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Influence of γ-irradiated biopharmaceutical films

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Influence of γ-irradiation on biopharmaceutical films

Sartorius : Dr S. Dorey, Dr F.Gaston | ECI - May 2017

Aix-Marseille University : Prof. N.Dupuy, Prof. S.Marque

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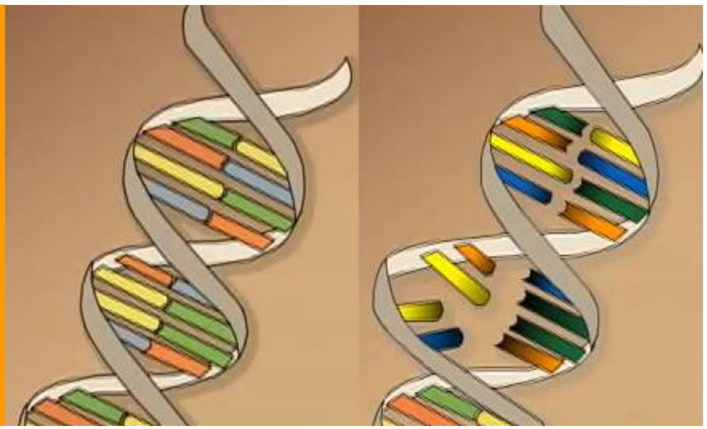
Purpose and scope



- Sterilization of Single use plastic bags made of multilayer films with PE, EVA, EVOH, etc. is achieved by γ irradiation
- Sterilization purpose : to kill micro-organisms
- 25-40|45 kGy : common dose range
- γ rays generated with a ^{60}Co source
- Norms (ISO 11137, ISO 11737) only deal with microbiological aspect

Purpose and scope

Unexpected phenomena could be observed even with in-purpose selected "γ-irradiatable" materials :

- Material color change
- Peptide oxidation
- pH shift
- Cell culture inhibition

➢ Gamma irradiation necessarily leads to the creation of radicals, small molecules, and unsaturations in alkane chains
    ➢ are there any other impacts ?
    ➢ if yes, what is the extent ?

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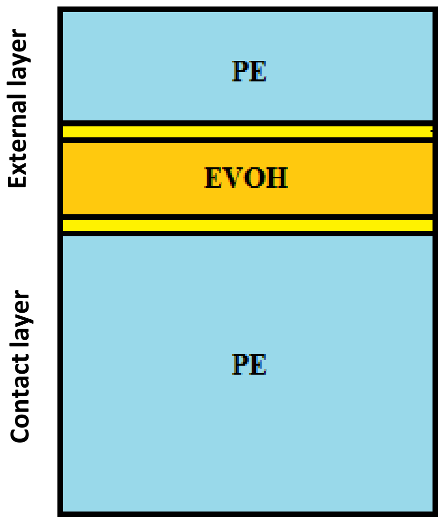
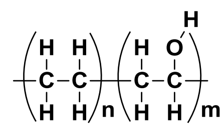
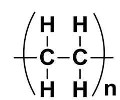
Materials and methods

- Multilayer PE based film (S80)




EVOH (poly-ethylene vinyl alcohol)


PE (polyethylene)

- 3 lots investigated
- Irradiated with a constant dose rate
- Several γ-doses investigated : 0, 30, 50, 115, 270 kGy
- Monitoring of the effects overtime

Materials and methods

Emphasis of chemical modifications

- ATR – FTIR
- Raman spectroscopy

Emphasis of radicals

- ESR Spectroscopy (electron spin resonance)

Emphasis of extreme surface modifications

- XPS (X-Ray Photoelectron Spectroscopy)

Structural modifications

- Tensile strength
- Gas permeability : WVTR

Chemometrics

- The data set size is huge → chemometric methods used (data in matrix)
  - PCA (Principal Component Analysis), AComDim (ANOVA in Common Dimension), SIMPLISMA (SIMPLe-to-use Interactive Self-modeling Mixture Analysis)

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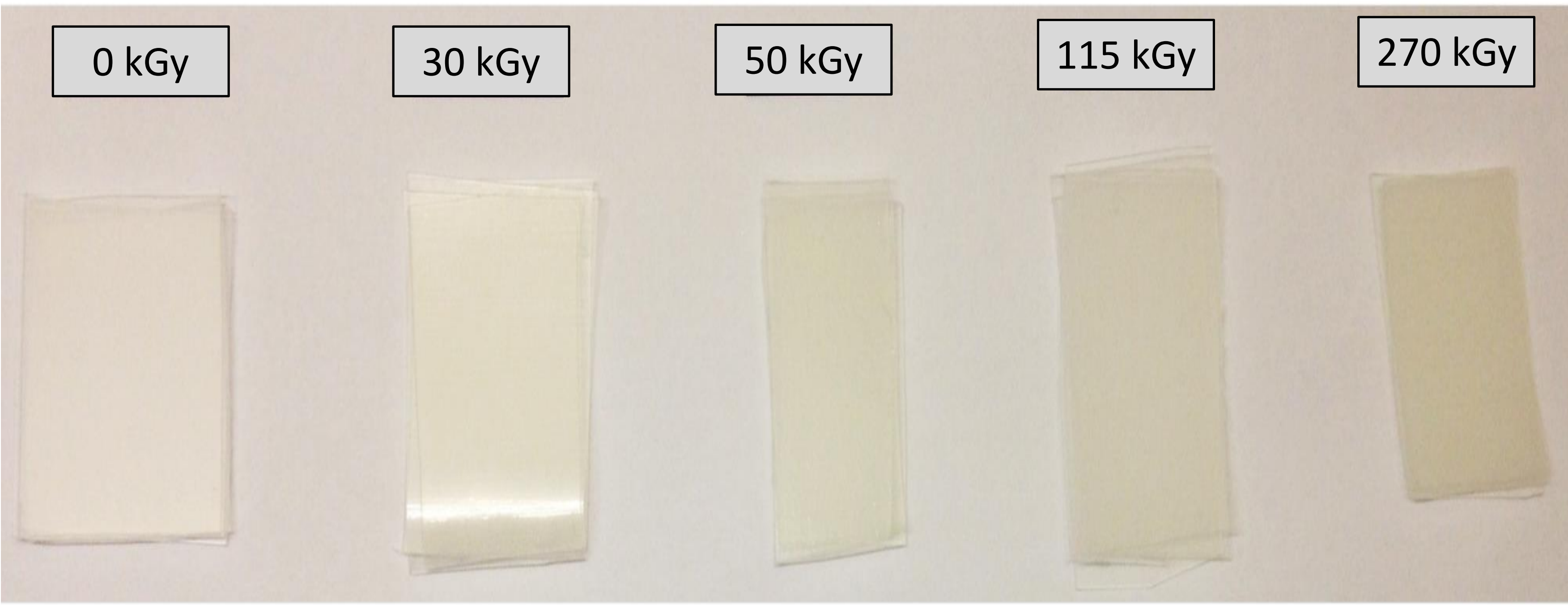
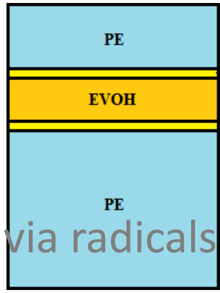
Discoloration

