Introduction to Plastics and their Additives

Extractables and Leachables
November 2010, IPS – SGS Seminar
SGS Life Science Services

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- Customer Service Project Manager -

Extractables und Leachables

- **Agenda**
  - **Introduction** to Polymers
    - Classification
    - Properties
    - Typical uses of Plastics
  - **Additives**
    - Relevant Additives / Chemical classes
    - Compendium Additives
  - **Examples / Applications**
    - LDPE / HDPE
    - Sterilization / Reaction Products
    - PVC

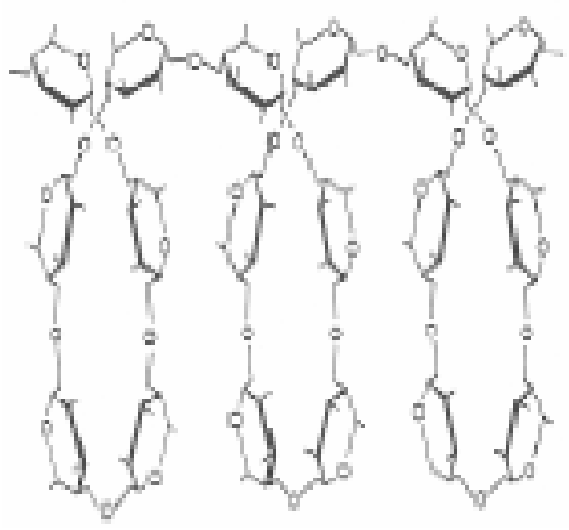
1. Introduction: -Polymers are typically classified by different Criteria

Polymers are classified by

- **Origin:** Natural Polymers, Synthetic Polymers
- **Chemical composition:** Organic Polymers, Inorganic Polymers
- **Thermoelastic properties:** Elastomers, Thermoplastics, Thermosets
- **Route of synthesis:** Chain-growth and step-growth polymers
- **Number of monomers:** Homo-Polymer, Co-Polymer.

2. Overview: -Classification of Polymers by its Origin and Chemical Composition

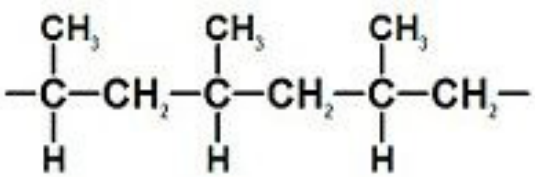
Natural Polymers



Amylose (Starch)

Synthetic polymers

Organic



Polypropylene

Inorganic

-[O-Si(CH_3)$_2$]n-

Silicone

2. Overview: -Thermoplastic Properties

- **The difference between thermoplastics and thermosettings plastics are, when heat is added:**
  - **thermoplastics become soft, remoldable and weldable**

Associated by dipole-dipole (nylon) or Van der Waals forces (polyethylen)

2. Overview: -Thermoset

- **Thermosetting plastics however can not be welded or remolded when heated, simply burning instead.**
  - **once a thermosetting is cured it tends to be stronger than a thermoplastic**

Curing may be done by heat, irradiation or by electron beam

2. Overview: -Plastic materials, classification

List of Thermoplastiks

Acrylonitrile butadiene styrene (ABS)	Ethylene-Vinyl Acetate (EVA)	Ethylene vinyl alcohol (EVAL)
Fluoroplastics (PTFE, along side with FEP, PFA, CTFE, ECTFE, ETFE)	Polyacetal (POM or Acetal)	Polyacrylates (Acrylic)
Polyacrylonitrile (PAN or Acrylonitrile)	Polyamide (PA or Nylon)	Polyamide-imide (PAI)
Polyaryletherketone (PAEK or Ketone)	Polybutadiene (PBD)	Polybutylene (PB)
Polybutylene terephthalate (PBT)	Polycaprolactone (PCL)	Polychlorotrifluoroethylene (PCTFE)
Polyethylene terephthalate (PET)	Polycyclohexylene dimethylene terephthalate (PCT)	Polycarbonate (PC)
Polyhydroxyalkanoates (PHAs)	Polyketone (PK)	Polyester
Polyethylene (PE)	Polyetheretherketone (PEEK)	Polyetherimide (PEI)
Polyethersulfone (PES)- see Polysulfone	Polyethylenechlorinates (PEC)	Polyimide (PI)
Polylactic acid (PLA)	Polymethylpentene (PMP)	Polyphenylene oxide (PPO)
Polyphenylene sulfide (PPS)	Polyphthalamide (PPA)	Polypropylene (PP)
Polystyrene (PS)	Polysulfone (PSU)	Polyurethane (PU)
Polyvinyl acetate (PVA)	Polyvinyl chloride (PVC)	Polyvinylidene chloride (PVDC)

2. Overview: -Plastic materials – Typical uses

Typical pharmaceutical uses of various plastics and associated materials

Material	Abbreviation	Typical Uses
Polyethylene	PE	Tubing, catheters, connectors, bottles, container/packaging systems
Poly (vinyl chloride)	PVC	Tubing, container/packaging systems
Polypropylene	PP	Disposable syringe, bottles, container/packaging systems, connectors, membranes
Polyethylene terephthalate	PET	Blow-molded components, bottles, containers
Polysulfone	---	Membrane for dialysis or ultrafiltration, oxygenator
Polyurethane	PU	Tubing, adhesives, pump, balloon and/or valve materials, prostheses
Polycarbonate	PC	Housings, connectors, packaging materials, bottles, syringe barrels
Poly(methyl methacrylate)	PMMA	Dental materials, bone replacement, lenses, membranes for dialysis or ultrafiltration, container material
Polyamide	PA	Container/packaging material, drug release systems
Polystyrene	PS	Container/packaging materials, tubing
Cellophane	---	Secondary packaging
Natural or synthetic rubber		Shunts, catheters, tubing, prostheses, closures, drug-release systems, container/packaging systems
Paper/cardboard	---	Secondary packaging, labels

