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Ozone impact on the rubber contained in the tip cap of medical prefillable syringes.

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Abstract

Becton Dickinson company which makes and sells syringes needs to expand the shelf-life of a specific product. A brief evaluation of this statement conducts to the study of the impact of ozone on the rubber part of the syringe tip cap which is considered as the most prone to degradation.
The formulation of the elastomer makes its susceptibility to ozone degradation high. As a result, a visual, material, and functional characterization is needed to estimate the impacts of ozone.
Some theoretical elements were confirmed such as the impact of stress on the rubber, but others remain unclear like the impact on the mechanical properties.
Thus, this thesis led to a greater understanding of ozone impact and enlighten further questions and analysis.

Keywords Syringe, Ozone, Elastomers, Stress, Concentration, Packaging, Characterization

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Preface and acknowledgements

I want to thank Professor Antti Kartunnen and my thesis advisor Gildas Esnault for their good advice and guidance.

I also want to thank my partners for their support.

Grenoble, 31 July 2023
Eliot GE

Symbols and abbreviations

Symbols

ppb	Parts per billion
pphm	Parts per hundred millions
°C	Degree Celsius
°F	Degree Fahrenheit
nm	Nanometers (1e-9 m)

Abbreviations

PFS	Prefillable Syringe
BD	Becton Dickinson and Company
ADDS	Advanced Drug Delivery System
FRM1	Studied syringe rubber formulation
FRM2	Other rubber formulation
SYR1	Studied syringe
PRTC	Tip Cap of SYR1 syringes
RiTC	Rubber part in PRTC
NSj	Rubber part in another type of tip cap
ppb	Parts per billion
pphm	Parts per hundred millions
SBR	Styrene-butadiene rubber
DMA	Dynamic Mechanical Analysis

1 Introduction

Medical devices' shelf-life has become increasingly important over the last years for safety and durability reasons. The focus of this study will be the pre-filled syringes used in the pharmaceutical area. Syringes are examples of medical devices for which storage shelf-life is a crucial factor. Several factors can lead to the degradation of syringes and cause hazardous effects such as some troubles concerning the container closure integrity of the device. This can result in serious complaints of patients and aftermaths on the suppliers. It either creates an economic crisis with a loss of market share and can influence the notoriety of the company.
As a result, each component of the syringe must be tested in the most severe conditions. One of the most crucial elements is the rubber part which guarantees the sealing. However, these elastomers are very much sensible to UV impact and ozone exposure. Hopefully, the light exposure can be avoided by an opaque packaging while there is no fully ozone-resistant packaging known nowadays.
Consequently, a precise analysis of the impact of ozone on rubber parts in biomedical devices is a necessity.
This work focuses on understanding the material and functional consequences of an ozone exposition to evaluate the shelf-life of a given widely produced syringe that will be called SYR1.

The literature part is divided in three parts: First part is focused on elastomer components, their properties, and weaknesses. Second part introduces ozone, its repartition and means of reaction. Eventually, the third part is centred around the studies and experiments that have been carried out regarding the impact of ozone on rubbers to precise the aim of this study.

The goal of the experimental part is to verify the link between the theoretical factors that influence ozone resistance and the results obtained on a given rubber formulation plugged in a syringe to simulate a real condition. In a second time, it is also to understand the repartition of ozone during the whole manufacturing process.

Conclusion based on the results and literature will be given and some recommendations will be added to put this study in perspective with the biomedical domain.

2 Literature review

2.1 Elastomer components

An elastomer is a polymer with special mechanical properties such as an ability to resume its original shape when a deforming force is removed due to its viscoelasticity. Some are from natural sources such as hevea rubber or guayule rubber and some others are artificial and made to obtain very specific properties (silicones, thermoplastic elastomers, hydrogels). Application of rubber worldwide is thus very diverse, one of the most common applications is rubber for tires but it can be used as seals, shoe soles, wetsuits, baby pacifiers, adhesives, hoses, gloves, or lubricants. [1]

Elastomers are widely used in biomedical application for its container closure integrity, its mechanical properties over high and low temperatures and its high viscosity. To obtain these properties, polymeric chains of a material are interconnected through a process that is called **crosslinking**. [2][3]

A crosslink is a bond that links one polymer chain to another. These bonds induce a change in the physical properties of polymers. This is mainly determined by the crosslinking density of the material which is defined by the density of chains that connects two infinite parts of the polymer network. It depends on the molecule arrangement of the monomers [4]. Table 1 shows the consequence of the crosslinking density on elastomers.

Table 1 : Crosslinking densities

Crosslinking density	Impact on the structure
Low	Decrease Viscosity
Intermediate	Gummy polymers gain a lot of strength
Very high	Become very rigid and glassy

Vulcanization is one of the most important processes for rubber technologies. During vulcanization, the rubber compound changes to an elastic final product: vulcanized rubber. This is done by consecutive and parallel changes of chemical and physical nature. Vulcanization occurs in the presence of vulcanizing agents formally divided into stages. The length of the crosslinks depends on the type of vulcanization system and the temperature. Most of the time, rubber is vulcanized with sulfur. [5] Figure 1 displays some schemes representing the vulcanization.

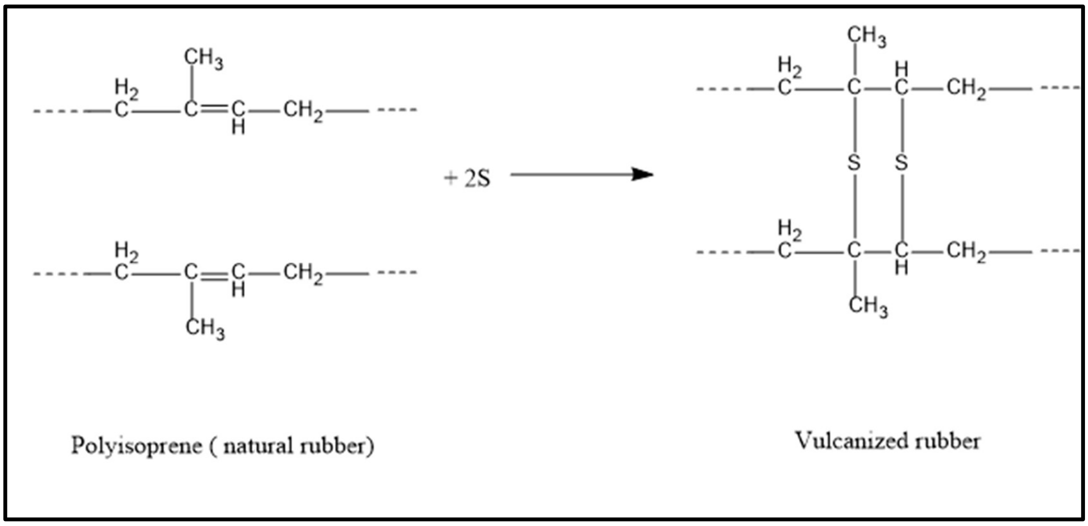


Figure 1 : General scheme of vulcanized network [5]

Figure 2 presents a more precise example of the sulphur bonds that are created through the process of vulcanization.

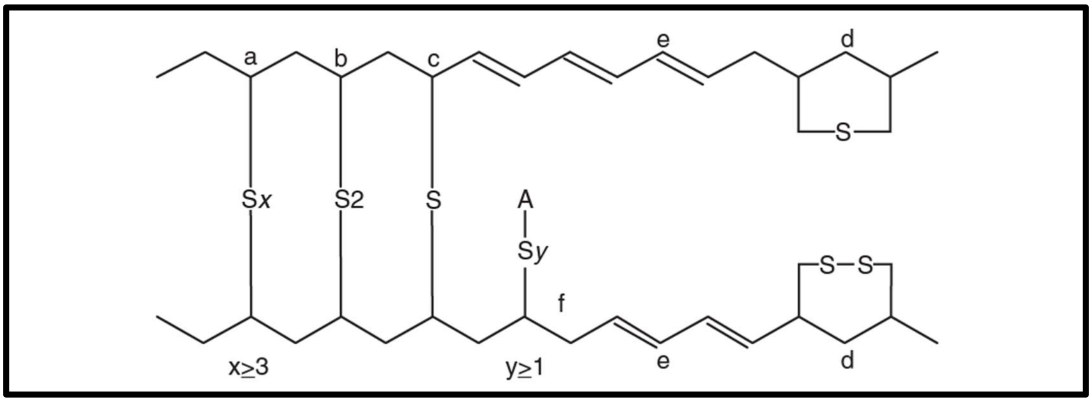


Figure 2 : Typical chemical bonds formed in sulfur vulcanized rubber: (a) polysulfid cross-links, (b) disulfid cross links, (c) monosulfid cross-links, (d) intra-chain cyclic monosulfides and intrachain cyclic disulfides, (e) conjugated diene and conjugated triene and (f) fendent sulfidic group terminated by moiety X derived from the accelerator. [5]

Elastomers are susceptible to different environmental attacks that can modify their structure and then induce degradation. One of the most important factors that lead to degradation is the chemical resistance of elastomers.

Here are some factors that can lead to the degradation of elastomers:

- Chemical liquid components: acids, hydroxides, alcohols, esters …
- Gases: Ozone
- Environmental properties: Temperature, Pressure, UV light exposure.

All the elastomers do not have the same susceptibility to degradation, and for example some are resistant to an acid while some others are weaker. The wide variety of elastomers lead to a precise choice when some properties are needed. Here are some examples [6]:

TYPICAL PROPERTIES OF ELASTOMERS									
ANSI/ASTM Designation	NR/IR	AU/EU	CR	EPDM	FKM	HNBR	NBR	TFE/P	VMQ
Common Name	Natural Rubber	Polyurethane	Chloroprene (Neoprene)	EPDM	Viton®	Hydrogenated Nitrile	Nitrile	Aflas®	Silicone
Low Temp	-60°F	-40°F	-30°F	-40°F	-10°F	-22°F	-30°F	25°F	-80°F
High Temp	220°F	175°F	212°F	300°F	400°F	300°F	250°F	450°F	420°F
Durometer Shore A	30-90 Shore A	10-100 Shore A	15-95 Shore A	30-90 Shore A	50-95 Shore A	55-95 Shore A	20-100 Shore A	60-100 Shore A	25-85 Shore A
Abrasion	Fair - Good	Excellent - Outstanding	Very Good – Excellent	Good - Excellent	Good	Good-Excellent	Good-Excellent	Good-Excellent	Poor
Adhesion	Excellent	Excellent	Excellent	Good - Excellent	Fair - Good	Excellent	Excellent	Fair - Good	Excellent
General Properties	Excellent physical properties including abrasion and low temperature resistance.	Good aging and excellent abrasion, tear, and solvent resistance. Poor high temperature properties.	Good Weathering Resistance. Flame retarding. Moderate resistance to petroleum- based fluids.	Excellent ozone, chemical, and aging resistance. Poor resistance to petroleum-based fluids.	Excellent oil and air resistance both at low and high temperatures. Very good chemical resistance.	Excellent heat and oil resistance, improved fuel and ozone resistance. Decreased elasticity at low temperatures with hydrogenation over standard nitrile.	Excellent resistance to petroleum-based fluids. Good physical properties.	High temperature polymer, good overall chemical resistance, poor compression set and a high minimum working temperature.	Excellent high and low temperature properties. Fair physical properties.
General Chemical Resistance									
Resistant to:	Most moderate chemicals, wet or dry, organic acids, alcohols, ketones, aldehydes.	Ozone, hydrocarbons, moderate chemicals, fats, oils, greases.	Moderate chemicals and acids, ozone, oils, fats, greases, many oils, and solvents.	Animal and vegetable oils, ozone, strong and oxidizing chemicals.	All aliphatic, aromatic and halogenated hydrocarbons, acids, animal and vegetable oils.	Many hydrocarbons, transmission fluids, refrigerants, diluted acids, hydraulic fluids, silicone oils, vegetable and animal fats and oils, water and steam.	Many hydrocarbons, fats, oils, greases, hydraulic fluids, chemicals.	Highly resistant to a wide range of chemicals, such as acid, base and steam. Superior resistance to strong bases in comparison with FKM.	Moderate or oxidizing chemicals, ozone, concentrated sodium hydroxide.
Attacked by:	Ozone, strong acids, fats, oils, greases, most hydrocarbons.	Concentrated acids, ketones, esters, chlorinated and nitro hydrocarbons.	Strong oxidizing acids, esters, ketones, chlorinated, aromatic and nitro hydrocarbons.	Mineral oils and solvents, aromatic hydrocarbons.	Ketones, low molecular weight esters and nitro containing compounds.	Chlorinated hydrocarbons, ketones, strong acids.	Ozone (except PVC blends), ketones, esters, aldehydes, chlorinated and nitro hydrocarbons.	Attacked to varying degrees by strong caustics; polar solvents such as acetone and MEK; ammonia; hydrogen sulfide.	Many solvents, oils, concentrated acids, dilute sodium hydroxide

Table 2 : Classification of some elastomers [6]

Rubbers can be classified according to their relative susceptibility to deteriorate. This is the main topic of the **ISO 2230 – Rubber Product – Guidelines for storage** [7].