- Yellowing – Photography of S80 films after different irradiation doses



→ Yellowing of films increases with irradiation doses

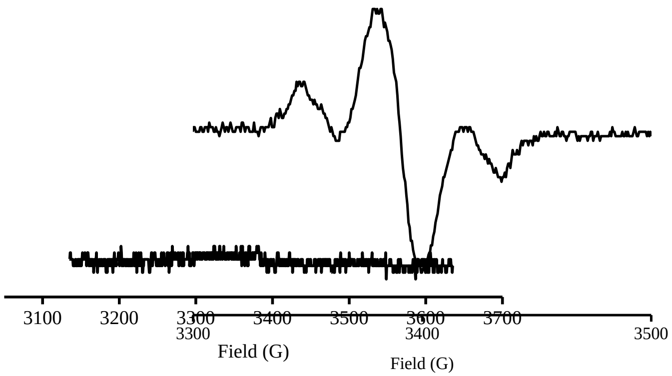
Emphasis of radicals



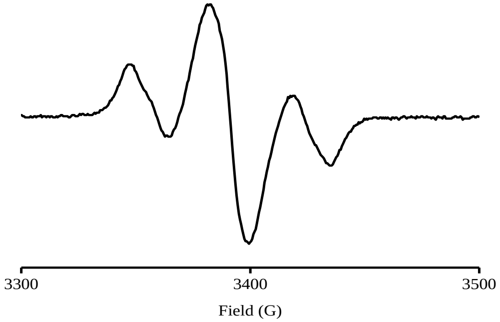
- Problematics : coloration | oxidation of protein | acid release
- Hypothesis : oxidation due to the presence of hydroperoxydes (ROOH) and thus via radicals

- No ESR signal in non sterile films
- ESR signal in films irradiated at 30-50-115-270 kGy

- S80 film irradiated → SIGNAL
- PE film irradiated → ~~SIGNAL~~



- EVOH films irradiated → SIGNAL



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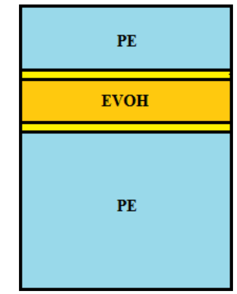
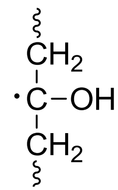
Emphasis of radicals

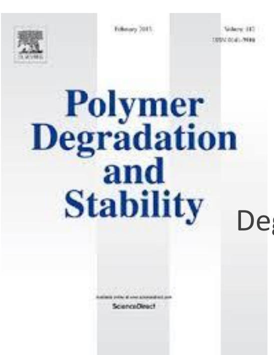


Radical detection by electron spin resonance (ESR) in S80 film:

- Same signal for all irradiation doses
- Radicals in S80 should be :



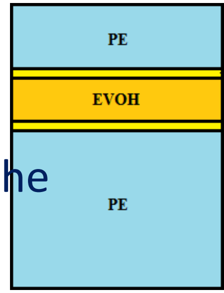
- Stable radical: persistant over ~10-13 weeks
- Migration weakly probable
- This radical cannot be responsible of protein oxidation
- Protein oxidation is certainly due to hydroperoxydes issued from non observable radicals R$^{\bullet}$



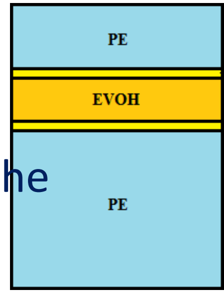
Degradation of γ-irradiated polyethylene-ethylene vinyl alcohol-polyethylene multilayer films: an ESR study
122 (2015) 169-179