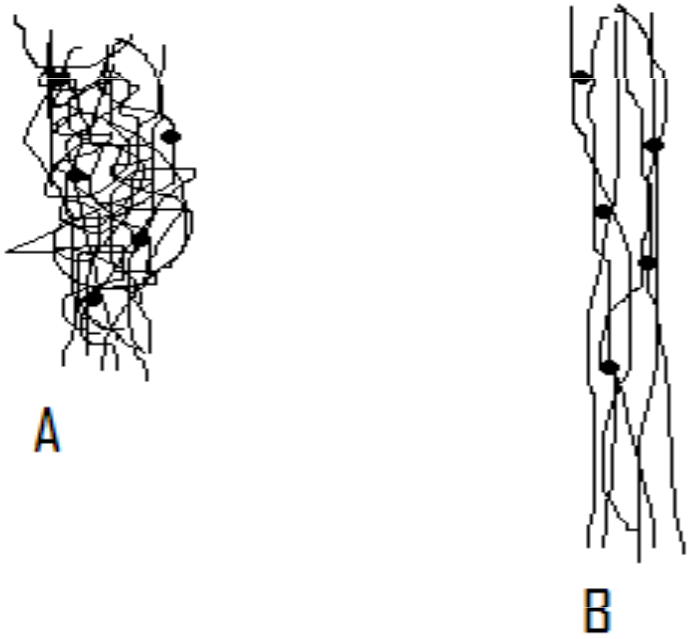
2. Overview: -Plastic materials, classification

Some examples of thermosets are:

- Vulcanized rubber
- Bakelite, a phenol-formaldehyde resin (used in electrical insulators and plasticware)
- Urea-formaldehyde foam (used in plywood, particleboard and medium-density fibreboard)
- Melamine resin (used on worktop surfaces)
- Epoxy resin (used as an adhesive and in fibre reinforced plastics such as glass reinforced plastic and graphite-reinforced plastic)
- Polyimides (used in printed circuit boards and medical tubing)

2. Overview: -Plastic materials, classification

- **The following properties properties define polymers as an Elastomer:**
  - **An elastomer is a polymer with the property of elasticity**
  - **Must be amorphous when unstretched**
  - **Must be above their glass transition temperature to be elastic**



A: is a schematic drawing of an unstressed polymer
B: is the same polymer under stress. When the stress is removed, it will return to the A configuration.

2. Overview: -Plastic materials, classification

- **Crosslinked elastomers constists of:**
  - **Base elastomeric polymer**
  - **Properity modyfing additives**
  - **A reactice cross linking agent**

- **Thermoplastic elastomer constists of:**
  - **Base elastomeric polymer in which the neat polymer has inherently elastomeric properties**
  - **It can be formed like thermoplastic but the final object has elastomeric behavior**

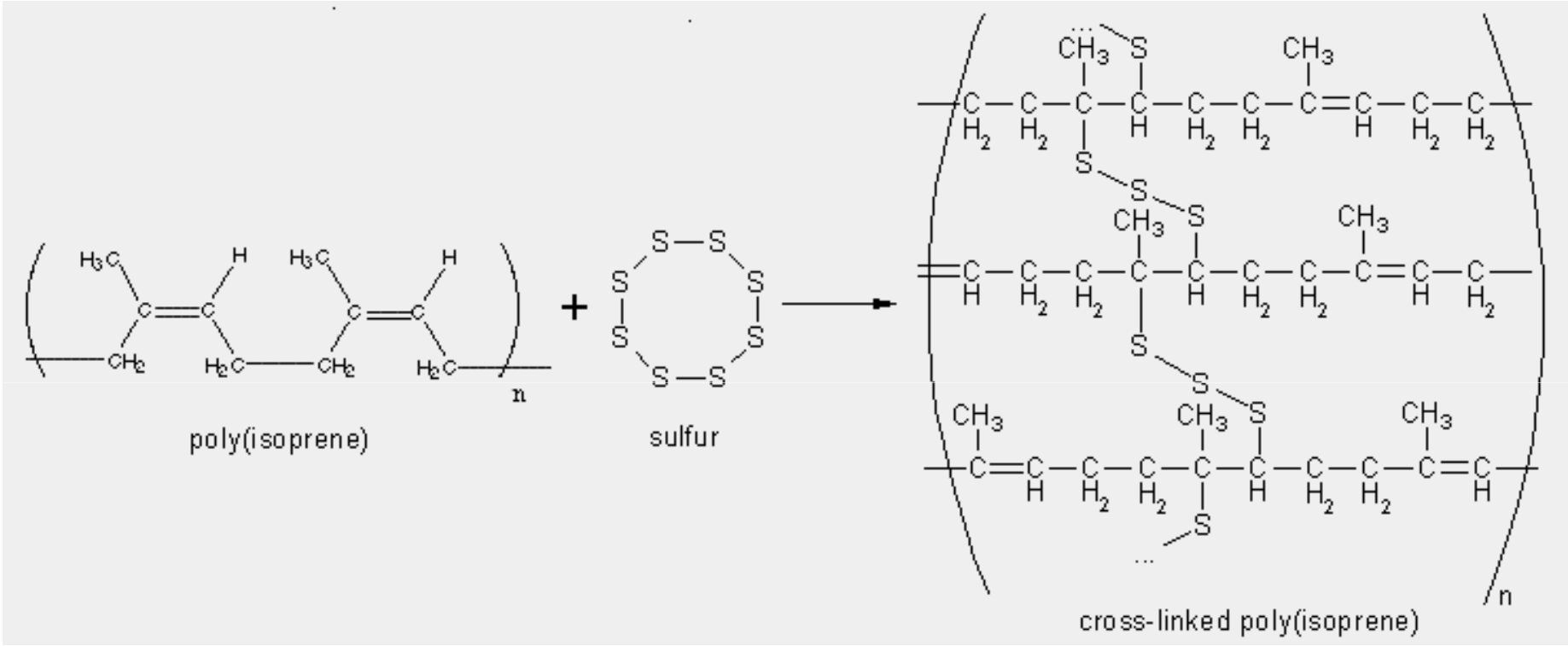
2. Overview: -Plastic materials, classification