ISO 2230 classifies rubber types in 3 categories according to their susceptibility to deterioration by aging:

- **Group A**: rubbers with moderate susceptibility to deterioration by aging as listed in Table 2
- **Group B**: rubbers with low susceptibility to deterioration by aging as listed in Table 3
- **Group C**: rubbers which are highly resistant to deterioration by aging as listed in Tables 4

Table 3 : Group A rubbers [7]

Abbreviation	Chemical name from ISO 1629	Common name
BR	Butadiene rubber	Polybutadiene
NR	Isoprene rubber, natural	Natural rubber
IR	Isoprene rubber, synthetic	Polyisoprene
SBR	Styrene-butadiene rubber	SBR
AU	Polyester urethane rubber	Polyurethane
EU	Polyether urethane rubber	Polyurethane

Table 4 : Group B rubbers [7]

Abbreviation	Chemical name from ISO 1629	Common name
NBR	Acrylonitrile-butadiene rubber	Nitrile
NBR/PVC	Blend of acrylonitrile-butadiene rubber and poly(vinyl chloride)	Nitrile/PVC
XNBR	Carboxylic-acrylonitrile-butadiene rubber	Carboxylated rubber
HNBR	Hydrogenated NBR (with some unsaturation)	Hydrogenated nitrile
CO, ECO	Polychloromethyloxiran and copolymer	Epichlorohydrin
ACM	Copolymer of ethylacrylate (or other acrylates) and a small amount of a monomer which facilitates vulcanization	Acrylic
CR	Chloroprene rubber	Neoprene
IIR	Isobutene-isoprene rubber	Butyl
BIIR	Bromo-isobutene-isoprene rubber	Bromobutyl
CIIR	Chloro-isobutene-isoprene rubber	Chlorobutyl

Table 5 : Group C rubbers [7]

Abbreviation	Chemical name from ISO 1629	Common name
CM	Chloropolyethylene	Chlorinated polyethylene
CSM	Chlorosulfonylpolyethylene	Chlorosulfonated polyethylene
EPM	Ethylene-propylene copolymer	EPM, EPR
EPDM	Terpolymer of ethylene, propylene and a diene with the residual unsaturated portion of the diene in the side chain	EPDM
FKM	Rubber having fluoro, perfluoroalkyl or perfluoroalkoxy substituent groups on the polymer chain	Fluorocarbon
Q	Silicone rubber	Silicone
FMQ	Silicone rubber having both methyl and fluorine substituent groups on the polymer chain	
PMQ	Silicone rubber having both methyl and phenyl substituent groups on the polymer chain	
PVMQ	Silicone rubber having methyl, phenyl and vinyl substituent groups on the polymer chain	
MQ	Silicone rubber having only methyl substituent groups on the polymer chain, such as dimethyl polysiloxane	
VMQ	Silicone rubber having both methyl and vinyl substituent groups on the polymer chain	

The formulation of the Tip Cap of the studied syringe is classified in group A. The formulation of the rubber will be named “FRM1”.

According to ISO 2230:2002, section 6.2.5 “Ozone”:

“As ozone is particularly deleterious to rubber, storage rooms should not contain any equipment that is capable of generating ozone, such as mercury vapour lamps or high voltage electrical equipment giving rise to electric sparks or silent electrical discharges. Combustion gases and organic vapors should be excluded from storage rooms, as they may give rise to ozone via photochemical processes.”

“NOTE 1 When equipment such as a fork-lift truck is used to handle large rubber products, care needs to be taken to ensure this equipment is not a source of pollution that may affect the rubber.”

“NOTE 2 Combustion gases should be considered separately. While they are responsible for generating ground-level ozone, they may also contain unburned fuel which, by condensing on rubber products, can cause additional deterioration.”

And according to ISO 2230:2002, section 7.3.3 “Duration of storage”:

> *“Unless otherwise specified in the product specification, the initial storage period and extension storage periods should be those given in Table 4.”*
>
> *“NOTE 1 The initial storage periods and extension storage periods for rubber types classified according to the groups defined in clause 4 are tabulated in Table 4. It is pointed out that these periods apply to unassembled rubber components packaged and stored in accordance with the recommendations of clause 5 and clause 6.”*

Table 6 : Initial and extension storage periods for unassembled components [7]

Classification of group	**Initial storage period**	**Extension storage periods**
Group A rubbers	5 years	2 years
Group B rubbers	7 years	3 years
Group C rubbers	10 years	5 years
NOTE If the storage temperature is over or under 25 ◦C, this will influence the storage time. Storage at a 10 ◦C higher temperature will reduce the storage time by about 50 % and storage at a 10 ◦C lower temperature will increase the storage time by about 100 %.		

For group A rubbers, the standard shelf-life is of **5 years**, and could be extended to 7 years (for the unassembled rubber component). [7]

2.2 Ozone

Ozone (O_3) is an unstable inorganic molecule present all over the planet and known for its layer in the atmosphere whose goal is to protect the earth surface from hazardous UV radiations. It is toxic for humans and its concentration is usually expressed in ppb (parts per billion) or pphm (parts per hundred million). Let's analyze its repartition over the environment and its reaction on rubbers.

Natural ozone is present in the so-called ozone layer which is located in the stratosphere between 10 and 50km above the surface. Its creation is due to the reaction between ultraviolet rays between 160 and 240 nm and the oxygen naturally present as dioxygen molecules. [8]

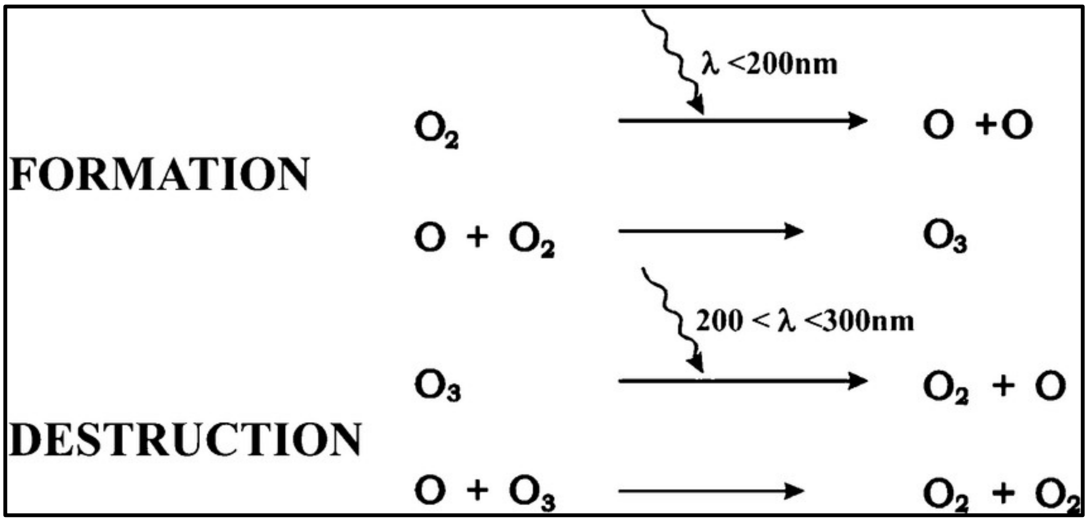


Figure 3 : Formation of ozone [8]

The repartition of the ozone creation in the atmosphere is not uniform at all and it depends on several factors such as the thickness of the atmosphere (tropics / poles), the season (atmosphere fluxes), the altitude, the hour of the day, the meteorological situation. As a result, it is difficult to estimate an average ozone concentration at a given location, but it is estimated that in this ozone layer, the concentration is between two to eight parts per million.

Ozone is passively created through car emissions by the creation of hydrocarbons and nitrogen oxides which react with UV light.

$$NO_2 + h\nu \longrightarrow NO + O, \qquad \lambda < 398 \text{ nm}$$

$$O + O_2 + M \longrightarrow O_3 + M$$

$$O_3 + NO \longrightarrow NO_2 + O_2$$

Figure 4 : UV-emissions reaction [8]

As a result, ozone concentration is not uniform at sea-level. It is higher in polluted and in high altitude cities while lower in rural areas.

Ozone can also be created by UV emission using printers, mercury vapors lamps or high-voltage electrical equipment. That is one reason to explain the moderate ozone concentration in offices for instance.

Here is a table which represent the typical ozone concentrations:

Table 7: Typical ozone concentrations [7][8][9][10]

Location / Situation	Concentration
Sea-level unpolluted	50 ppb
Atmosphere	0 – 10 ppm
Ozone increasement over the altitude	+70ppb/km
Average transatlantic concentration	50 - 500 ppb
WHO guidelines for 8h mean concentration	50 ppb
Fatality of ozone	50 ppm for 60 min
Industrial working areas	100ppb
Peak concentration in American cities	150 – 500 ppb

In this study, ozone is seen as an environmental hazard for rubbers which are polymers with high unsaturation. Indeed, there is a chemical reaction between ozone and some specific molecules that lead to a change in the molecular structure of the component which is called **ozonolysis**.

Ozonolysis is an organic reaction between multiple bonds (alkenes, alkynes) and ozone which lead to the cleavage of the atomic chain. [9,19]

Figure 5 shows the chemical mechanism of the attack.

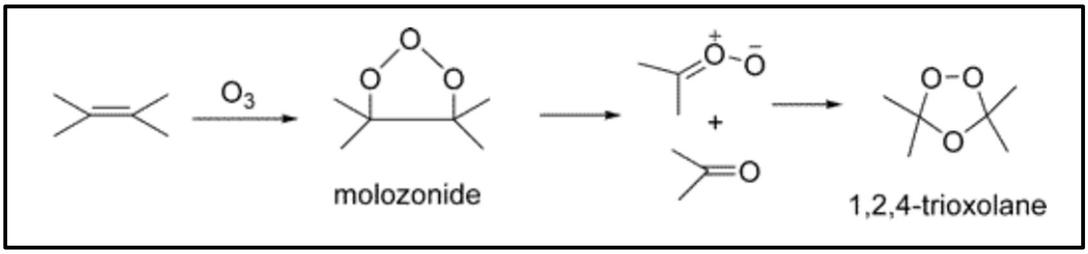


Figure 5: Ozonolysis mechanisms [13]

The results of the split of these chains can be very important for the properties of the elastomer. In fact, the degradation of an elastomer can cause what is called ozone cracking. Cracks usually occurs in the direction perpendicular to the applied strain when a critical stress value is exceeded.

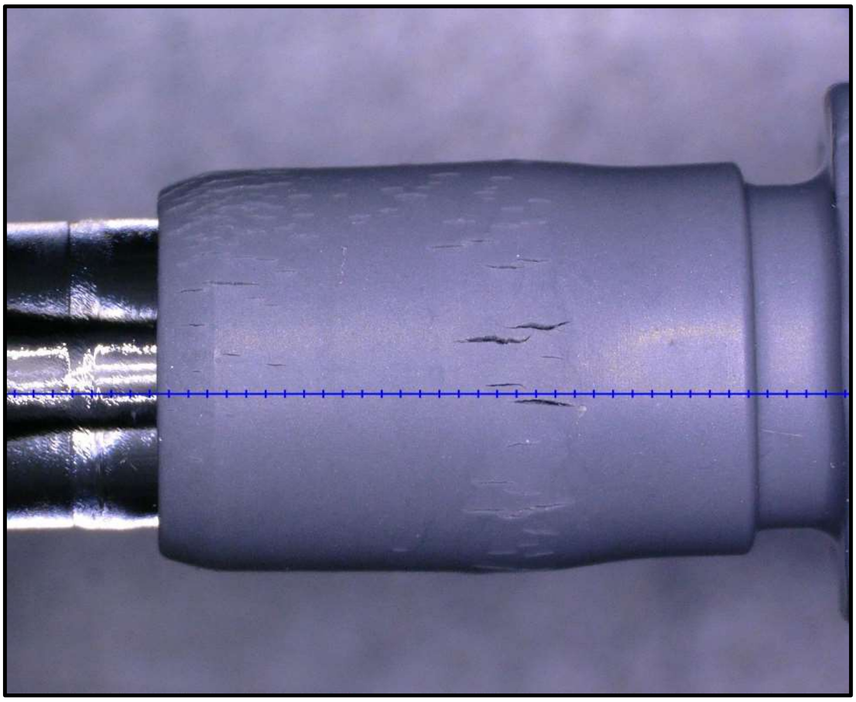


Figure 6 : Ozone cracks

At rather low stress values just above the critical value, the ozone cracks become more numerous and are finer in size. whereas at high stress values, long and deep cracks are observed. The microscopic disintegration of the surface causes dulling and a bluish sheen of the surface of rubber goods. This phenomenon is known as "frosting" because it often resembles actual frost. It is greatly accelerated by humidity and heat and is most noticeable on the bright finish of air-cured rubber goods.[11]

Here is a study that shows the impact of stress on the ozone attack. It is composed of a rubber mushroom with a higher stress value at the top of the septum while the surrounding is less stressed:

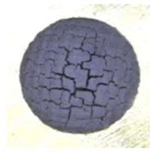
Exposure time (h)	0.33	0.58	20	48	134
Total crack area (mm^2)	0.045 ± 0.002	0.089 ± 0.012	0.229 ± 0.038	0.234 ± 0.034	0.237 ± 0.037
Image of cracked mushroom					

Figure 7 : Effect of stress on total crack area [12]

As it is shown, there are more cracks early after ozone exposure in the middle of the mushroom rather than at the extremities where there is less stress induced. [12]

2.3 Studies carried previously

As it is an important subject, some studies have already been carried out in the past and it is necessary to learn from them and not to begin a new study without taking the previous one into account.

Resistance to ozone cracking tests is even standardized into the ISO 1431-1: ‘Rubber, vulcanized or thermoplastic — Resistance to ozone cracking'. It summarizes the important parameters to take into account such as pressure, temperature, stress and concentration.