Modification on film surface

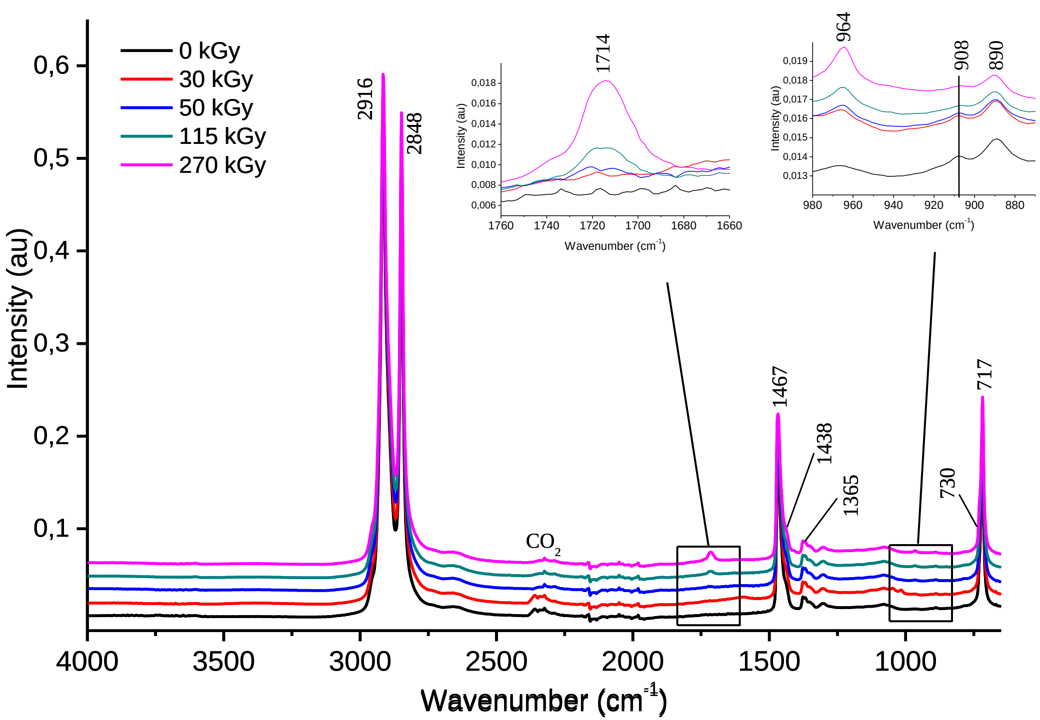
- The presence of radicals leads necessarily to structural and chemical changes of the film surface



Modification on film surface



- The presence of radicals leads necessarily to structural and chemical changes of the film surface
- ATR-FTIR spectra of non-sterile PE (i.e. 0 kGy) and γ-irradiated PE



- Global PCA → no evidence of impact of irradiation and ageing
- Unchanged PE peak positions | intensity
- The PE is not impacted globally
- Need to scrutinize zone by zone

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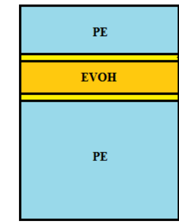
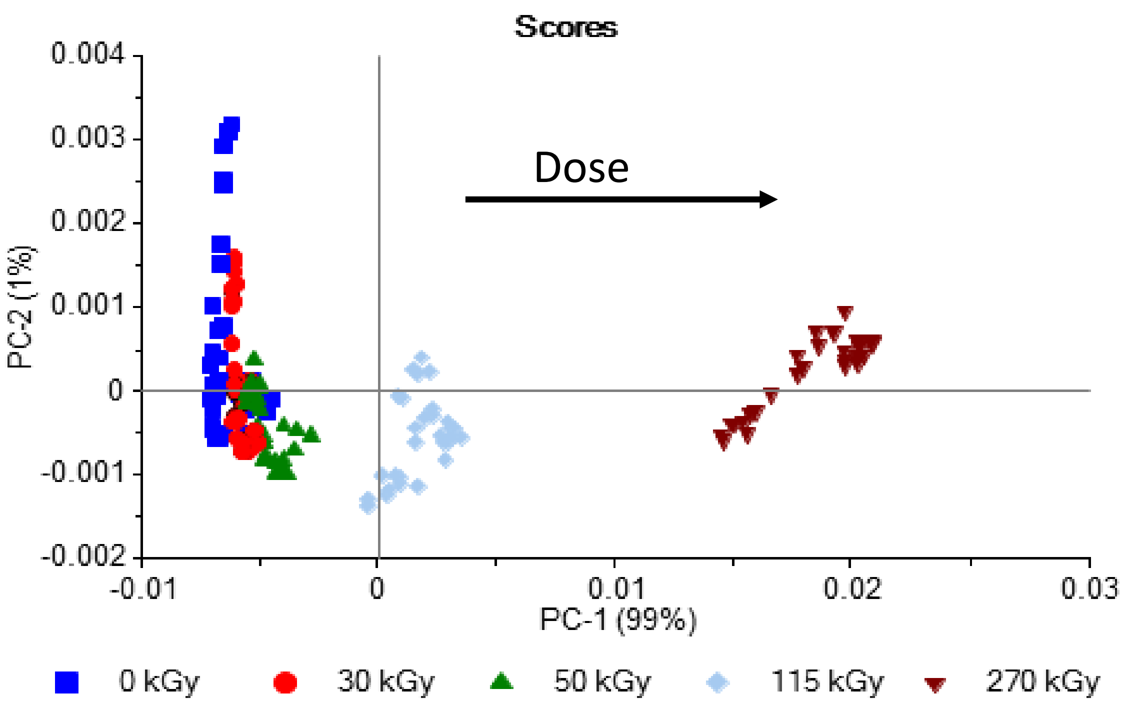
Modification on film surface

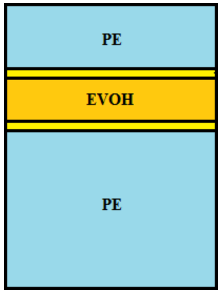


- Chemometrics (PCA) outputs on the 1760-1680 cm^{-1} range:

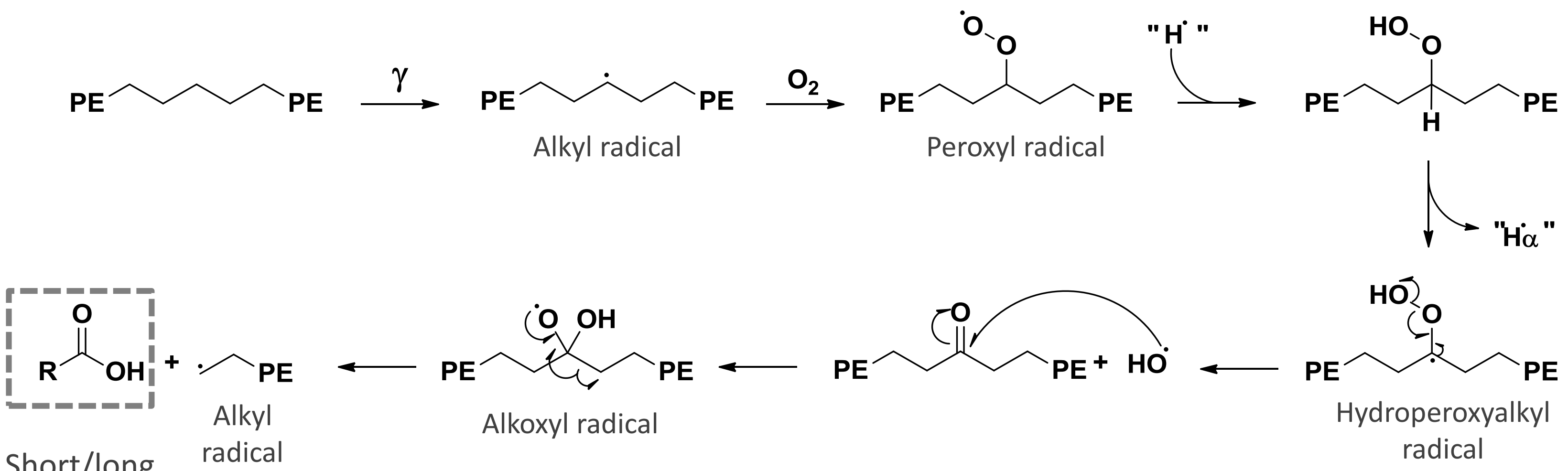


- Overlapping 0/30/50 kGy = minor impact below 115 kGy
- Acids and unsaturated products ↗ with the gamma dose

Modification on film surface



- One possible mechanism



Short/long

pHmetry
IC
GC-MS

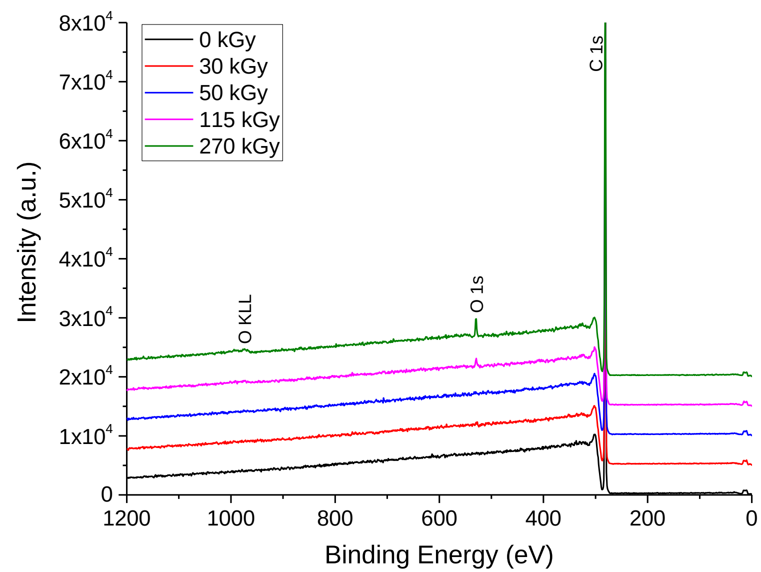
Modification on film surface

ATR-FTIR analysis and chemometric analysis emphasize :

- The polyethylene is globally weakly impacted
- Modifications taking place essentially > 115 kGy
- Modifications deal with chemical moieties having a high ε (coefficient of absorption)
- γ dose ⇨ impact on carboxylic acid generation and unsaturation