- **The material properties of natural rubber make it an elastomer and a thermoplastic.**

- **Examples of saturated Rubbers that cannot be cured by sulfur vulcanization:**
  - **Silicone rubber (SI, Q, VMQ)**
  - **Fluorosilicone Rubber (FVMQ)**
  - **EPM (ethylene propylene rubber, a copolymer of ethylene and propylene) and EPDM rubber (ethylene propylene diene rubber, a terpolymer of ethylene, propylene and a diene-component)**

2. Overview: -Plastic materials, classification

- **However it should be noted that as the rubber is vulcanized it will turn into a thermoset.**



2. Overview: -Plastic materials, classification

- **Examples of unsaturated rubbers that can be cured by sulfur vulcanization:**
  - **Synthetic Polyisoprene (IR)**
  - **Butyl rubber (copolymer of isobutylene and isoprene, IIR)**
  - **Halogenated butyl rubbers (Chloro Butyl Rubber: ClIR; Bromo Butyl Rubber: BIIR)**

3. Additives –Advantages / Drawbacks of Plastic materials

- ☺ **Light materials**
- ☺ **Rigid or flexible**
- ☺ **Mouldable**
- ☺ **Reasonable inert**
- ☺ **Printable**
- ☺ **Transparent or colored**
- ☺ **Combinable with other materials**

- ☹ **Ageing by UV or Oxygen impact**
- ☹ **Tread grove cracking**
- ☹ **Damage to the environment**
- ☹ **Migration of plastic components**

3. Additives: -Improvement of selected Properities

Typical classes of additives

I. Antioxidants
II. Plasticizers
III. Antidegradants
    a. Photostabilizer
    b. Antiozonants
IV. Coupling agents
V. Flame retardants
VI. Lubricants
VII. Acid scavengers
VIII. Peroxides / Crosslinking agents
IX. Blowing agents
X. Pigments / colorants
XI. Antistatic agents
XII. Barrier forming additives
XIII. Metall chelators
XIV. Adhesives
XV. Bacterizides
XVI. Clarifying agents
XVII. Antifogging agents

3. Additives: -I. Antioxidants (antidegradant)

- **Assure protection against thermal and oxidative degradation during processing and during environmental exposure.**

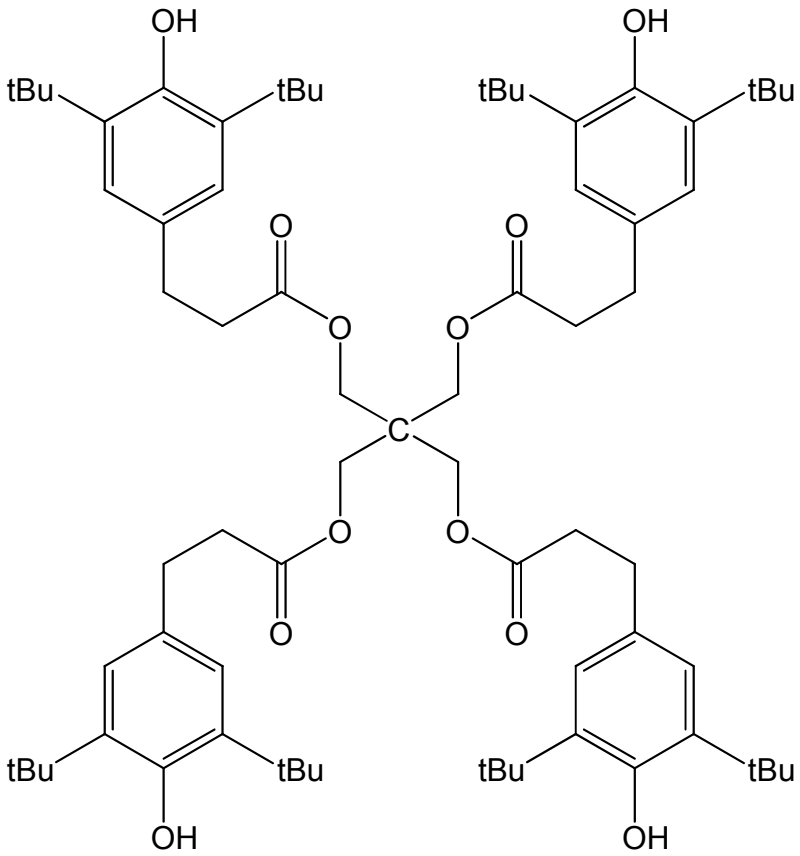
Chemical classes are:

- **Sterical Hindered phenols BHT (radical scavengers)**
- **Organic phosphites / phosphonates (peroxides decomposers)**
- **Thioethers**
- **Thiocarbamates**
- **Mercaptobenzimidazoles**
- **Thiobisphenols …..and others**

More than 380 patents dealing with new compounds acting as antioxidants are recorded each year!!!

