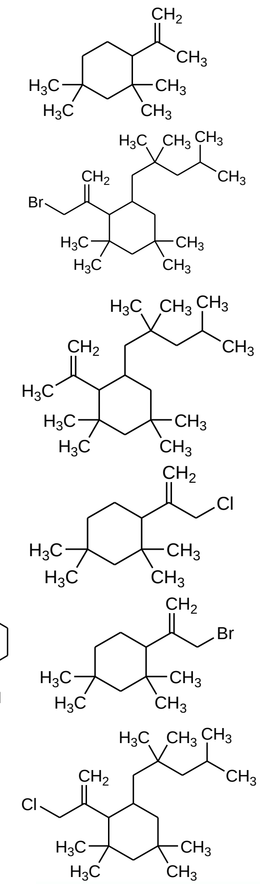
Nylon 6



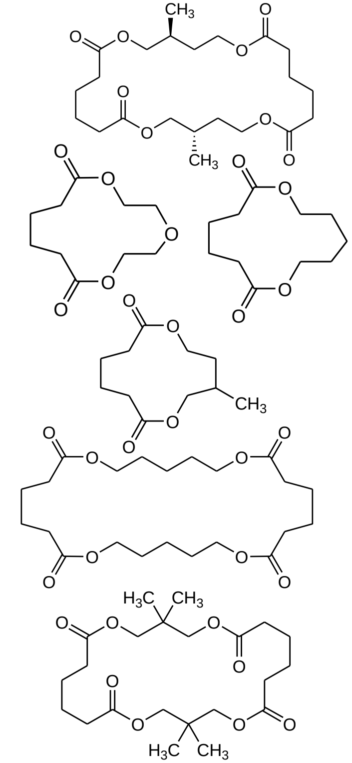
Nylon 6.6



Butyl Rubber



Polyester adhesive



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

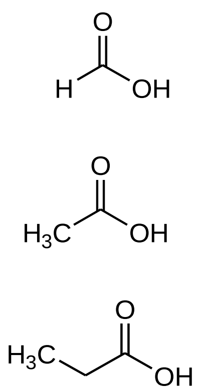
4. POLYMER DEGRADATION COMPOUNDS

Polymer degradation Compounds

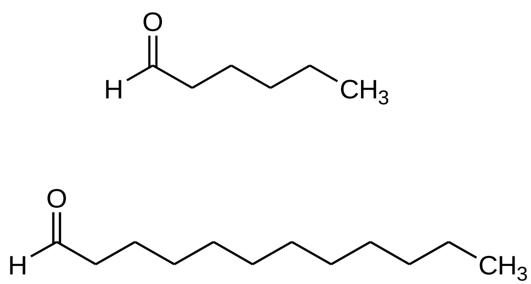
Origin: Oxidative degradation of the polymers

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

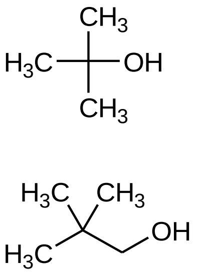
Example of Polymer Degradation Compounds from **Polypropylene**