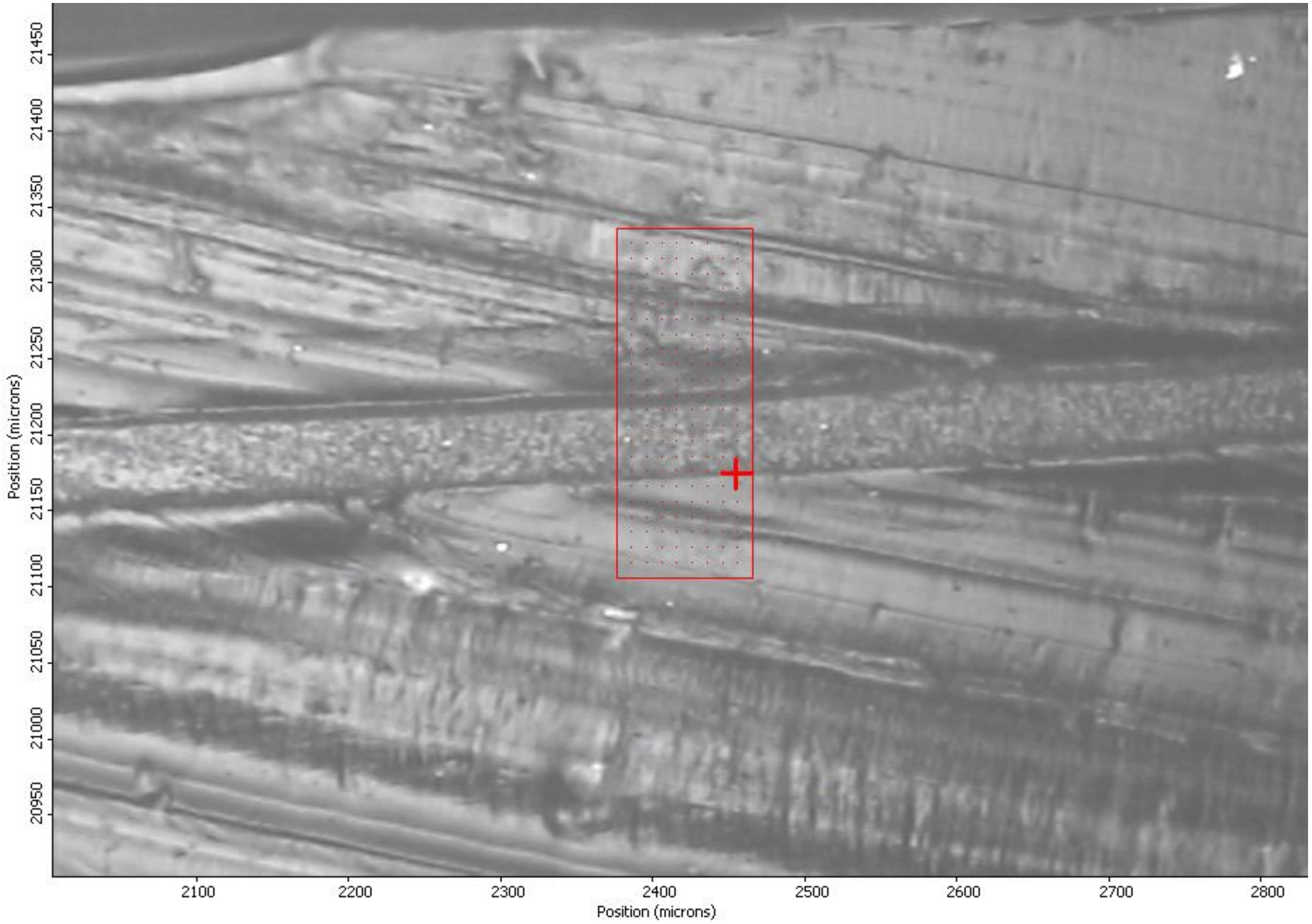
XPS analysis confirms:

- Oxidation occurs
- No trace of hydroperoxide detected



Modification in film core

- Material core chemical change on sample cross section by Raman spectroscopy – S80



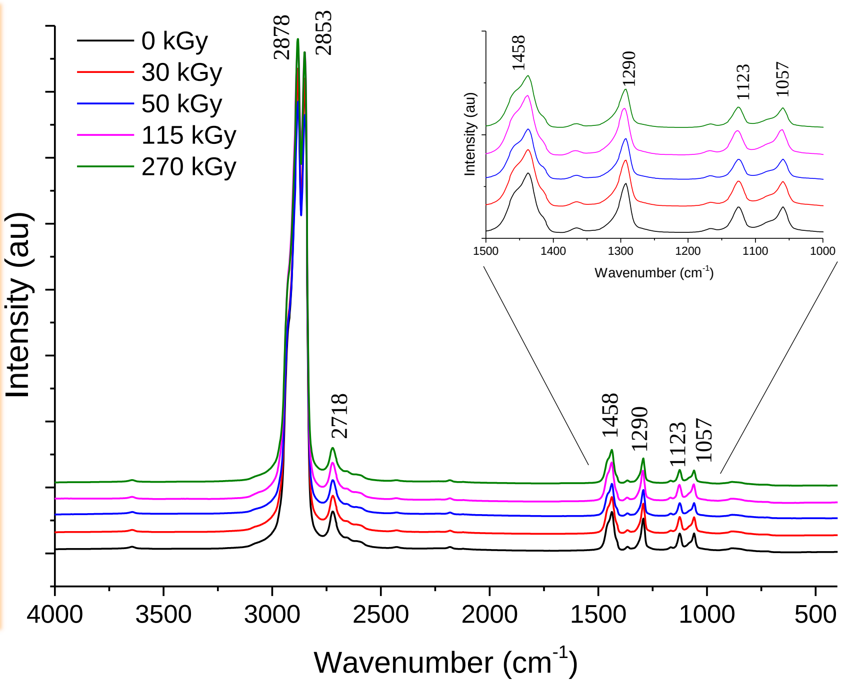
Conditions :