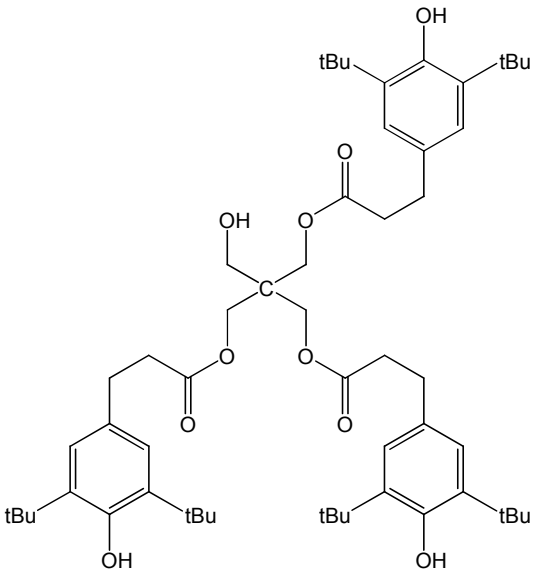
3. Additives: -I. Antioxidants (Phenolic)

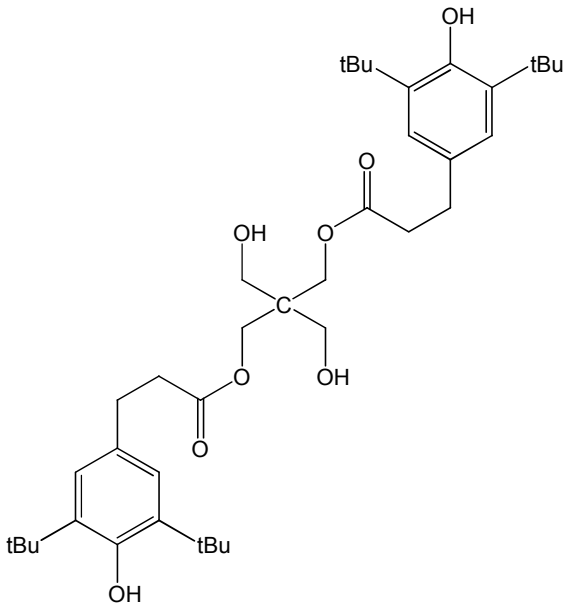
- **Irganox 1010 (secondary antioxidant)**