<u>Concentration</u>: “*The test shall be carried out at one of the following ozone concentrations, expressed in parts of ozone per billion of air by volume (ppb) and, in brackets, parts per hundred million (pphm)):*

- *250 ppb ± 50 ppb (25 pphm ± 5 pphm)*
- *500 ppb ± 50 ppb (50 pphm ± 5 pphm)*
- *1 000 ppb ± 100 ppb (100 pphm ± 10 pphm)*
- *2 000 ppb ± 200 ppb (200 pphm ± 20 pphm)*

Unless otherwise specified, the test shall be carried out at an ozone concentration of 500 ppb ± 50 ppb (50 pphm ± 5 pphm). If a lower concentration is required for testing rubbers known to be used at low ambient ozone concentrations, an ozone concentration of 250 ppb

± 50 ppb (25 pphm ± 5 pphm) is recommended. If highly resistant polymers are being tested, a concentration of 1 000 ppb ± 100 ppb (100 pphm ± 10 pphm) or 2 000 ppb ± 200 ppb (200 pphm ± 20 pphm) is recommended. "

Temperature: *"The preferred test temperature is 40 °C ± 2 °C. Other temperatures, such as 30 °C ± 2 °C or 23 °C ± 2 °C, may be used if they are more representative of the anticipated service environment, but the results obtained will differ from those obtained at 40 °C ± 2 °C."*

Humidity: *"The relative humidity of the ozonized air shall normally be not more than 65 % at the test temperature. Very high humidity can influence the results; when applicable, for products intended for use in damp climates, the test shall be carried out at a relative humidity in the range 80 % to 90 %, if this is practicable."*

Stress: *"Tests shall normally be carried out using one or more of the following strain levels: (5 ± 1) %, (10 ± 1) %, (15 ± 2) %, (20 ± 2) %, (25 ± 2) %, (30 ± 2) %, (40 ± 2) %, (50 ± 2) %, (60 ± 2) %, (80 ± 2) %. The elongation(s) used should be similar to those anticipated in service."* [9]

Some ozone exposure tests have already been carried out to understand the concentration limits to obtain ozone cracking. 10 pieces of each rubber configurations were sent to ozone exposure. The concentration chosen was the one following the ISO 1431-1 method for rubbers known to be weakly resistant to ozone:

"Strain the test pieces at one or more of the elongations given in 9.4 and condition them in accordance with 8.2.

If only one elongation is used, this shall be 20 %, unless otherwise specified. Examine the test pieces after 2 h,

4 h, 8 h, 24 h, 48 h, 72 h and 96 h and, if necessary, at suitable intervals thereafter in the test chamber and

note the time until the first appearance of cracks at each elongation".

"Test conditions were: Temperature: 40±2°C;
Ozone concentration: 25±5 pphm;
Relative humidity: 50±5%;
Time: 120 hours.
The samples were examined for cracks after 2, 4, 8, 24, 48 and 120 hours."[12]

Two types of syringe tip caps were tested: Rubber parts in PRTC (RiTC) which is the one later used in this study and Needle Shield rubber (NSj).

Two rubber formulations were tested: FRM1 (studied one) and FRM2.

Figure 8 : BD PRTC syringe [14]

Figure 9 : BD NSj syringe [15]

Here are the results obtained: [16]

First crack seen on total of 10 pcs		2h	4h	8h	24h	48h	120h
NSj	FRM1	/	/	/	10		
	FRM2	/	/	/	9	/	1
RiTC	FRM1	/	/	/	/	/	10
	FRM2	/	/	/	/	/	7

Table 8 : Ozone cracking results in the study

Figure 10 depicts the typical cracks that were observed:

Figure 10 : Cracks seen in the study [16]

NSj tip caps used to crack earlier than RiTC ones. It can be explained by the fact that they are exposed to a more severe stress and are then more likely to degrade because of ozone.
These data are first steps to the study that will be carried in this thesis. It gives guidelines on the concentration that should be set to obtain cracks. However, from one formulation to another, the time needed to obtain cracks is significantly different. Thus, it is important to study a large range of time and concentration in the beginning and then specify and precise the concentration.

Ozone seems to have a lot of different effects depending on the configuration chosen. It is now time to think about all the elements that can be used to

perform a complete study of the impact of ozone. Influences as well as methods to characterize rubbers will be studied to create an effective test plan and obtain the most relevant results.
It will be the theme of “Research material and methods” part.

3 Research material and methods

To introduce properly the methodology that will be done, it is important to understand what are the key metrics that can influence rubber shelf-life and what are the tests that can be used to measure them.

3.1 Influences

The scope of this study is to characterize the impact of ozone on a specific formulation of a rubber contained in the tip cap of a syringe. As a result, there are plenty of configurations that would have been interesting to exploit such as understanding the behaviour of other rubber formulations or other types of syringes. The study will only be focused on this specific formulation called FRM1.

There are still a lot of influences that can help to understand the overall behaviour of FRM1 RiTC.

3.1.1 Stress

Stress is an important factor in the ozone resistance of rubbers. The higher the stress is applied, the lower the rubber is ozone resistant. As a result, to observe ozone cracks, it can be interesting to vary the stress applied on the RiTC.

To do this, an analysis of the stress applied on the RiTC is necessary. Let's look at the shape of a RiTC assembled on a syringe.

Figure 11 : BD Syringe [17]

In this figure, the RiTC is plugged between a plastic part and the tip of the glass barrel. Prima facie, the barrel seems to extend the size of the RiTC while the plastic part constricts it. It seems then necessary to do further investigations on the stress applied on the rubber.

Thanks to a computer simulation using a finite element analysis, simulation have been carried out to simulate the stress repartition on the RiTC when the barrel is clipped on it and plastic parts are screwed.

To visualize more ozone cracks after an exposure that will be analysed later, a way can be to extend the diameter of the barrel tip to apply more stress on the RiTC. As a result, it has been decided that the critical diameter of the tip of the barrel will be 0.27 mm increased from the initial diameter. This value is linked to the dimensional specifications applied to produce the barrel tips and the rubber tip caps.

Figure 12 to Figure 16 depicts the stress repartition on nominal and enlarged diameter barrel tips.

Here are the results of this study:

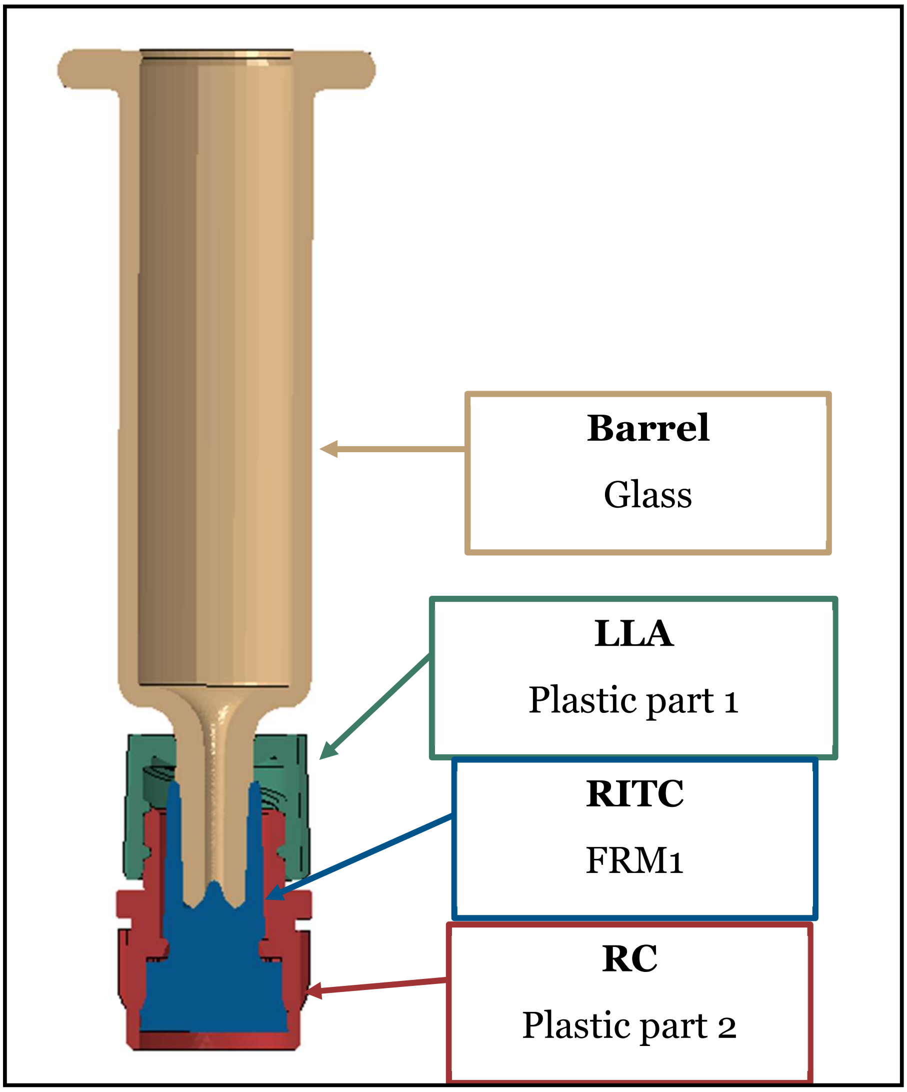


Figure 12 : Syringe configuration for the stress study [18]

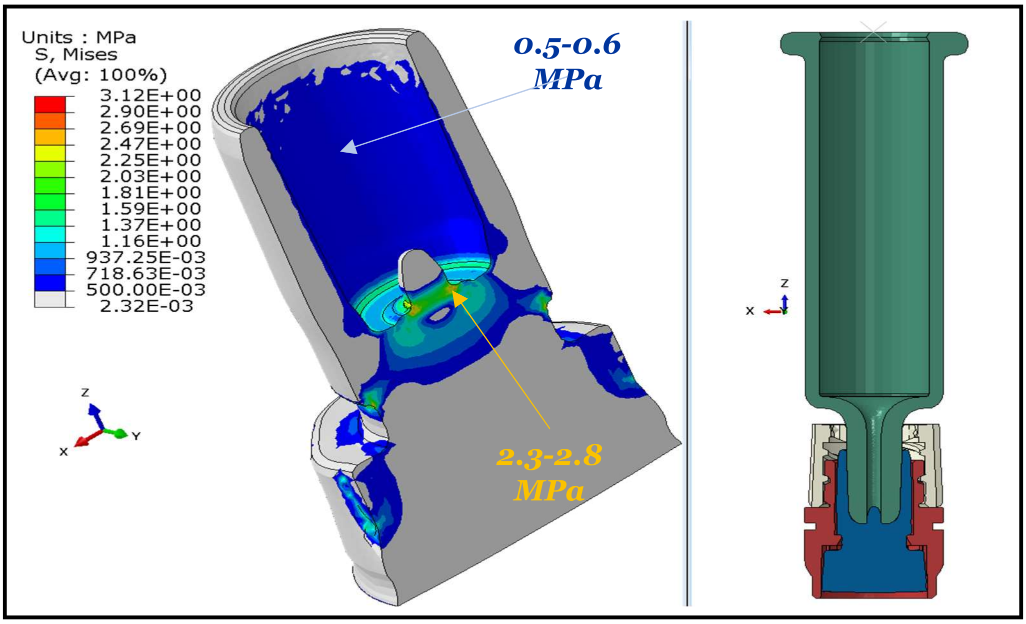


Figure 13 : Stress repartition on nominal barrel (1) [18]

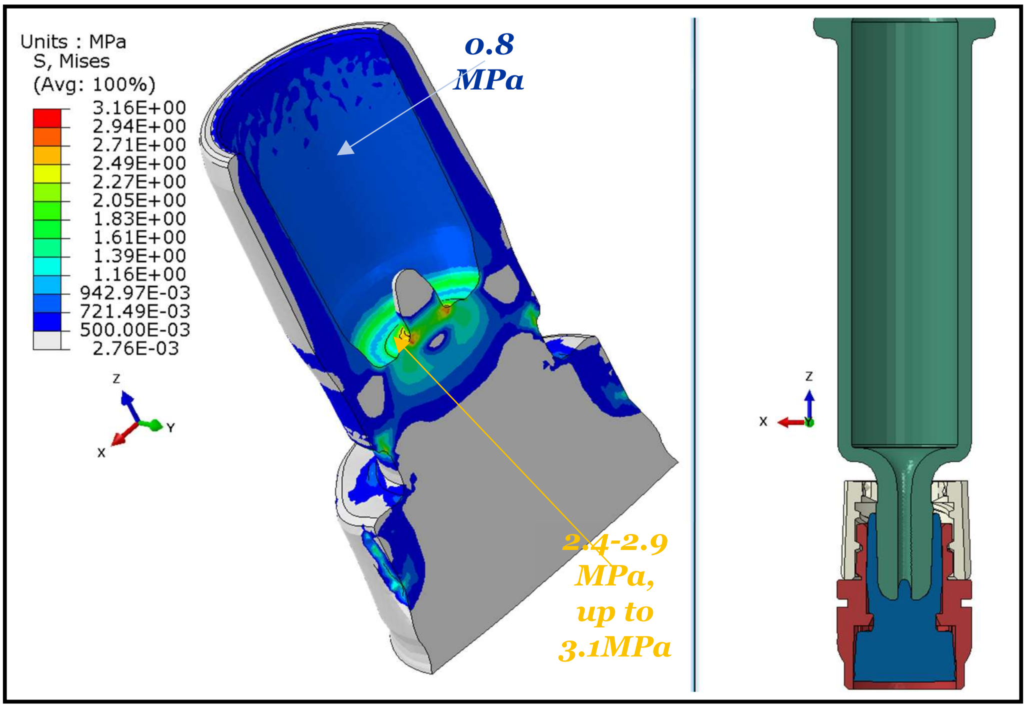


Figure 14 : Stress repartition on enlarged barrel (1) [18]