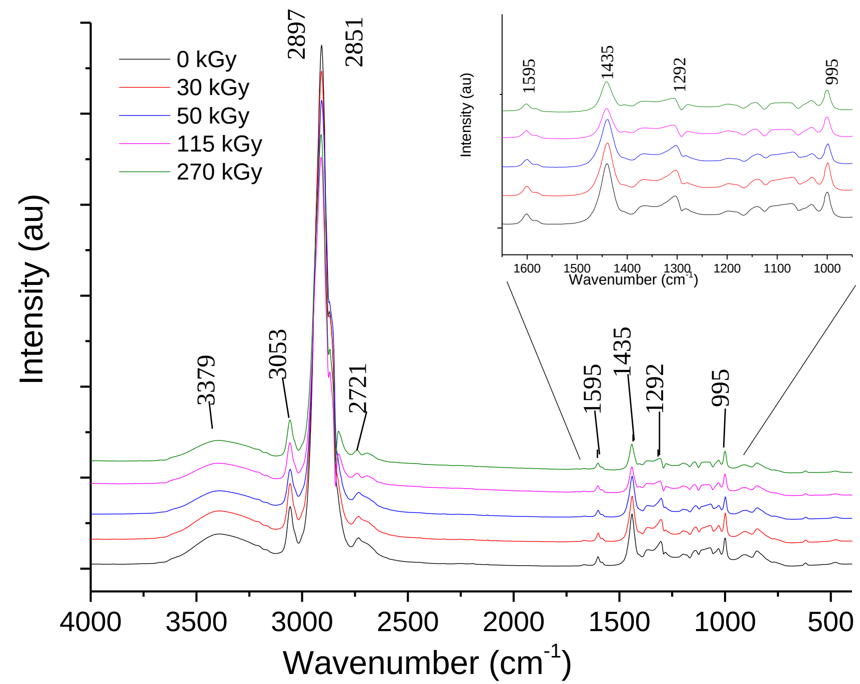
- 5µm step
- Spot of 1.3µm

Modification in film core

Material core chemical change on sample cross section by Raman spectroscopy:

→ No modification observable by Raman spectroscopy of the PE and EVOH





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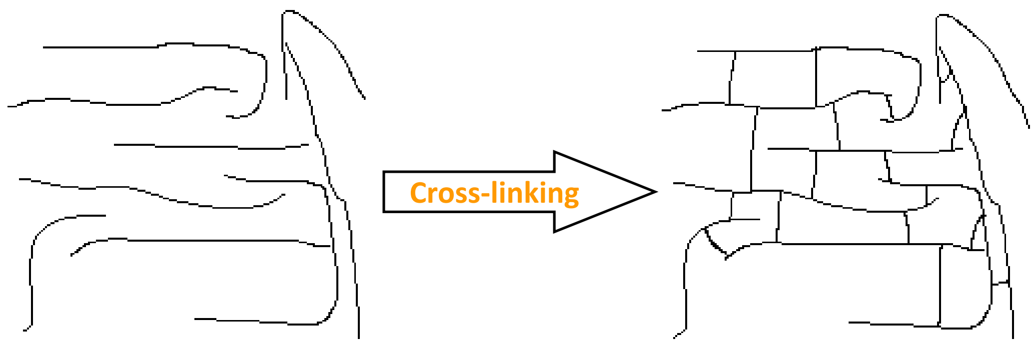
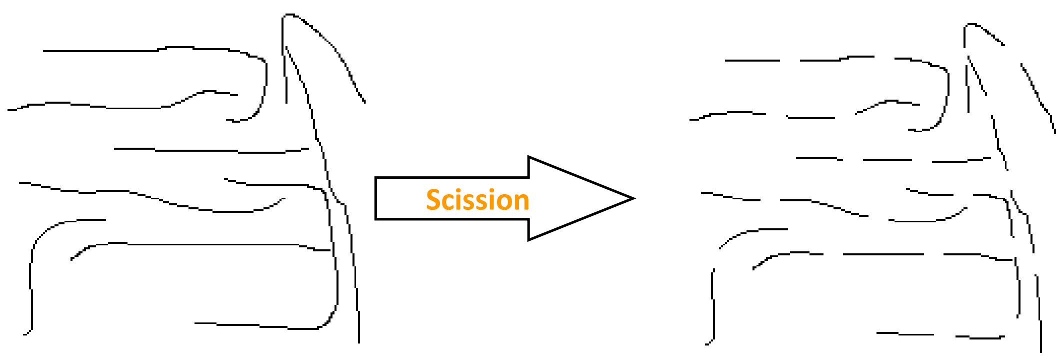
Structural modifications

- Radicals could lead to :
  - Cross-linking or/and scission → changes in tensile features and thermal properties



→ UTS ↗ - Elongation ↘



→ UTS ↘ - Elongation ↗

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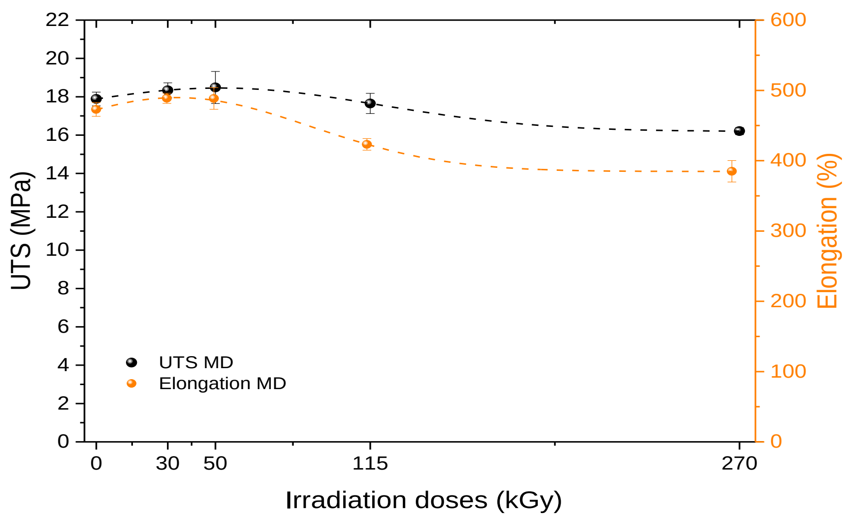
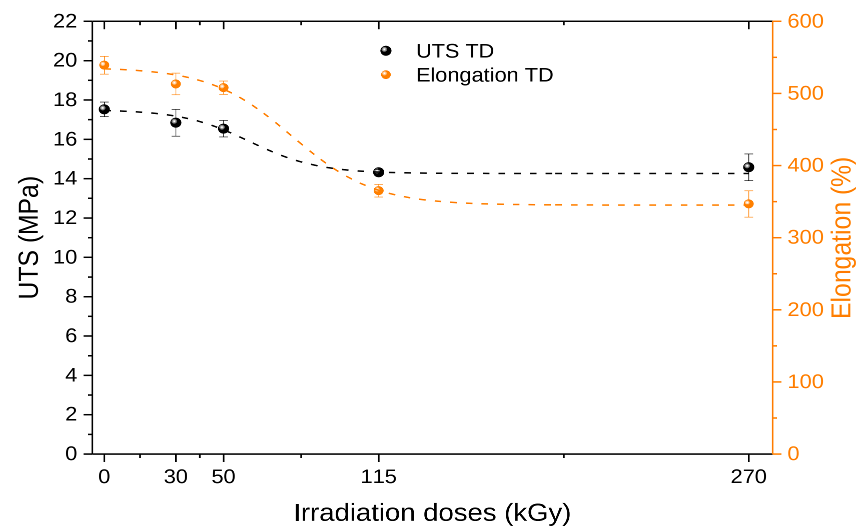
Structural modifications