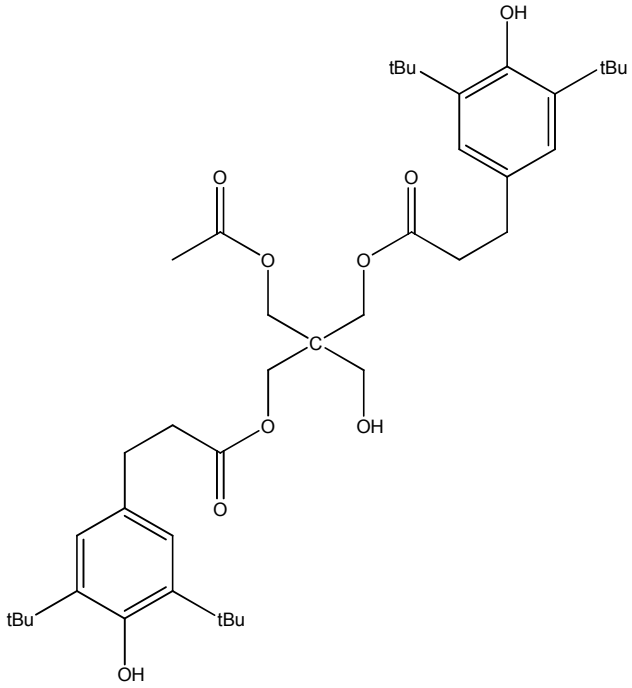


3. Additives: -I. Antioxidants (Phenolic)

- **Irganox 1010 break down products I**

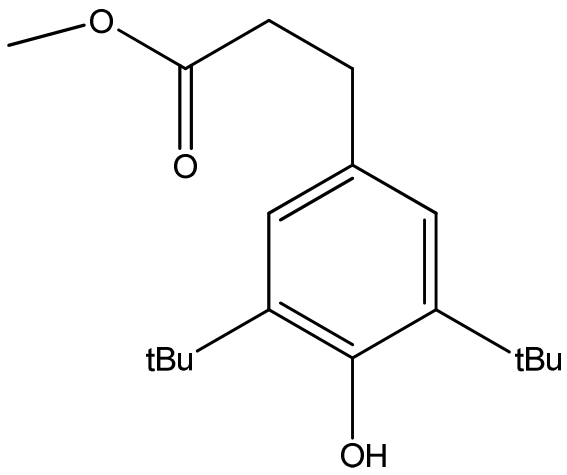


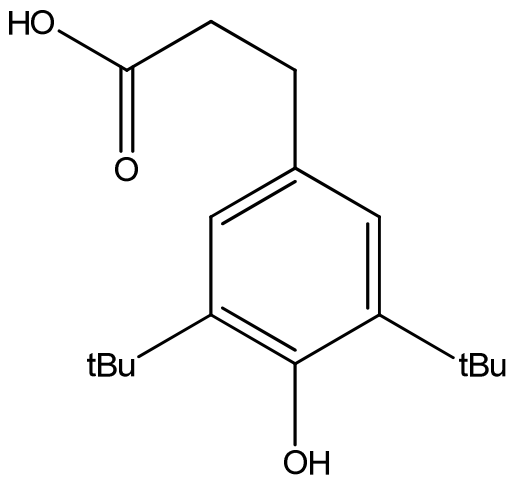


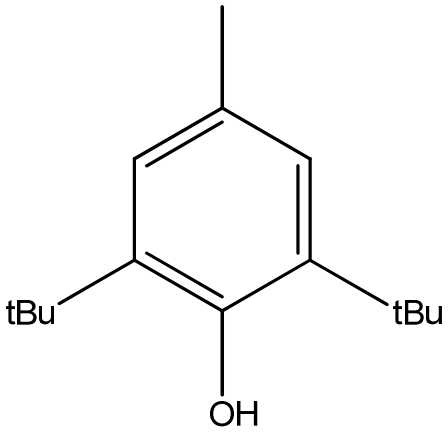


3. Additives: -I. Antioxidants (Phenolic)

- **Irganox 1010 break down products II**

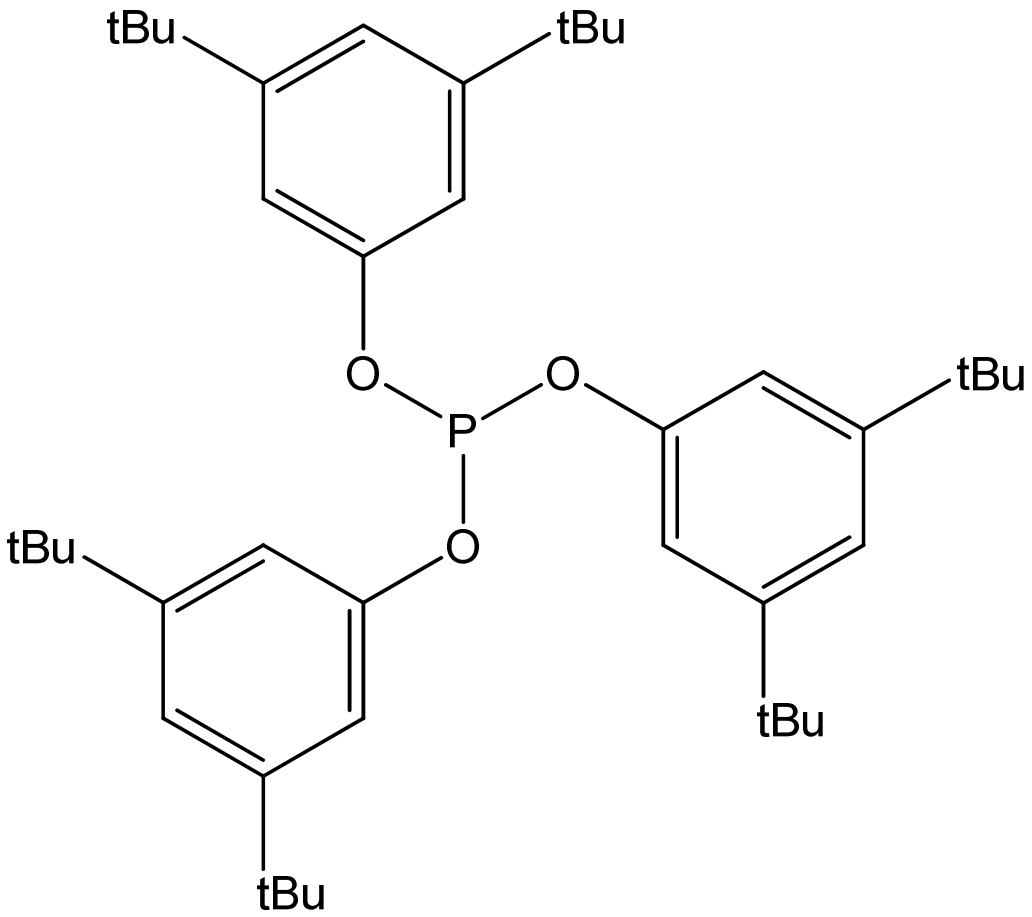






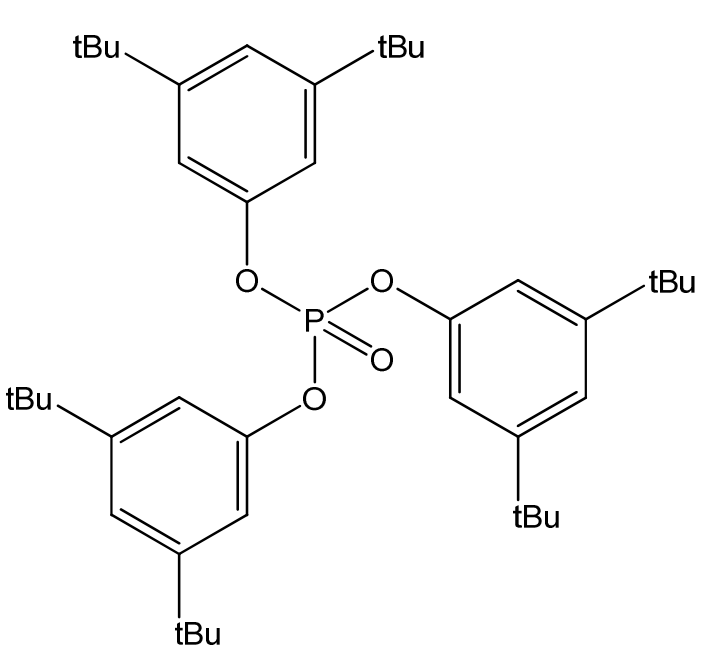
3. Additives: -I. Antioxidants (Phosphites)