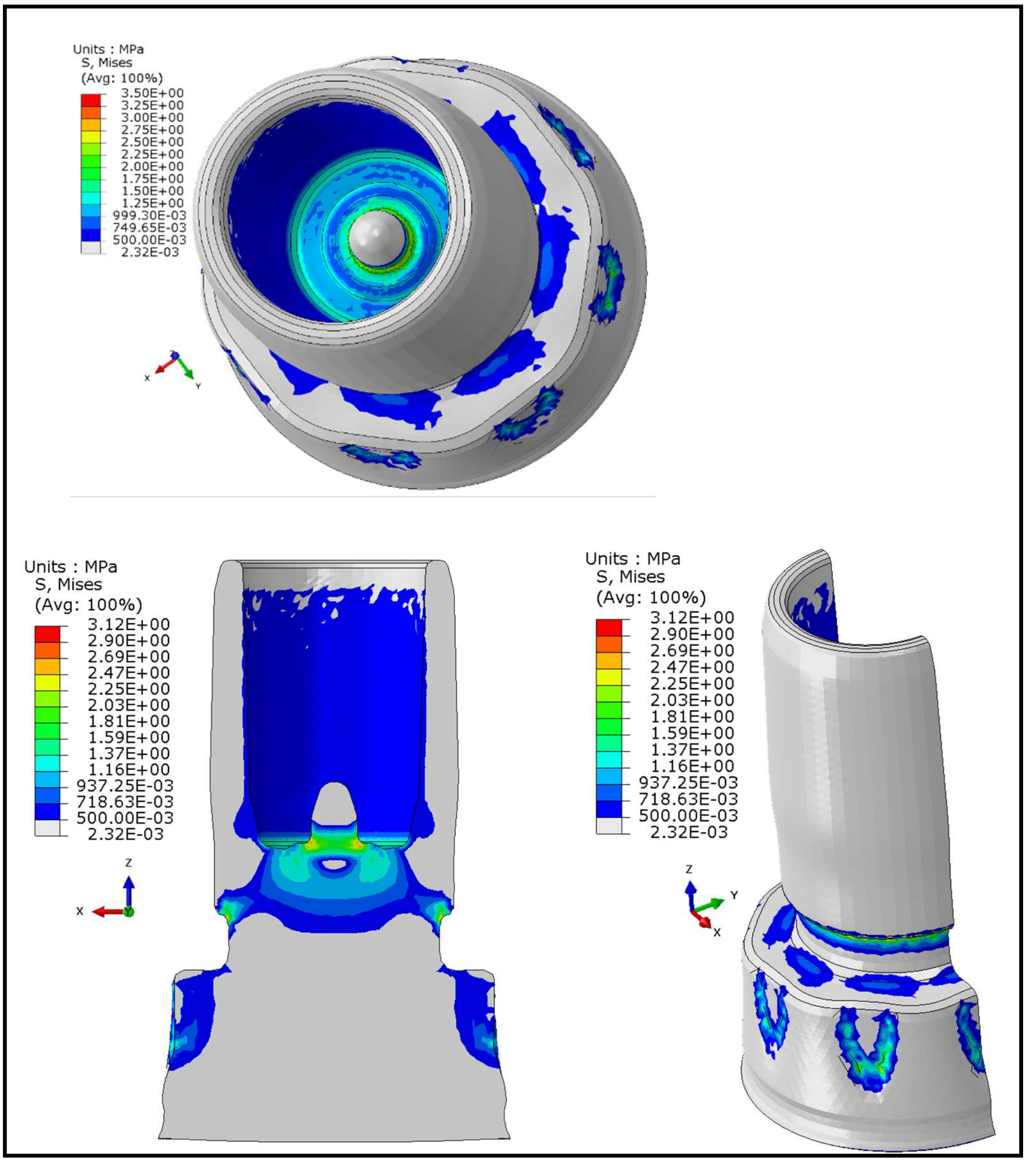


Figure 15: Stress repartition on nominal barrel (2) [18]

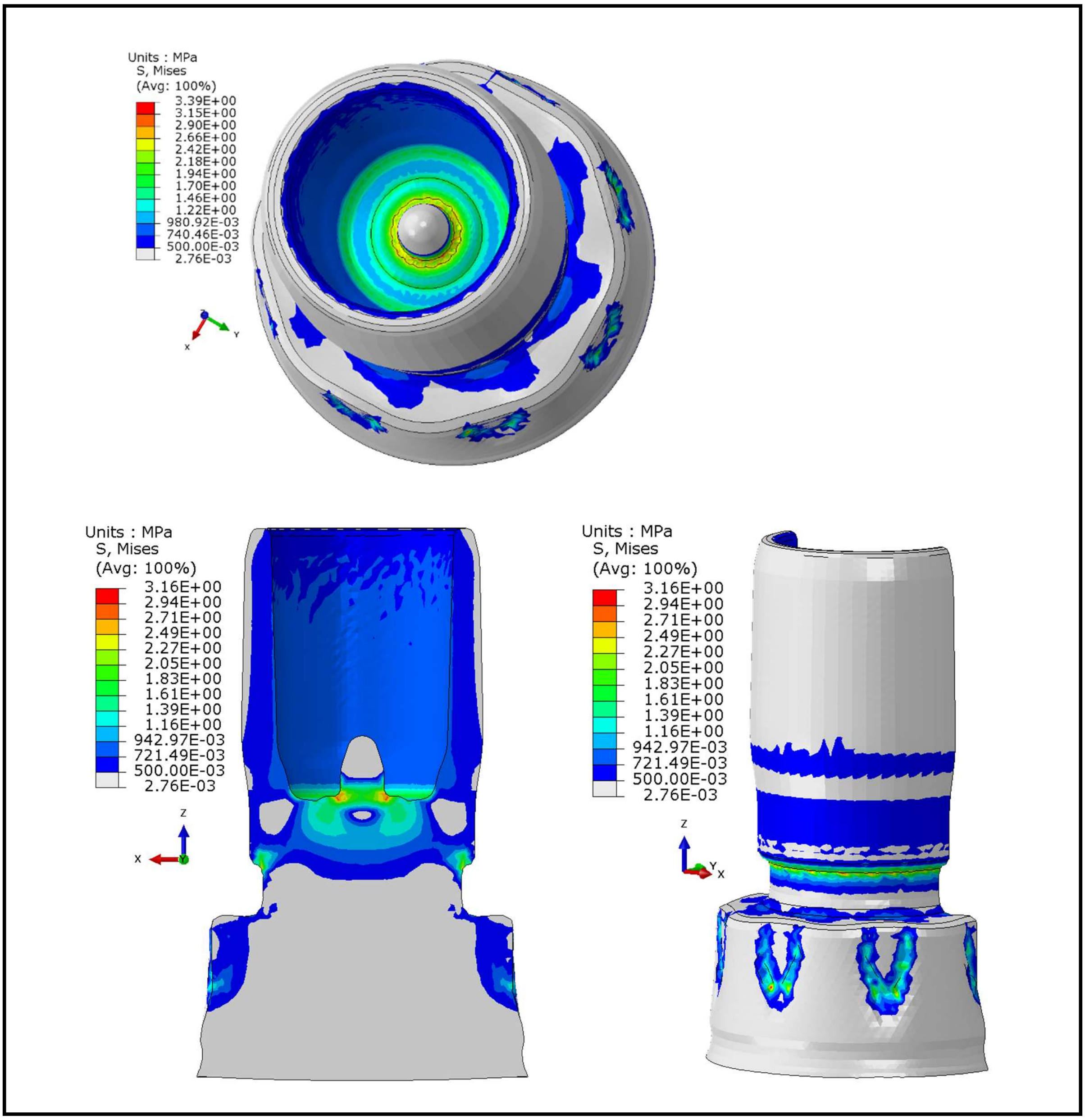


Figure 16 : Stress repartition on enlarged barrel (2) [18]

The enlargement of the barrel tip has a significant impact on the stress that is applied to the RiTC and most specifically on the external part. Indeed, it goes from 0.5MPa to 0.8MPa in the inner part of the RiTC and some stress can be seen in the external cylinder of the RiTC when the tip is enlarged while invisible for a nominal dimeter tip.

This is, as a result, a factor that must be tested during the ozone exposure.

3.1.2 Protection

RiTC will not degrade the same way whether it is packed in packaging or let alone in an ozone chamber. Indeed, all the packaging layer seems to play a role in the ozone resistance.

Even the plastic pieces can have an either compressive or protective effect. Here are the standard packaging layers that protects the syringe:

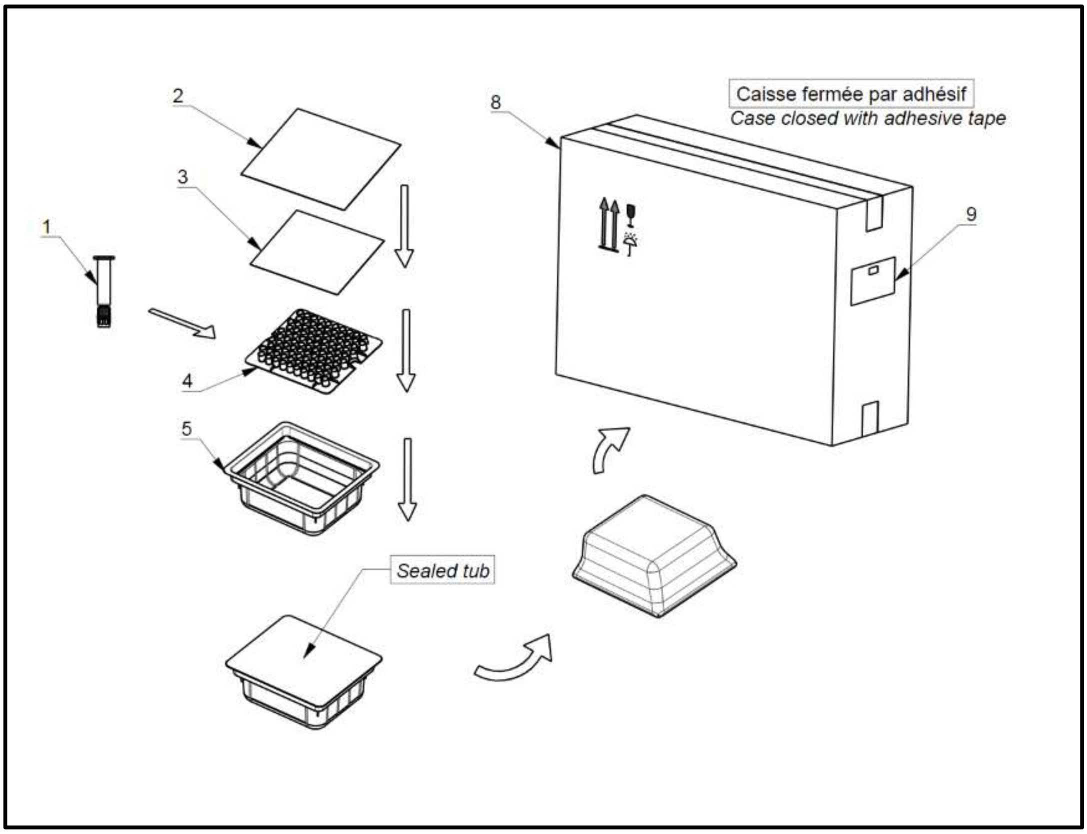


Figure 17 : Packaging scheme [19]

To understand the impact of ozone on the rubbers, these elements will need to be considered. The consequences of ozone exposition of single syringes and packed ones must be compared.

3.1.3 Concentration and Time

As ozonolysis is a phenomenon taking place when there is ozone and organic compounds, it seems interesting to understand the link between the concentration applied on the rubbers and the cracks / changes that occurs on it. At the same time, the exposure time is also important to determine a law between material properties and time/concentration.

The concentration to choose will be guided by the ISO standards. In this case, the elastomers are known to be very susceptible to degradation. As a result, 250ppb +/- 50ppb, is the adequate environment. Thus, it is interesting to observe the behaviour of these samples over higher concentrations like 500 ppb +/- 50ppb.

3.2 Characterization

Now that the parameters of the tests are known, it is necessary to think about the characterization that can be done on the rubbers.

There are mainly divided in three parts: Visual, Functional and Material properties.

3.2.1 Visual characterization

Visual characterization is a way to verify the presence of cracks on the outer part of the tip cap. This precision is important because inner and outer cracks are very different and lead to different functional or material aftermaths. As a result, a non-destructive way to look at the tip cap is to use microscopes.

One of the most common used one at BD is the numerical microscope from Keyence named VHX. There are several models with higher or lower precisions. I chose to work on the VHX-7020.