Tensile properties of S80 film :



MD = Machine Direction



TD = Transversal Direction

Constant

Drop from 115 kGy

Identical observations with film/film welding

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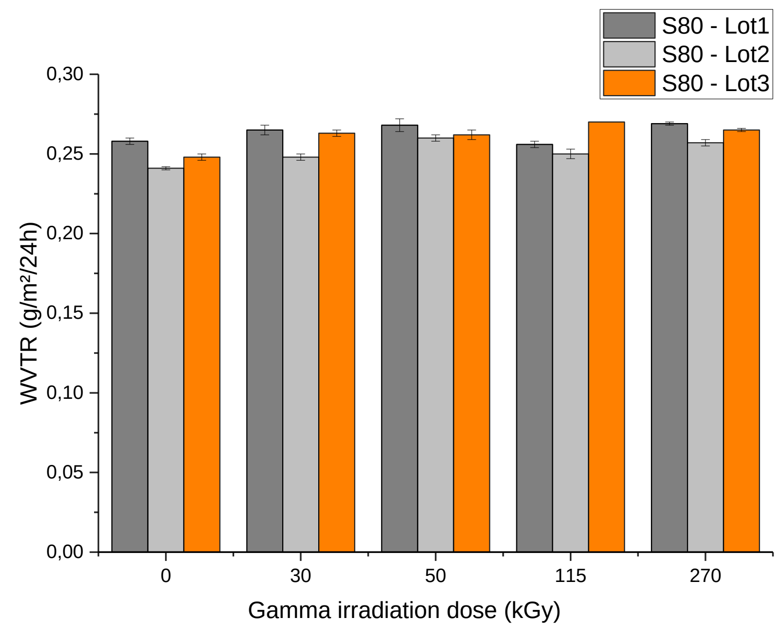
Modification on film core

Water permeability

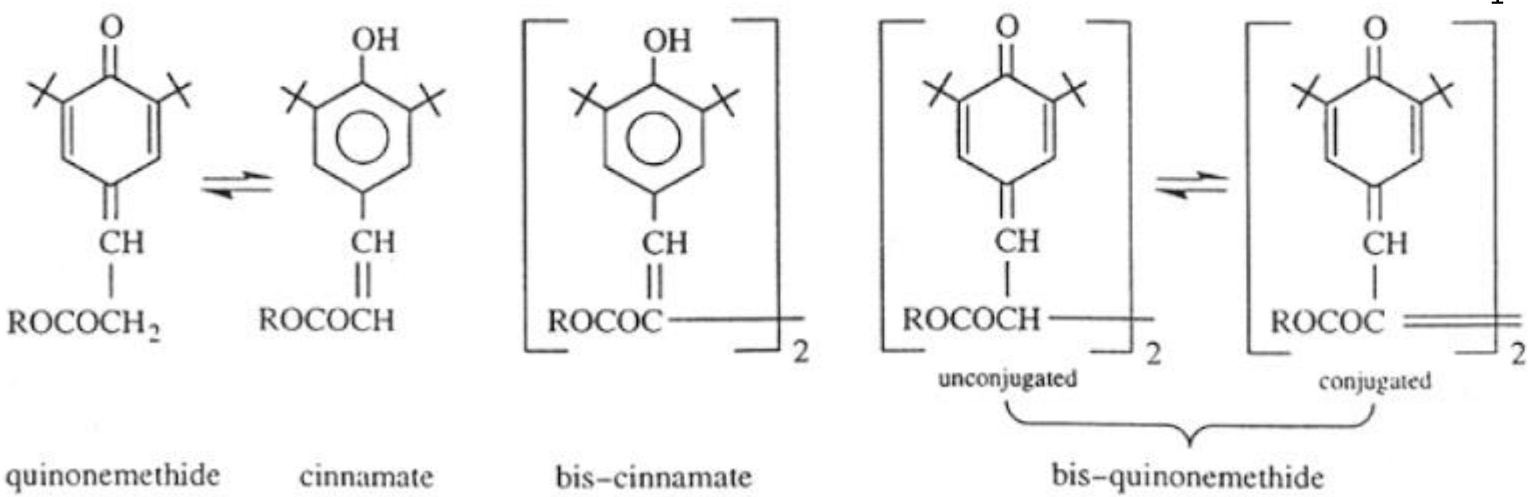
Measured via the water vapor transmission rate (WVTR) ($cm^3/m^2/24h$):