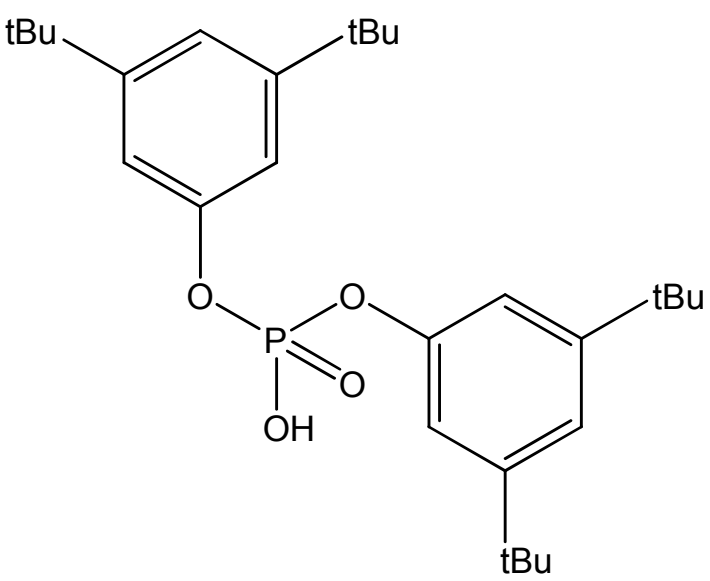
- **Irgafos 168 (primary antioxidant)**

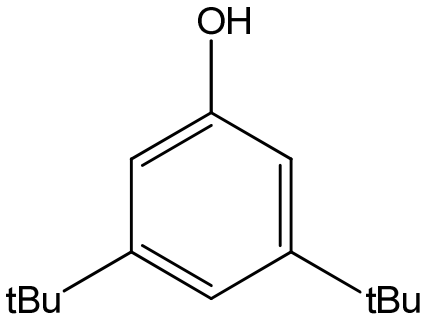


3. Additives: -I. Antioxidants (Phosphites)

- **Irgafos 168 break down products II**







3. Additives: -II. Plasticizer

- **gives the plastics flexibility and durability.**
- **Some requirements for plasticizer should be:**
  - **Low extractability by water and solvent**
  - **Stability to heat and light**
  - **Low odor, taste and toxicity**

Chemical classes are:

- **Phthalates (esters)**
- **Fatty acids (Stearic acid, Palmitinixc acid)**
- **Oils such as epoxidized linseed oil, tall-oil**
- **Adipates, azelates, sebacates**
- **Derivates of glycols and aliphatic dicarboxylic acids**

3. Additives: -III. Antidegradants

- **Stops the degradation of the finished plastic product.**

- **Antiozonants (ozone protection, barrier):**
  - **Alkylphenylamines**

- **UV-Stabilizers (UV protection against discoration):**
  - **Benzophenones**
  - **Benzotriazoles**
  - **Salicylate eters**
  - **Cyanoacrylates**
  - **Malonates**
  - **Benzilidenes**
  - **Polimeric sterically hindered phenols**

3. Additives: -IV. Coupling agents

- **Are substances that are capable of bonding organic polymer systems to inorganic substrates such as glass, mineral fillers and metals**

Chemical classes are:

- **Silanes**
  - **Aminoalkyl silanes**
  - **Alkyl-alkoxy silyl-sufides**
  - **Epoxy-alkyl-silanes**
  - **Vinyl-alkoxy-silanes**

3. Additives: -V. Flame Retardants

- **Added to inhibit ignition or flammability of the end-use product and used in thermoplastics:**
  - **Polystyrene, polyesters, polyolefins…**

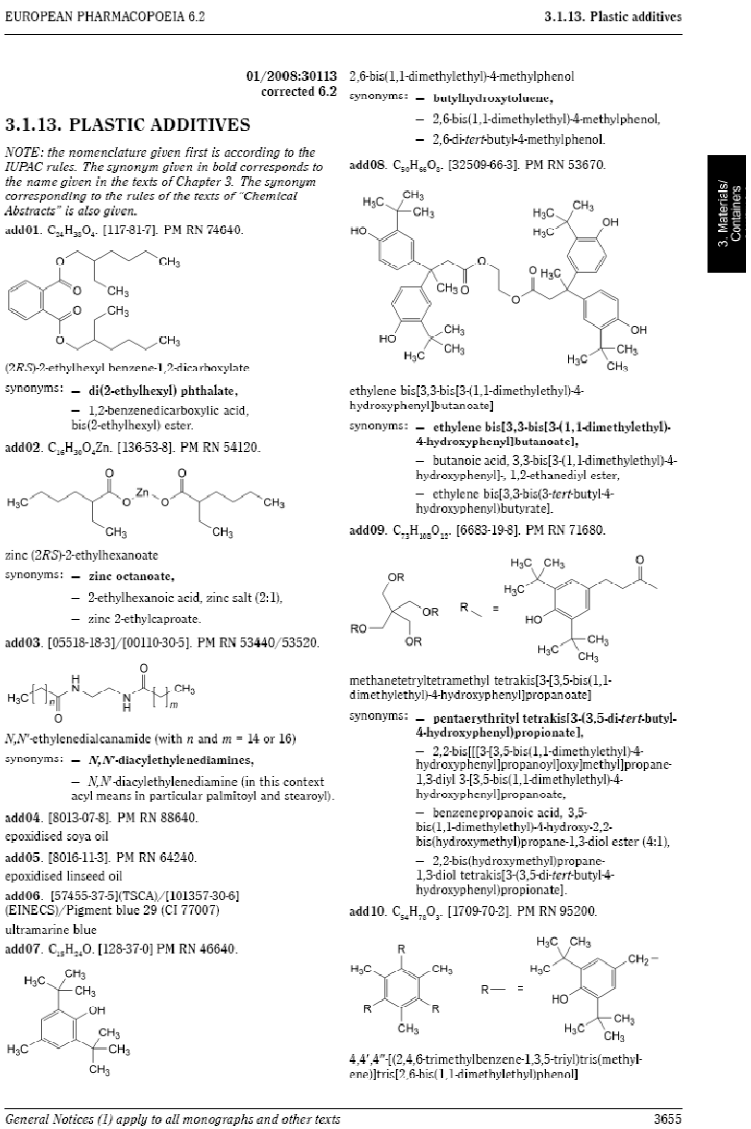
Chemical classes are:

- **Inorganic**
  - **Aluminium trihydrate**
  - **Antimony oxide**
  - **Boron compounds**
- **Organic**
  - **Brominated and chlorinated compounds**
  - **Brominated diphenyl ethers (PBDE)**

3. Additives: -XX. Other Components of Interest

- **Cross linking agents are used to form links between molecular chains**
  - **Sulfur**
  - **Thiazoles**
- **Processing aids lower the viscosity, provide additional stability, prevent attack bacteria, etc.**
  - **Amides (Erucamide)**
- **Retarders slow down the reaction process**
  - **Phatalic anhydride**

4. Additives: -Compendium Additives – Ph. Eur. 3.1.13



EUROPEAN PHARMACOPOEIA 6.2 — 3.1.13. Plastic additives

01/2008:30113
corrected 6.2

3.1.13. PLASTIC ADDITIVES

NOTE: the nomenclature given first is according to the IUPAC rules. The synonym given in bold corresponds to the name given in the texts of Chapter 3. The synonym corresponding to the rules of the texts of "Chemical Abstracts" is also given.

add01. $C_{24}H_{38}O_4$. [117-81-7]. PM RN 74640.

(2*RS*)-2-ethylhexyl benzene-1,2-dicarboxylate

synonyms: – **di(2-ethylhexyl) phthalate**,
– 1,2-benzenedicarboxylic acid, bis(2-ethylhexyl) ester.

add02. $C_{16}H_{30}O_4Zn$. [136-53-8]. PM RN 54120.

zinc (2*RS*)-2-ethylhexanoate

synonyms: – **zinc octanoate**,
– 2-ethylhexanoic acid, zinc salt (2:1),
– zinc 2-ethylcaproate.

add03. [05518-18-3]/[00110-30-5]. PM RN 53440/53520.

N,*N*′-ethylenedialcanamide (with *n* and *m* = 14 or 16)

synonyms: – ***N*,*N*′-diacylethylenediamines**,
– *N*,*N*′-diacylethylenediamine (in this context acyl means in particular palmitoyl and stearoyl).

add04. [8013-07-8]. PM RN 88640.

epoxidised soya oil

add05. [8016-11-3]. PM RN 64240.

epoxidised linseed oil

add06. [57455-37-5](TSCA)/[101357-30-6](EINECS)/Pigment blue 29 (CI 77007)

ultramarine blue

add07. $C_{15}H_{24}O$. [128-37-0] PM RN 46640.

2,6-bis(1,1-dimethylethyl)-4-methylphenol

synonyms: – **butylhydroxytoluene**,
– 2,6-bis(1,1-dimethylethyl)-4-methylphenol,
– 2,6-di-*tert*-butyl-4-methylphenol.

add08. $C_{59}H_{86}O_5$. [32509-66-3]. PM RN 53670.

ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate]

synonyms: – **ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]butanoate]**,
– butanoic acid, 3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl]-, 1,2-ethanediyl ester,
– ethylene bis[3,3-bis(3-*tert*-butyl-4-hydroxyphenyl)butyrate].

add09. $C_{73}H_{108}O_{12}$. [6683-19-8]. PM RN 71680.

methanetetryltetramethyl tetrakis[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]propanoate]

synonyms: – **pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate]**,
– 2,2-bis[[[3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]propanoyl]oxy]methyl]propane-1,3-diyl 3-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]propanoate,
– benzenepropanoic acid, 3,5-bis(1,1-dimethylethyl)-4-hydroxy-2,2-bis(hydroxymethyl)propane-1,3-diol ester (4:1),
– 2,2-bis(hydroxymethyl)propane-1,3-diol tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate].

add10. $C_{54}H_{78}O_3$. [1709-70-2]. PM RN 95200.

4,4′,4″-[(2,4,6-trimethylbenzene-1,3,5-triyl)tris(methylene)]tris[2,6-bis(1,1-dimethylethyl)phenol]

3. Materials/ Containers

General Notices (1) apply to all monographs and other texts — 3655

- **Additiv 07** ≤ 0,125%
  2,6-di-tert-butyl-4-methylphenol (BHT)
- ***Additiv 08*** ≤ 0,3%
  ethylen bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxy-phenyl]butanoate] (Hostanox 19)
- ***Additiv 09*** ≤ 0,3%
  pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxy-phenyl)propionate] (Irganox 1010, Ethanox 310)
- *[….]*

4. Examples -Polyolefines – Ph. Eur. 3.1.3

Typical Compendium „bushwa“:

- … ***polyolefin's may contain a certain number of additives … to adapt them for their intent of use. All additives are chosen from an appended list which specifies for each product a maximum allowable content.***

- ***Polyolefin's may contain a most three antioxidants, one of several lubricants or antiblocking agents ….***