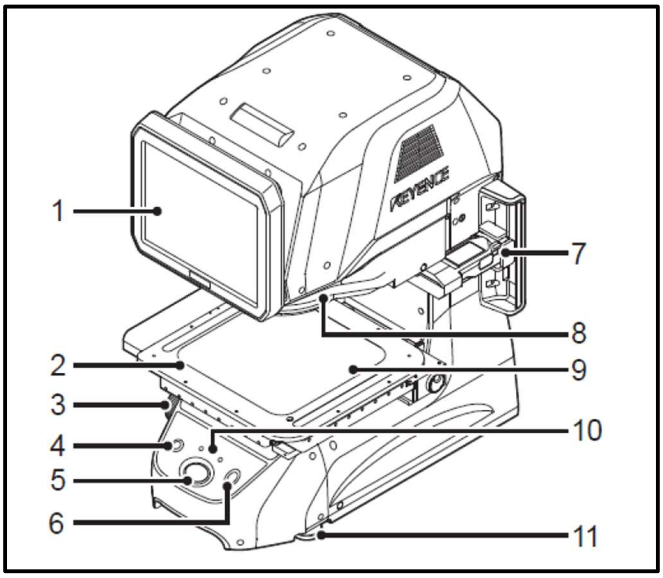


Figure 18 : Keyence VHX scheme [20]

The rotation of the microscope lead to the ability to create rotating pictures and interesting angles such as below:

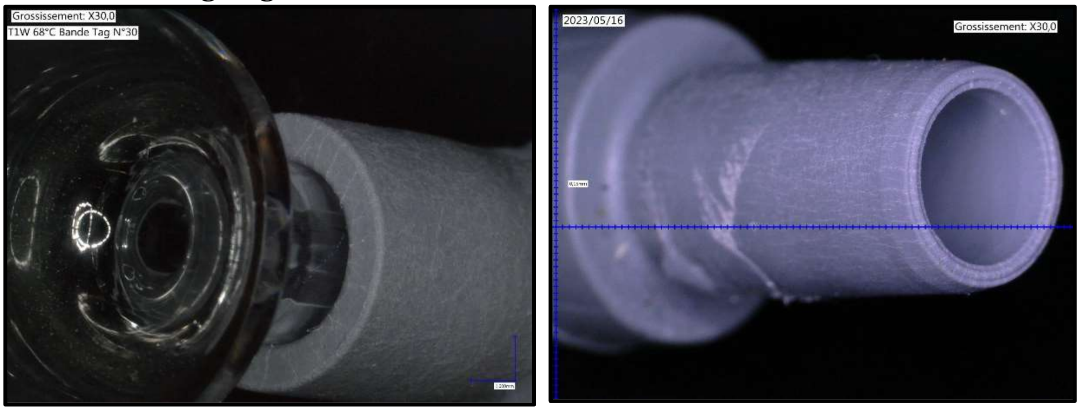


Figure 19 : VHX examples

Even if the device is not calibrated, it is still able to make indicative measurements to analyse the dimensions of cracks.

3.2.2 Functional characterization

Functional characterization are the tests that can check if the syringe is still usable with respect to a specification. There are dozens of specifications related to different parts of the syringe: Size, force needed to unscrew, force needed to unplug the tip, glass resistance, container closure resistance…
Not all these tests are linked with the RiTC, that is why a bright selection of tests must be done.

Moreover, some tests are validated which means that they give a certification to the customer that the product meets the expected level of performance. In this context of investigation, it is useful to fit with the norms, by performing validated tests but also to look more into details with other tests.

Here are the characterizations that were done:

3.2.2.1 Container Closure Integrity

This is what is called as an attribute test which means that it is either 'Pass' or 'Fail'. It is a validated method and is the bigger scope test. This test is usually 100% 'pass' with exceptions when there are very big pins on the tip cap which can lead to 'fail' but it is very rare.

The test is performed with empty syringes to check the tip cap.
The test aims to check the product integrity after vacuum.

Syringe is plunged in a methylene blue solution; result is pass if no methylene blue is observed inside the syringe after vacuum cycle.

Vacuum: -350mbars ±10mbars in relation to the atmospheric pressure (which depend on the testing site).
Vacuum duration: 16 hours.

Positive samples are not needed anymore as it was used to ensure that the vacuum had been done in the vacuum chamber. It is replaced by vacuum chamber pressure curve recording.

In case of special treatment as ETO or steam sterilization, aging, hood study, samples should remain at ambient temperature at last 12 hours before performing the test.[23]

3.2.2.2 Closure system liquid leakage test with compressed air pressurization system

It is mainly designed to verify whether the closure system is able to withstand any potential overpressure inside the syringe during the filling process or during transportation (ISO11040-4:2015(E) §G.2). [22]
1.1bars compressed air pressure is applied for 5 seconds into a syringe filled with Water For Injection (WFI). Conditions are based on ISO11040-4:2015(E) §G.2.
The test is passed if the tip caps are not falling off and/or if no droplet is visible around the external surfaces of the closure system (wet surface of tip cap or needle shield).

ATEQ bench with a 500Pa range is used to measure the leak pressure. Air is pushed inside the barrel with an iron plunger rod with a conical tip.

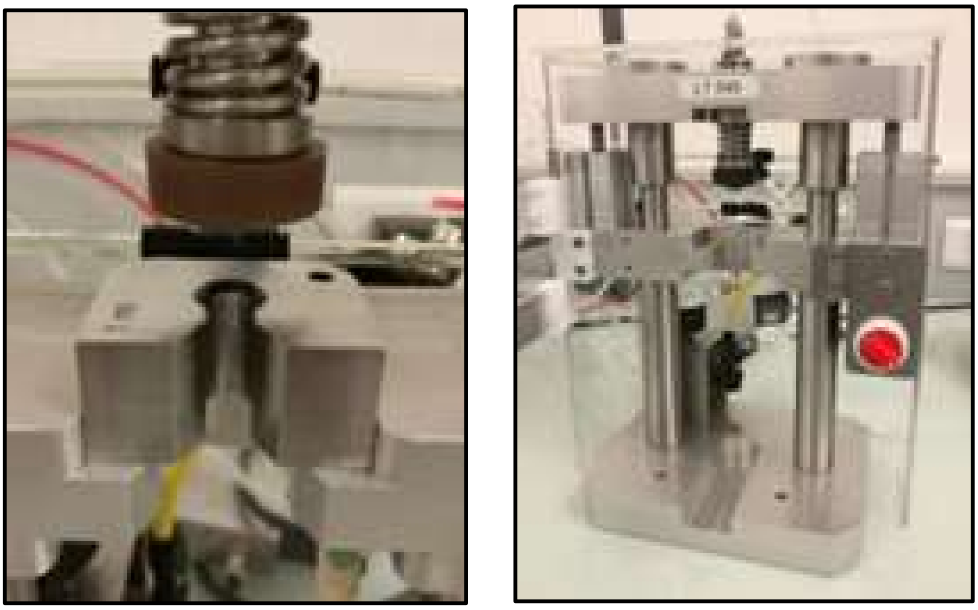


Figure 20 : Leak ATEQ principle [21]

The output of this test is double, if the syringe leaks, it is automatically ejected and marked as ‘Fail’. Otherwise, a pressure (in Pa) is measured and there is an acceptance limit (~100Pa) to mark the sample as ‘Pass’.
It is a validated test which is semi quantitative. In fact, there is a pressure value but the information that is taken out of this test is an attribute test ‘pass’ or ‘fail’. It is still important to perform it to fit with the norms.[21]

3.2.2.3 Helium leak detection

This is another leak test using helium as the reference gaz. It is performed using a device called ASM2000.

The ASM2000 has two functions: the administration of helium (the tracer gas) and the detection of this gas. The assembled syringe is placed as the only barrier between these 2 elements. Helium detection is evidence of leakage from the syringe at the interface of the syringe under test.

Here is how it works:

Emptying the detection chamber	Switching on the detector	Emptying the loading chamber	Tracer gas injection and measurement

Figure 21 : Helium leak functioning system (1) [24]

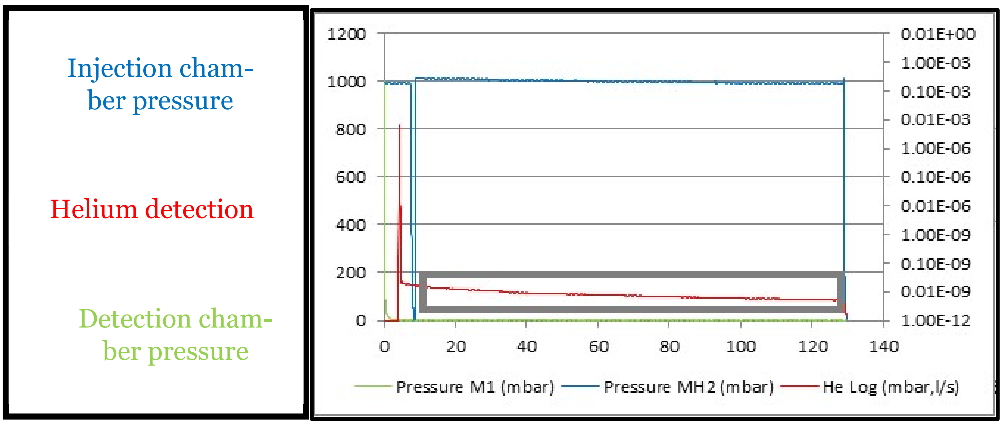


Figure 22 : Helium leak functioning system (2) [24]

The "duration" leakage flow measurement time, shown by the grey rectangle, allows us to observe:
- The leakage profile (graph above stabilized, acceptable leakage)
- permeation phenomenon
- an unstable signal (e.g. pin forgotten or incorrectly positioned) [24]

3.2.3 Material characterization

Apart from knowing if the sample has defects that lead to leakages, it is as well interesting to analyse and characterize the material properties of the rubber such as its mechanical properties or some information about its chemical properties.
Among all the tools available, I had to make choices depending on the time needed to make these characterizations, the legitimacy regarding the project and the expense engaged.
I decided to work on this following material characterization:
Tensile Strength tests, Swelling tests and Dynamic Mechanical Analysis.
Here are some deeper explanations about these methods.

3.2.3.1 Tensile Strength

The aim of this test method is to assess the elastic properties of rubber as moulded in the real component.
It determines the tensile stress properties of vulcanized rubbers real parts.

Test method is only for investigation, and it will not be used in design verification activities. No validation is required for such investigation test method.
Cut samples in real part are stretched in a tensile-testing machine at a constant rate. Readings of tensile strength, elongation at break, stress at

given elongation and elongation at a given stress are taken during the uninterrupted stretching of the test piece and when it breaks.

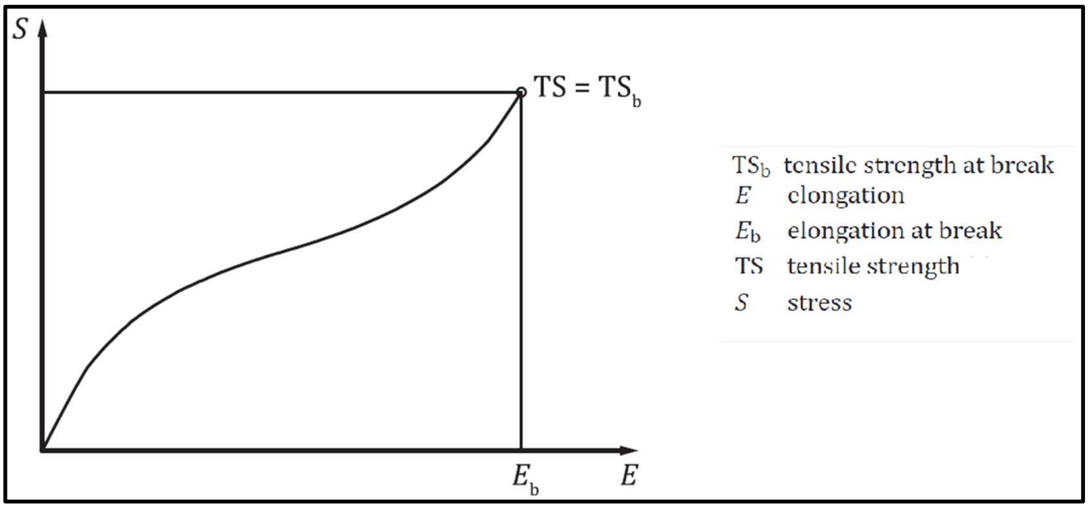


Figure 23 : Illustration of tensile terms [2]

Figure 24 : Tensile Strength jaws [25]

To perform tensile strength test on the RiTC, it has been mandatory to cut a rectangular piece of the sleeve. The piece was then dimensionally measured and tested.
This test gives different data that can be analysed independently: The maximum load before breaking, the tensile strain at maximum load, the tensile stress at maximum load and the stresses at M100-M200-M300 and M400

which represent the force applied to obtain a 100%-200%-300% or 400% elongation. [25]

3.2.3.2 Swelling method

The purpose of this method is to compare semi-qualitatively the reticulation state of several rubber tip caps putting them in a solvent. Indeed, it gives information about the reticulation state through a percentage but does not describe it precisely.

It consists in putting the samples to swell in xylene for 48±2h.

(The swelling period of 48h is the only validated period but some internal documents detailing swelling investigations shows that longer period can be used if needed and if it is the same for each considered sample.)

After swelling, the samples are strained vigorously from the solvents for 90 seconds, transferred into a closed weighing container and the final weight is recorded: **Swelling mass % result**

Then the containers are either cleaned or let to dry to obtain the soluble fraction% and corrected swelling mass % (not validated results)

In this latter case, the solvent is poured back in the swelling container to evaporate until constant weight (often 48h to 96h are necessary).