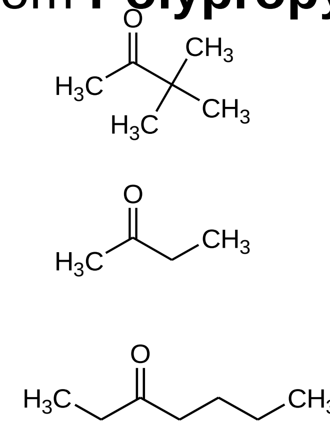
Acids



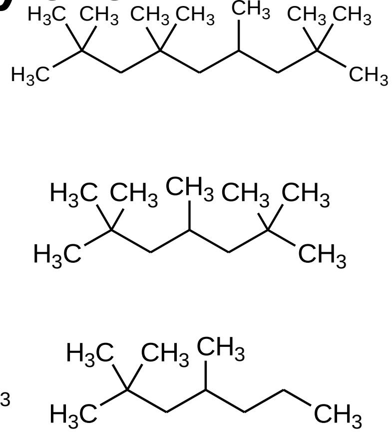
Aldehydes



Alcohols



Ketones

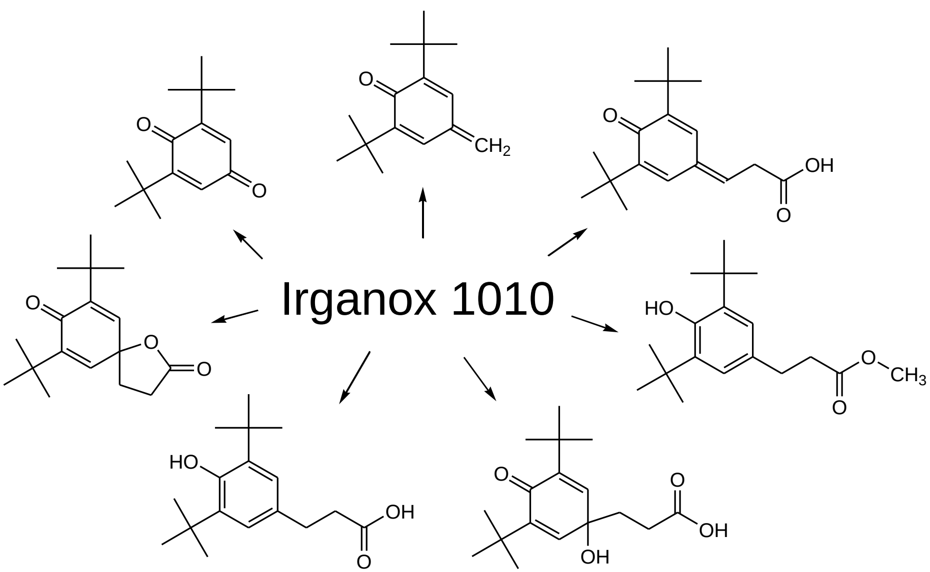


Polymer Fragments

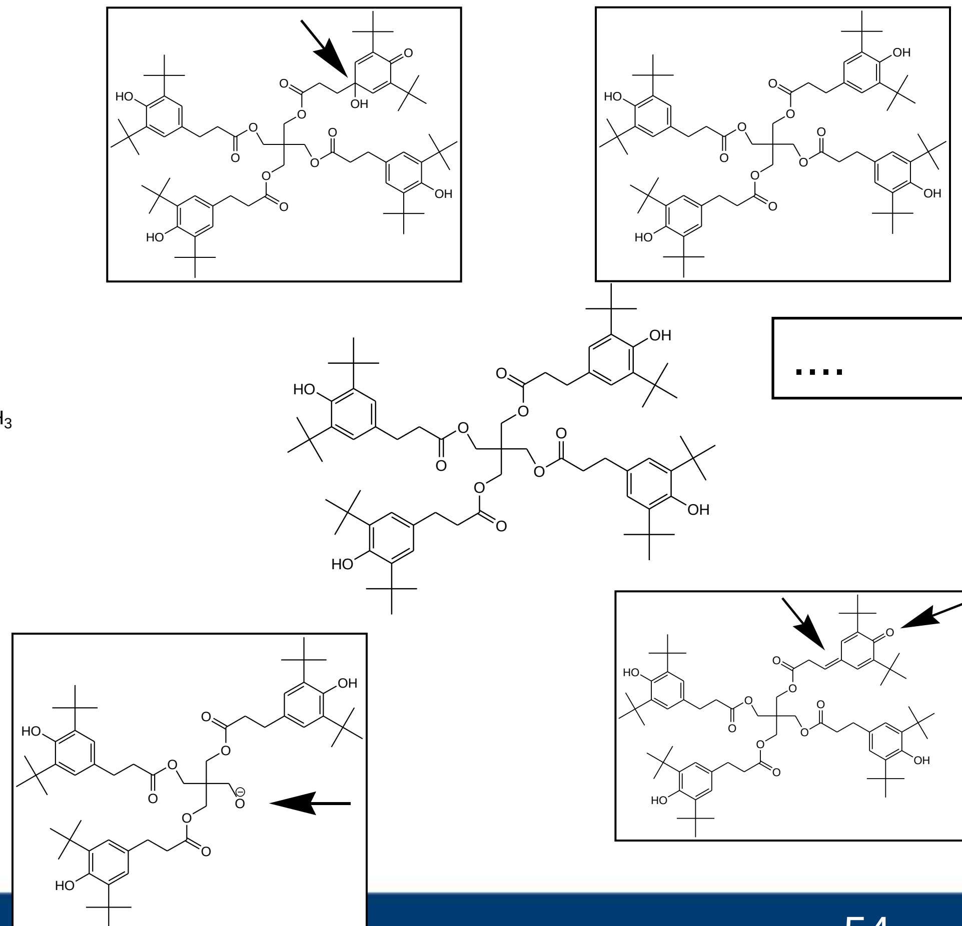
5. POLYMER ADDITIVE DEGRADATION COMPOUNDS

Example Degradation of **Irganox 1010**

SMALL degradation Compounds



LARGE degradation Compounds



GLASS 101

WORKSHOP
EXTRACTABLES - LEACHABLES

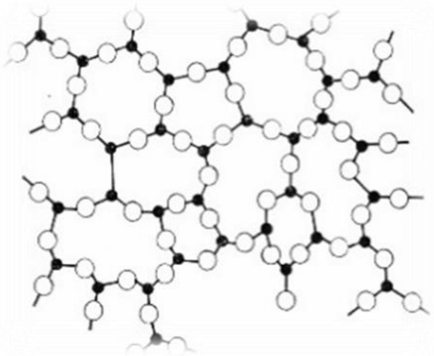
Dr. Piet Christiaens

GLASS 101

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.

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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

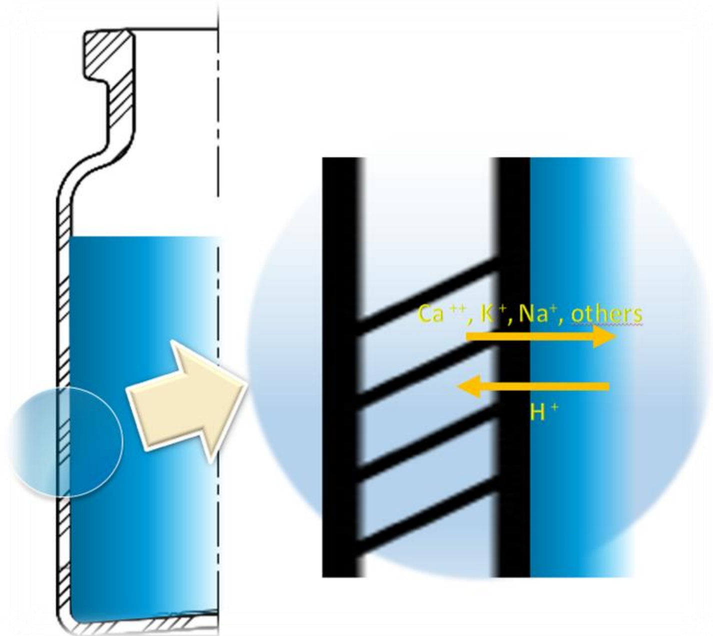
How to (try to) prevent Glass Leaching

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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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?