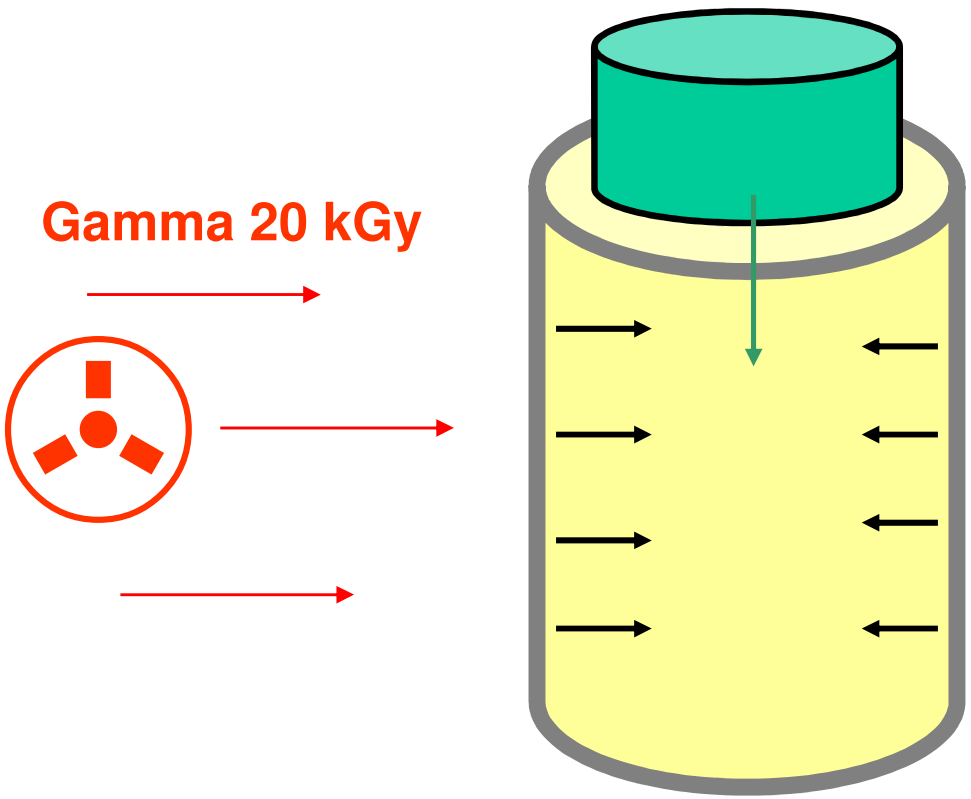
☹ **Pharmaceutical products could be contaminated by additives and particularly by their reaction products!**

4. Examples: Polyolefines I – Extractables from LDPE and HDPE

Component	Source
Aliphatic hydrocarbons	Not polymerized monomers
Branched aliphatic hydrocarbons	Mould release agents
Irganox 1010, 1076, Irgafos 168	Antioxidants
Tetra-methyl succinonitrile	Catalyst
Fatty acids	----
Alcohols	Hydrolyze product of DEHP

DEHP: Di-(2-ethylhexyl) phtalate

4.Examples: Polyolefines– Extractables / Extractables from LDPE / HDPE



- Carbonic acids: C_1, C_2, C_3 etc.
- C_2 – C_5 -Aldehydes
- Ketones
- BHT derived from Irganox 1010, 1076
- 2,5-di-tert-butyl benzene and 2,5-di-tert- butyl phenol from Irgafos 168

BHT: 3,5-di-tert-butyl-4-hydroxytoluol

4. Examples: Polymers and Additives can degrade during Processing and upon Sterilization

Radiation Resistance of Polymers			
Polymer	**Classification**	**Polymer**	**Classification**
ABS	1	Polyimide	1
Acetyl	4	Polymethylmethacrylate	2
Aliphatic polyamide	2-3	Polymethylpentene	4
Aromatic polyamide/polyimide	1	Polypropylene	3
Butyl rubber	4	Polytetrafluoroethylene	4
Cellulosic	2	Polystyrene	1
EPDM rubber	1-2	Polysulfone	1
Epoxy	1	Polyurethane	1
Flexible PVC	2	Radiation resistant rigid polyvinyl chloride	2
Fluorinated ethylene propylene	4	Radiation stable polypropylene	2
Phenolic	1	Rigid polyvinyl chloride	3
Polycarbonate	2	Silicone	1
Polyester	1	Styrene-butadiene rubber	3-4
Polyethylene	1	Nitrile rubber	2
Classification: 1 = Excellent 2 = Good 3 = Problematic 4 = Not Advisable			

Acrylonitrile butadiene styrene (ABS)

4.Examples: Extractables from PVC I

Component	Origin
Ethylenoxide	Sterilization residue
Di-(2-Ethylhexyl)phtalat (DEHP)	Plasticizer
Phthalic acid	Hydrolysis of DEHP
Mono-(ethylhexyl)phtalat (MEHP)	Hydrolysis of DEHP
Dibutyl phtalate	Impurity of DEHP
2-Ethyl-1-hexanol	Hydrolysis of DEHP
Vinyl chloride monomer	PVC
Acetic acid	Oxidation of PVC
Formic acid	Oxidation of PVC
Cyclo hexanone	Residue solvent
9,10-Epoxy stearic ester	Impurity

Dennis Jenke, PDA J. Parm. Sci. and Tech. 56 (6) 2002 332-371.

4.Examples: Extractables from PVC II

Component	Orign
Ethanol	Residue solvent
Toluene	Residue solvent
1,1 –Dimethylethyl-4-methoxyphenol (BHA)	Antioxidant
Bisphenol A	Antioxidant
3,5-di-tert-butyl-4-hydroxytoluene (BHT)	Antioxidant
t-Butyl cyclohexanol	Inks

Dennis Jenke, PDA J. Parm. Sci. and Tech. 56 (6) 2002 332-371.

4. Examples: Different Plastics – Metals / Minerals

Material	Analytics /Extract	Component / Level [ppm]
PE	ICPMS, ICP-OES microwave digestion	Mg / 0,5 Si / 16,0 Ca / 32 Zn / 1,8
LDPE	ICPMS microwave digestion	Mg / 2,3 Al / 8,9 Mn / 0,01
PVC	ICP-OES /Extraction with 5% acetic acid 2h 122°C	Al / 0,2 Ca / 0,4 Si / 0,9 Zn / 0,4
Perfluoro elastomer	ICP-MS, IC /water 4 weeks 80°C	F / 1,1 Metals < 0,1 TOC 1,54

5. Discussion

Questions?

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