Then the soluble fraction (which concerns both the soluble additives of the rubber formulation and the non-bounded elastomer fraction that migrate to the solvent and do not contribute to swelling) is weighted

Soluble fraction% result

Corrected swelling mass% result [27]

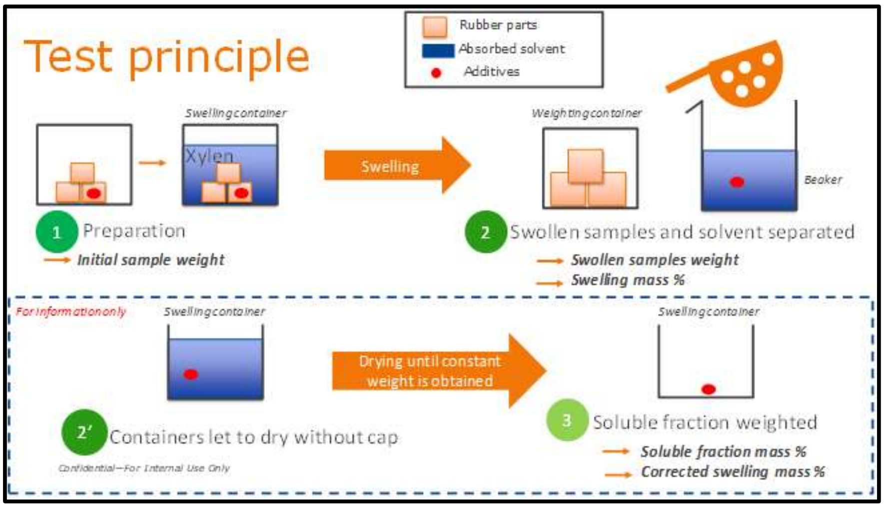


Figure 25: Swelling Method Principle [27]

3.2.3.3 Dynamic Mechanical Analysis

Dynamic Mechanical Analysis is a rheology tool which means that it deals with deformation and flow of materials. It is usually used as below:

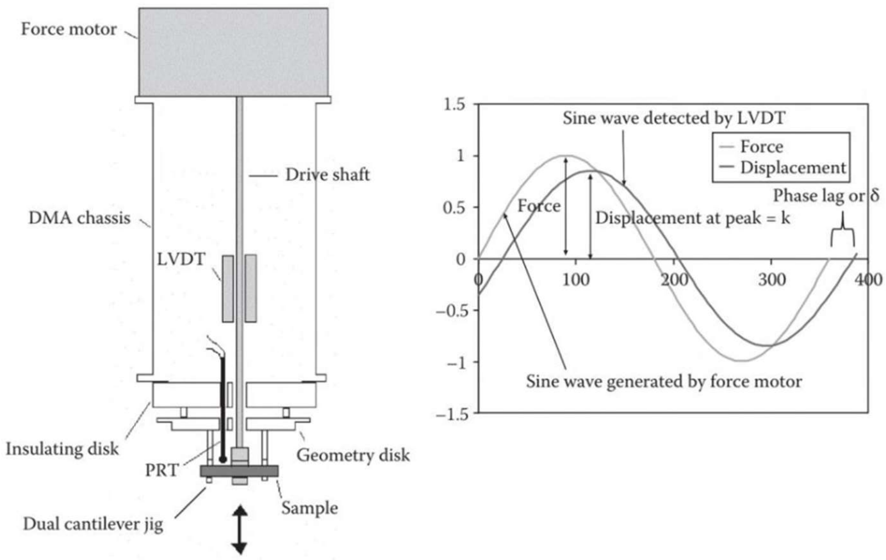


Figure 26 : DMA mechanics [28]

The DMA supplies an oscillatory force, causing a sinusoidal stress to be applied to the sample, which generates a sinusoidal strain. By measuring both the amplitude of the deformation at the peak of the sine wave and the lag between the stress and strain sine waves, quantities like the modulus, the viscosity, and the damping can be calculated. The schematic shows the arrangement of many DMAs where the motor is above the furnace. [28]

3.3 Test plan

Now that the characterization is explained, the focus will be set on the samples chosen, their preparation and the sample size for each configuration.

3.3.1 Configurations

There are mainly based on the influences that needed to be tested:
To analyse the influence of the concentration, two of them have been chosen: 250ppb and 500ppb.
To understand the influence of time, and to create links with the ISO 1431-1, here are the time that were chosen: 8h, 24h, 48, 72h, 96h. Depending on the configuration, not all the exposure time were tested.

Since the stress appeared to be an important factor, it was decided to design barrels with different diameters: Nominal diameter, +0.07mm, +0.12mm and +0.27mm.
The protection of the packaging as well as the protection of the plastic parts play a role on the ozone exposure. As a result, here are the configurations that were tried: RiTC directly plugged on barrels, syringes in tubs, syringes in rondos, syringes in bags.
RiTC and PRTC were also tested alone to understand the impact of the tip of the barrel. (Pictures below)

All in all, there are around 10 configurations multiplied by 2 concentrations and 5 exposure time. Consequently, choices were performed to look at the most relevant configurations.

Here are the different configurations and packaging:

RiTC only

PRTC Only

RiTC on barrel

PRTC on barrel

Figure 27 : Configuration of samples

Bags

Rondos

Tubs

Figure 28 : Packaging configurations

3.3.2 Preparation of the samples

Samples were taken from the same batch which was composed of more than a thousand syringes ready to fill and sterilized. The goal was to limit the variations linked to the batch particularity. As a result, some the syringes have the following configuration: nominal diameter barrel tip assembled with a PRTC made of plastic part and a RiTC.
To isolate the RiTC, a disassembly was needed. To perform this, a tool was used to separate the PRTC from the barrel, then the complex RiTC + RC was unscrewed from the LLA. Finally, a metal finger led to the isolation of the RiTC.
Eventually, to reassemble PRTC with new enlarged barrels, there is a third tool that has been used to perform this.

Here are some pictures of the tools used:

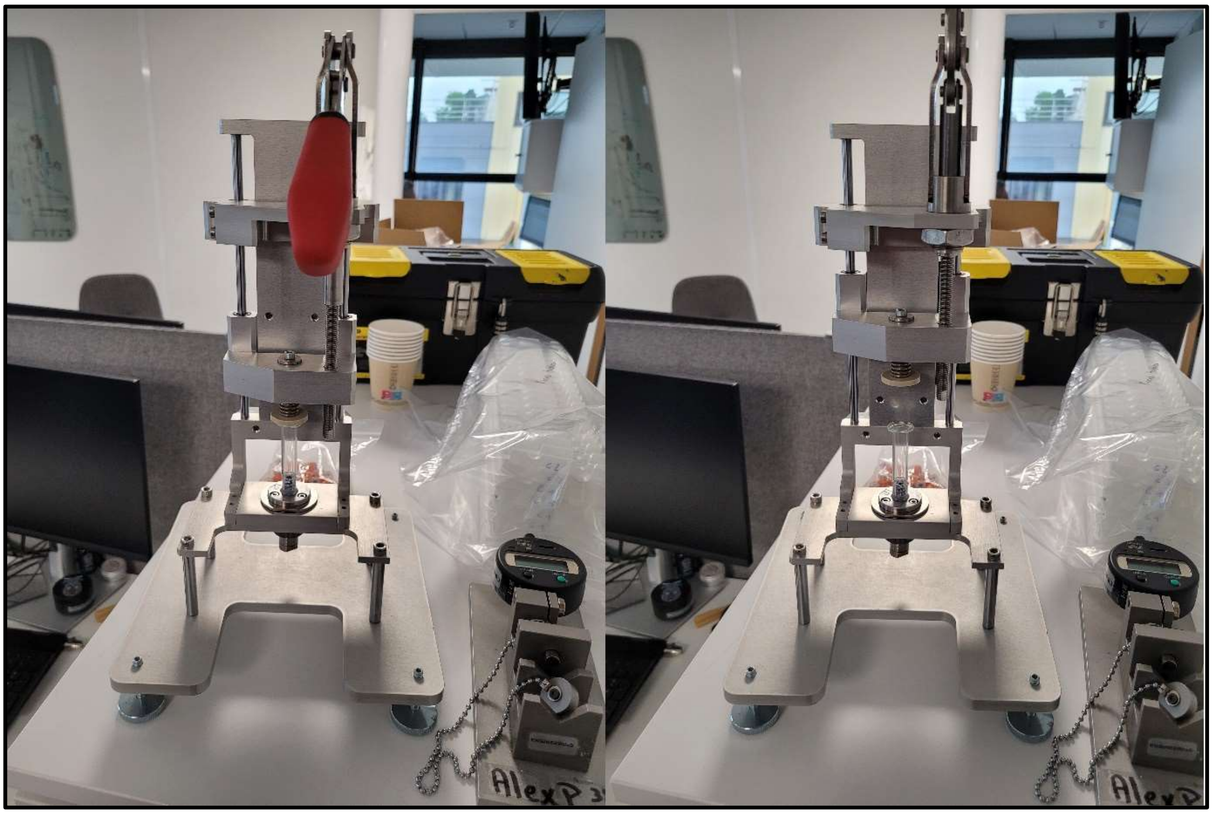


Figure 29 : Tool to assemble PRTC and barrel.

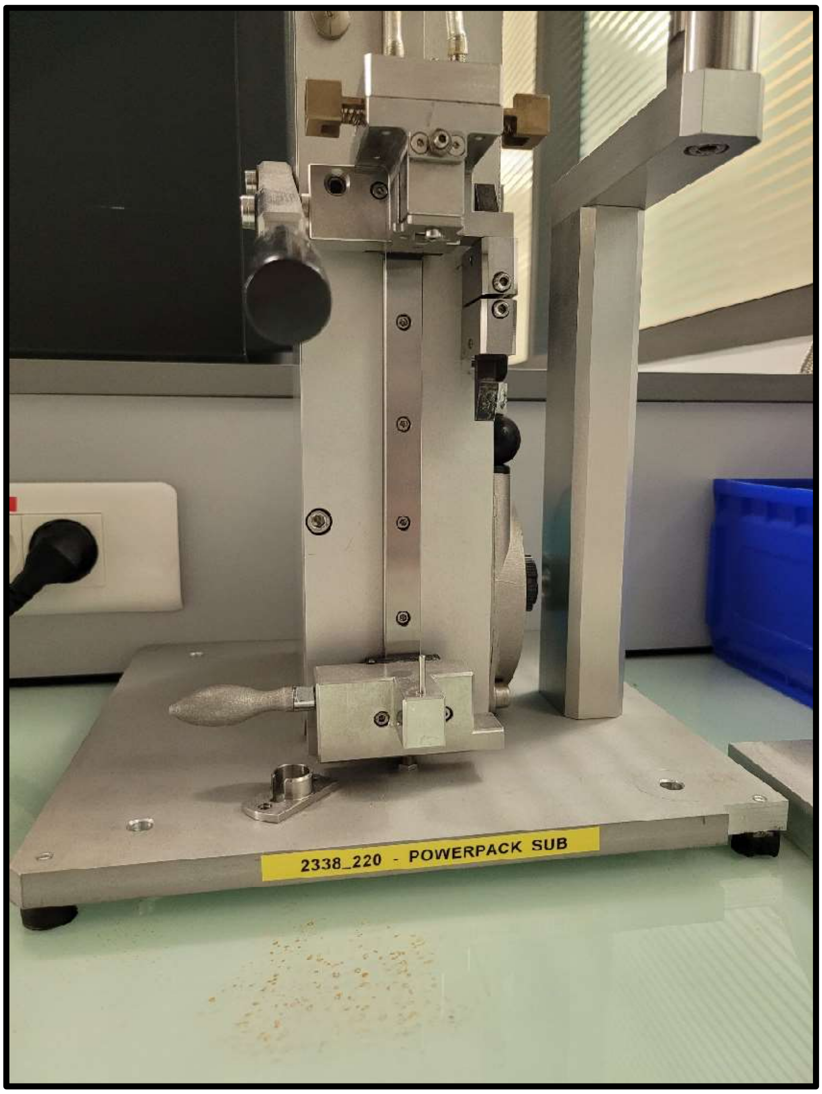


Figure 30 : Tool to remove the RiTC from the plastic parts.

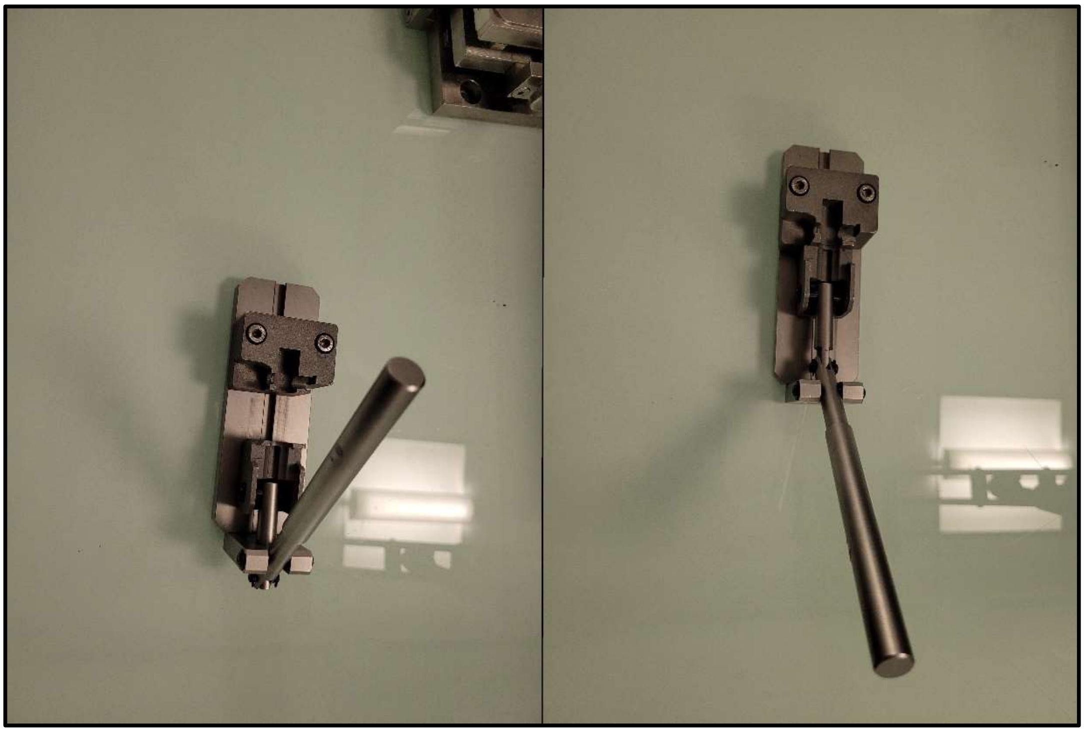


Figure 31 : Tool to remove the PRTC from the barrel.