- WVTR constant in the 0-270 kGy range
- PE thus slightly modified :
  - no scission or cross-linking took place in a way to influence the WVTR

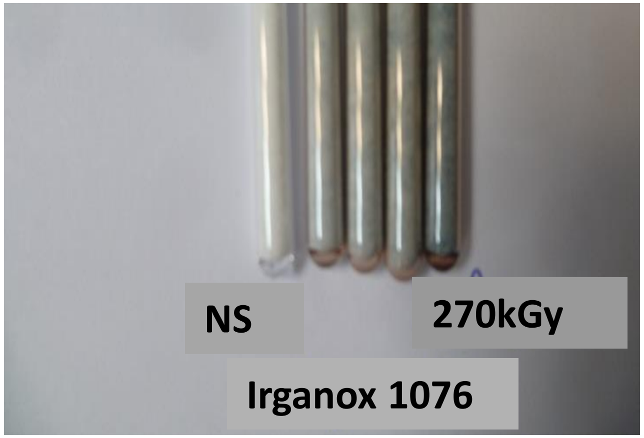
WVTR results



By-products formation



[1]



→ Detection in extractables study

[1] Jan C. J. Bart, Polymer Additive Analytics: Industrial Practice and Case Studies, Firenze University Press, 2006, p27

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Contents

Conclusion

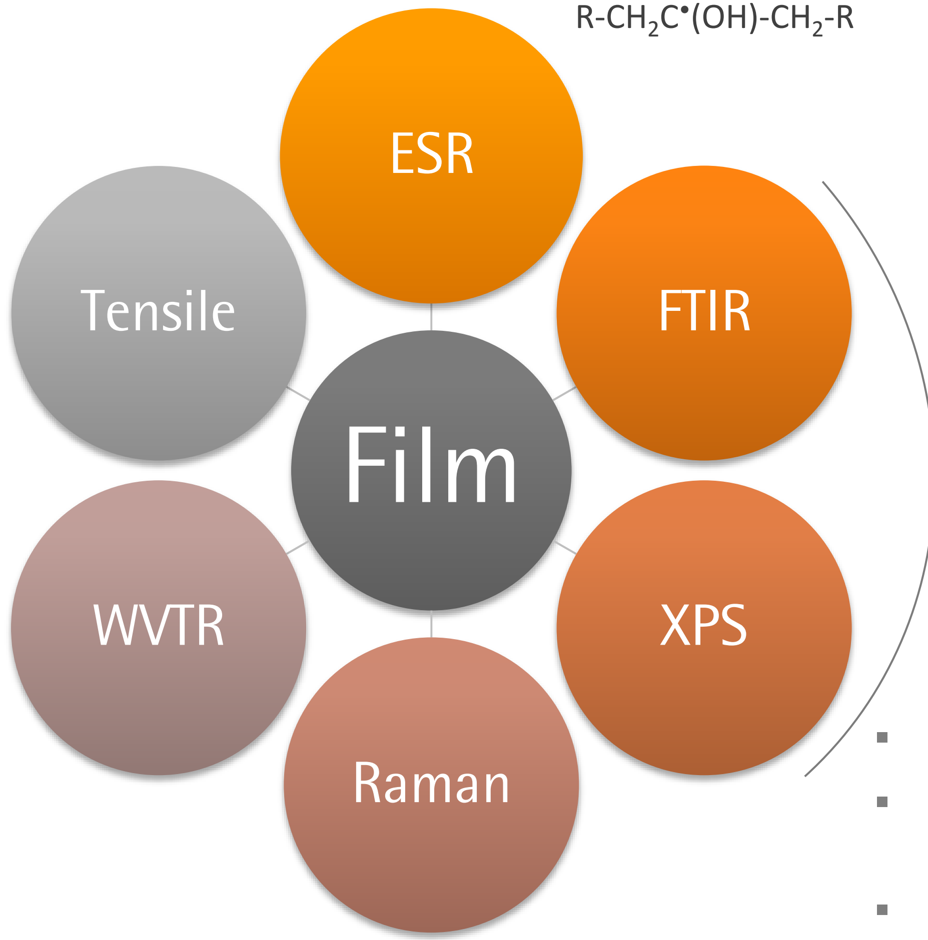
What is the impact of the γ-irradiation on the S80 film ?

- The S80 globally not impacted by the γ-irradiation

Conclusion

- Presence of the hydroxyalkyl radical $R\text{-}CH_2C^{\bullet}(OH)\text{-}CH_2\text{-}R$

- Film handling features unchanged in the range 30-50 kGy



- No change of the WVTR
- PE globally not impacted

- PE slightly impacted
- Presence of carboxylic acids
- Presence of unsaturated products

- PE and EVOH not globally impacted

Conclusion

What is the impact of the γ-irradiation on the S80 film ?

- The S80 globally not impacted by the γ-irradiation
- Gamma irradiation is the starting point of the modifications
- Interactions of films with environment should be evaluated

Perspectives

- The principal plastic materials used for the fluid contact are mainly made up of semi crystalline polymers:
  - Polyolefins (PE, PP & EVA)
  - PVC
  - Silicone (Siloxane, PDMS)
  - PA(X,Y)
  - Polyesters (PET, etc.)
  - Thermoplastic elastomer (TPE)

- Other materials are used to bring special features:
  - EVOH
  - Binding agents

→ Material behavior to gamma irradiation will be different

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Acknowledgments

- Sylvain Marque, Prof.
- Nathalie Dupuy, Prof.
- Fanny Gaston, PhD
- Magali Barbaroux, PhD
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