Pieces were tested in an external laboratory in a cubic ozone chamber of 47x50x55cm with measurement instruments inside. The optimization of the volume led to the use of rondos instead of tubs. However, it induces packaging differences that could be analysed and understood. The two first exposition campaigns were realized with rondos as well as tubs while the two last were done using little bags with less protection against ozone.

Here are the details:

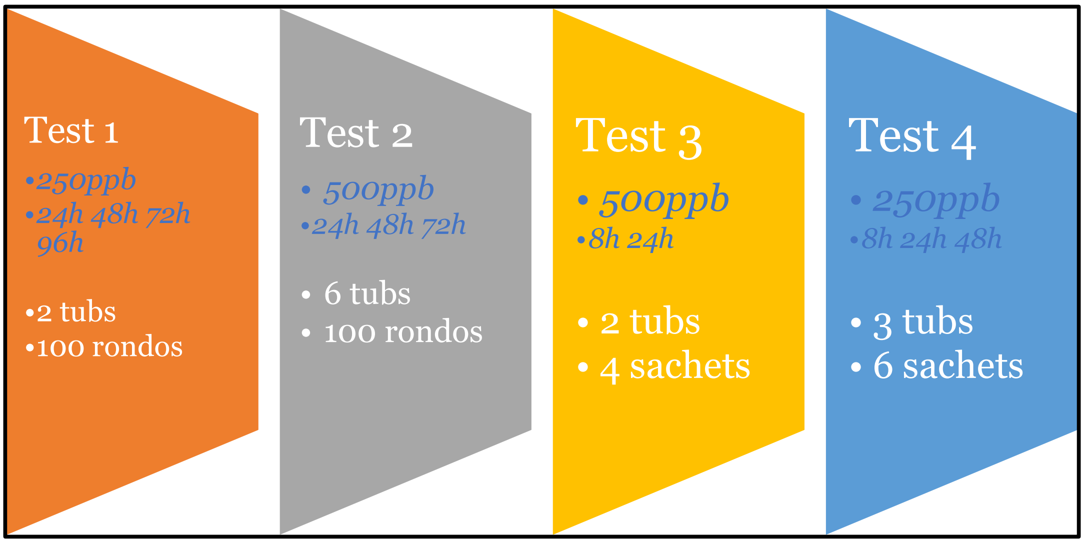


Figure 32 : Tests details

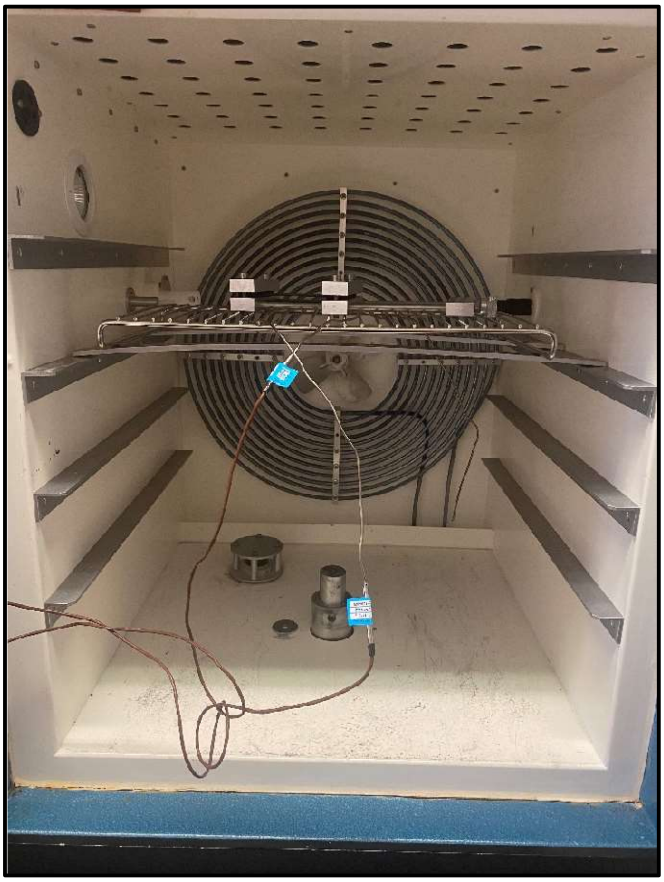


Figure 33 : Ozone chamber

3.3.3 Sample size

Depending on the characterization, the sampling required to obtain relevant results is not the same. For instance, attribute tests such as 'dye test' requires more samples tests than 'DMA' tests. However, the legitimacy of each test was also considered regarding the limitations of samples inside the ozone chamber.
Moreover, some considerations were judged as more relevant than others, so the sampling was higher.

Table 9 : Full names and surnames of the configurations

Full name	Surname	Reason
Syringes in tub	**Tub**	Impact of packaging
Syringes in rondos with nominal diameter	**PRTC 0,0**	Impact of protection
Syringes in rondos with enlarged diameter (+0,27mm)	**PRTC 0,27**	Impact of stress
RiTC assembled on barrels without plastic parts with nominal diameter	**RiTC 0,0**	Impact of protection
RiTC assembled on barrels without plastic parts with enlarged diameter (+0,27mm)	**RiTC 0,27**	Impact of stress
Syringes in rondos with enlarged diameter (+0,12mm)	**PRTC 0,12**	Impact of stress
RiTC assembled on barrels without plastic parts with enlarged diameter (+0,07mm)	**RiTC 0,07**	Impact of stress
RiTC assembled on barrels without plastic parts with enlarged diameter (+0,12mm)	**RiTC 0,12**	Impact of stress
RiTC assembled on barrels without plastic parts with enlarged diameter (+0,27mm) packed inside a bag made of plastic and a permeable layer	**RiTC 0,27 in bags**	Impact of packaging
RiTC assembled on barrels without plastic parts with nominal diameter packed inside a bag made of plastic and a permeable layer	**RiTC 0,0 in bags**	Impact of packaging

The next Table will explain the sampling for only one concentration and one exposition time which mean that the real sampling required must be multiplied by a value from 7 to 10.

Table 10 : Sampling for the configurations

	Sampling
Visual	5
Container Closure Integrity	15
Leak ATEQ	15
Helium leak test	20
Tensile strength	15
Swelling	24
DMA	5

Assuming that the following temperature/concentration will be applied (250ppb: 24h / 48h / 72h /96h 500ppb: 24h / 48h / 72h), here will be the real sampling:

Table 11 : Sampling multiplied by the exposure time and the concentrations chosen.

	Tub	PRTC 0.0	PRTC 0.27
Visual	35	35	35
Container Closure Integrity	105	105	105
Leak ATEQ	105	105	105
Helium leak test	140	140	140
Tensile strength	105	105	105
Swelling	168	168	168
DMA	35	35	35
TOTAL	693	693	693

Now that all the configurations and characterizations are explained, results need to be analyze to draw conclusions on the impact of ozone on RiTC.

4 Results

The results will be explained characterization after the other. Inside each characterization analysis, different factors will be exploited like the influences and the limitations of the results.

As explained above, there are mainly three groups of characterizations. They will be considered separately.

4.1 Visual characteristics

The visual analysis has multiple goals, it is a way to testify the presence of ozone cracks but also to describe them to characterize them if there are differences from one group to another.
Let's look at the presence of cracks over the impact of the packaging and the impact of the stress.

Table 12: Packaging influence over the visual characterization. Green squares represent the absence of cracks, red squares the presence of cracks while grey squares means that the configuration has not been tested.

TUBS	8h	24h	48h	72h	96h
250ppb					
500ppb					

Rondos	8h	24h	48h	72h	96h
250ppb					
500ppb					

Bags	8h	24h	48h	72h	96h
250ppb					
500ppb					

Table 13 : Stress influence over the visual characterization

RiTC 0,27mm	8h	24h	48h	72h	96h
250ppb					
500ppb					

RiTC 0,0mm	8h	24h	48h	72h	96h
250ppb					
500ppb					

Here are some of the cracks that can be obtained from the ozone exposure:

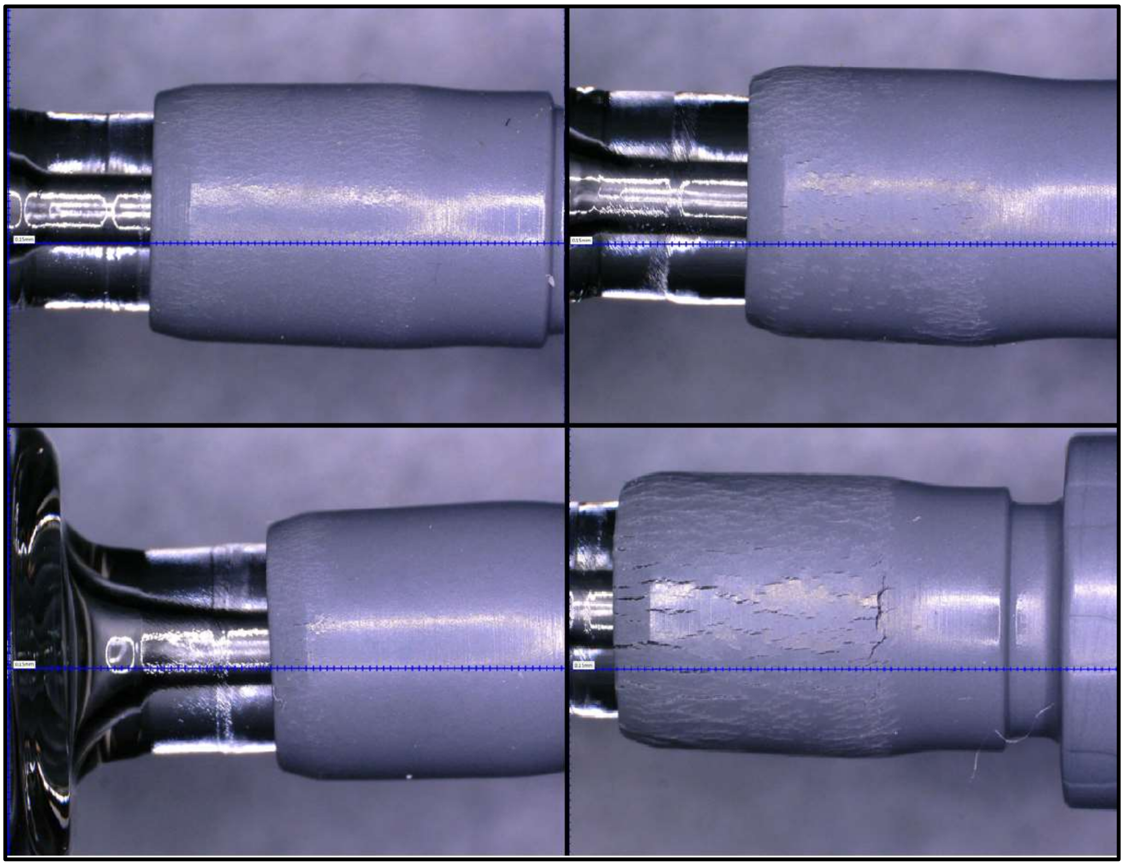


Figure 34 : Different types of cracks (a) RiTC 0,27 96h 250ppb (b) RiTC 0,27 96h 250ppb (c) PRTC 0,27 72h 500ppb (d) RiTC 0,27 72h 500ppb

From one configuration to another, there are cracks patterns that can be observed. (a) represents tiny cracks that are invisible with the naked eye and who looks like blooming which is another phenomenon where antioxidants are taken out of the rubber through the look of a white powder at the surface of it. (b) patterns is more visible and the last step can be represented by the image (d) where cracks can be observed either horizontally and vertically. Eventually, the cracks obtained after ozone exposure for PRTC syringes (image (c)) are only located at the edge of the RiTC as seen below.

Figure 35: Location of the cracks on PRTC syringes

However, not all the rubbers from the same configurations have cracks, it varies between 0% and 80% depending on the configurations.
Here are values for RiTC 0,27mm: (The other values are in the appendix if needed)

Table 14 : Cracks proportions on RiTC 0,27

RiTC 0,27mm	8h	24h	48h	72h	96h
250ppb			13/15 (bags)	13/15 (bags)	4/36 (rondos)
500ppb	7/9 (bags)	6/9 (bags)	7/9 (bags)	12/36 (rondos)	

Several things can be analysed from these data.
First, the more rubbers are exposed to ozone, the more cracks appear at the surface of the rubber. Due to the thinness of the tip cap jupe, the cracks are transversal which mean that they can either be seen from the inner and the outer part of the rubber. However, thin cracks do not penetrate deeply in the

thicker part of the rubber. It means that the attack happens from the outside of the rubber.
Second, the impact of the packaging can be clearly seen with the Table 12, no cracks have been identified when syringes were packed in tubs while rondo packaging seems more resistant to ozone exposure than bag packaging.
Third, no RiTC assembled on nominal barrel tip have suffered from cracks while the one assembled on enlarged tips did. The influence of stress on ozone resistance can be seen through the visual inspection.
Fourth, when the concentration of ozone seen by the samples, cracks are more present or present sooner than for lower concentrations.

4.2 Functional characteristics

Now that the visual has been inspected, let's look further in the functionality of the material to understand the aftermath of ozone exposure on the quality of the rubber.
From the larger specification to the thinner one, Dye Test, Ateq Leak Test and Helium Leak Test will be analysed.

4.2.1 Dye test

Table 16 summarizes the sampling for the dye test as well as the results. Usually, attribute tests require more samples to be tested to conclude that there are no leaks in the syringes but considering the samples limitations, it has been decided not to overpass 30 samples for each configuration.

Table 15 : Results for Dye test

Concentration	Time	Tub	PRTC 0,0	PRTC 0,27
0 ppb	0	Pass	Pass	Pass
250 ppb	8h	Pass	Pass	Pass
	24h	Pass	Pass	Pass
	48h	Pass	Pass	Pass
	72h	Pass	Pass	Pass
	96h	Pass	Pass	Pass
500ppb	24h	Pass	Pass	Pass
	48h	Pass	Pass	Pass
	72h	Pass	Pass	Pass

Even if these results are not surprising since this test only detects very big leaks, it is still reassuring to obtain these results.
It means that the ozone cracks obtained after 250ppb and 500ppb have no impact on the first leakage test.
It can be justified by the fact that the cracks are mainly located on the skirt of the RiTC, which is not the first component to assure the container closure integrity. It is in fact the nipple that can be observed on Figure 13 to Figure 16.

4.2.2 ATEQ Leak Test

The results of the ATEQ Leak test are not so different from the dye test. Indeed, Table 16 represents the pass/fail results of this functionality tests while Table 17 summarizes the mean values of pressure measured in Pa.

Table 16 : Results for Leak test

Concentration	Time	Tub	PRTC 0,0	PRTC 0,27
0 ppb	0	Pass	Pass	Pass
250 ppb	8h	Pass	Pass	Pass
	24h	Pass	Pass	Pass
	48h	Pass	Pass	Pass
	72h	Pass	Pass	Pass
	96h	Pass	Pass	Pass
500ppb	24h	Pass	Pass	Pass
	48h	Pass	Pass	Pass
	72h	Pass	Pass	Pass

Table 17 : Detailed results for Leak test

Concentration	Time	Tub	PRTC 0,0	PRTC 0,27
0 ppb	0	3.4	N/A	N/A
250 ppb	8h	N/A	0,7	0
	24h	0,7	0,1	0,4
	48h	N/A	0	0
	72h	0,3	0,5	0,2
	96h	1,9	0	3,3
500ppb	24h	1,7	0,5	2,9
	48h	2,1	1,8	3,9
	72h	3,4	N/A	N/A

A mean value of ~10Pa is mostly due to measurement imprecision created by the measuring tools. As a result, it can be seen as an absence of leaks.
It represents another proof of great container closure integrity.
Let's look at more precise measurements to investigate smaller leaks.

4.2.3 Helium Leak Test

For this test, 15 to 30 samples have been tested by configurations. In fact, it is an unvalidated method and the consistency of the measurements are not well known yet. Since the results were expressed in mbar.l/s, most of the results were between 1e-10 and 9e-10mbar.l/s. For reading ease, all the results were multiplied by a factor 10e12 which corresponds to fbar.l/s.

The first figures to analyse represents the evolution of helium leak over time in different concentrations and configurations.

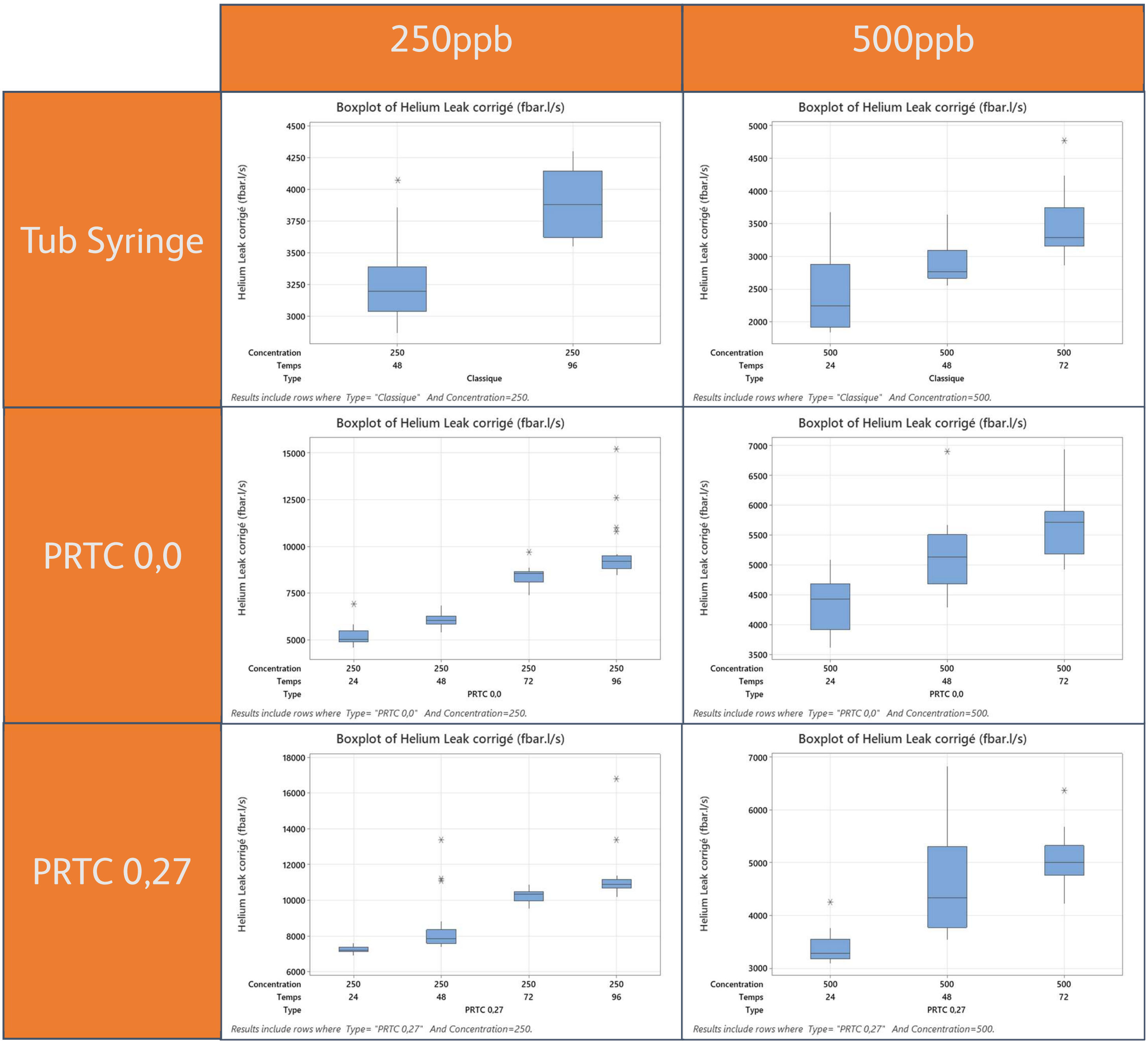


Figure 36 : Helium leak on time/concentration comparison. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile.

For all the configurations tested here, the helium leak results are higher over the time which mean that the more a sample is exposed to ozone, the more the leak pressure is high. When looking at the boxplots, not all the configurations seem to follow the same increasing rate, as a result, it can be interesting to look at the regression equation. However, the population observed are generally not enough alike to be able to create a regression equation which makes sense.

Figure 37 represents the comparison between concentrations for a single configuration over time.

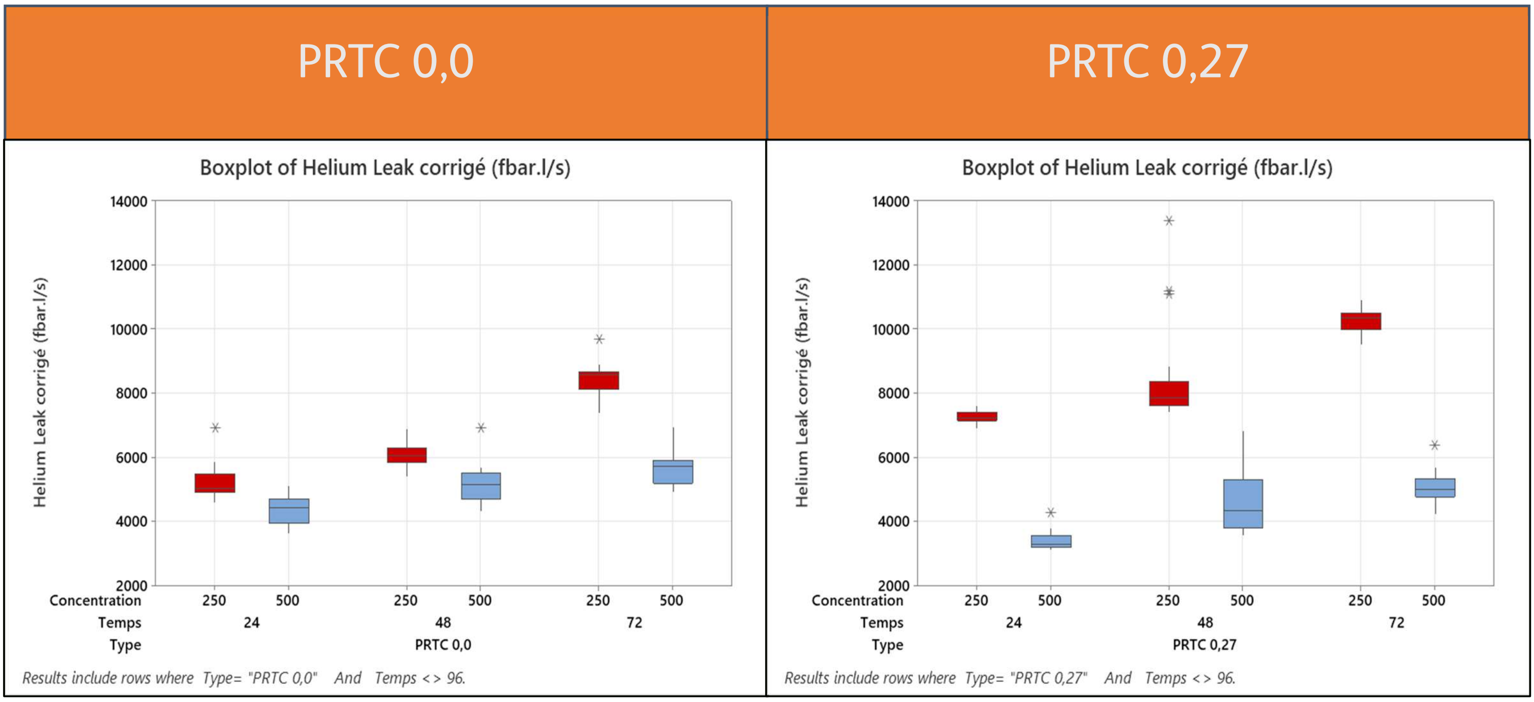


Figure 37 : Helium leak Concentration comparison. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile. Red boxplots stand for 250ppb concentration while blue boxplots represent a 500ppb concentration.

The red boxplots represent a 250ppb exposition while the blue boxplots represent a 500ppb exposition. An interpretation of these results can be that the more the concentration is high, the less the sample leaks. Looking at the literature, it is not logical to obtain this can of result and reasons will be given at the end of this part.

Figure 38 shows the comparison of helium leaks between syringes that were packed in tubs and syringes packed in rondos.

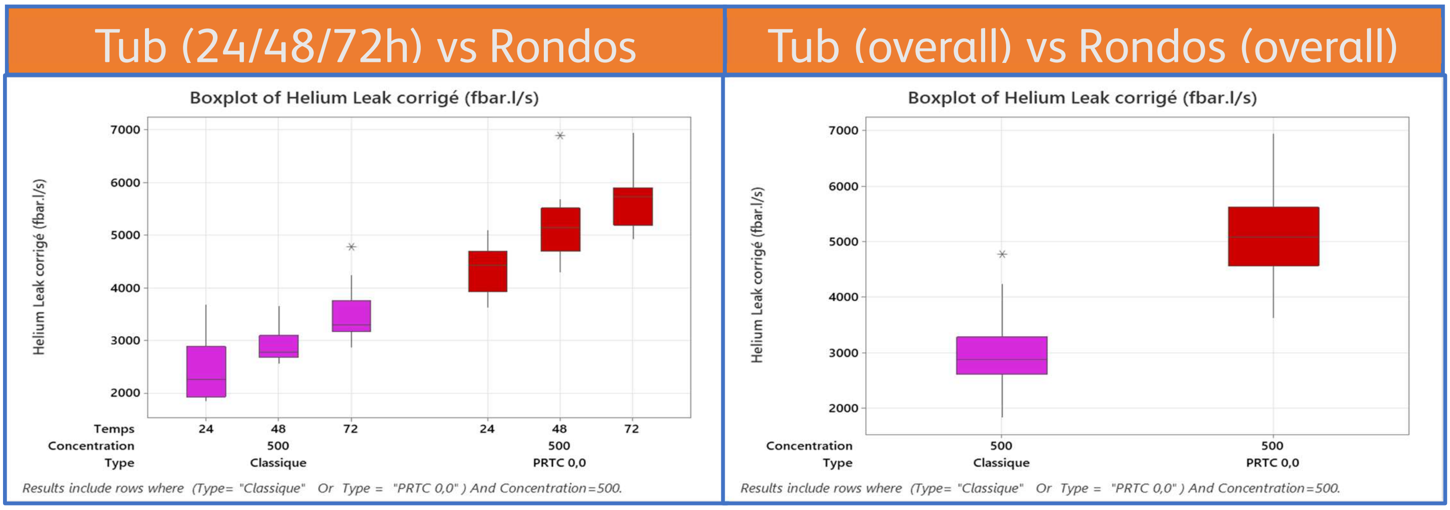


Figure 38 : Helium leak Packaging comparison. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile

The more samples are packed, the less the sample leak.
Another comparison of protection can be seen through the PRTC/RiTC comparison:

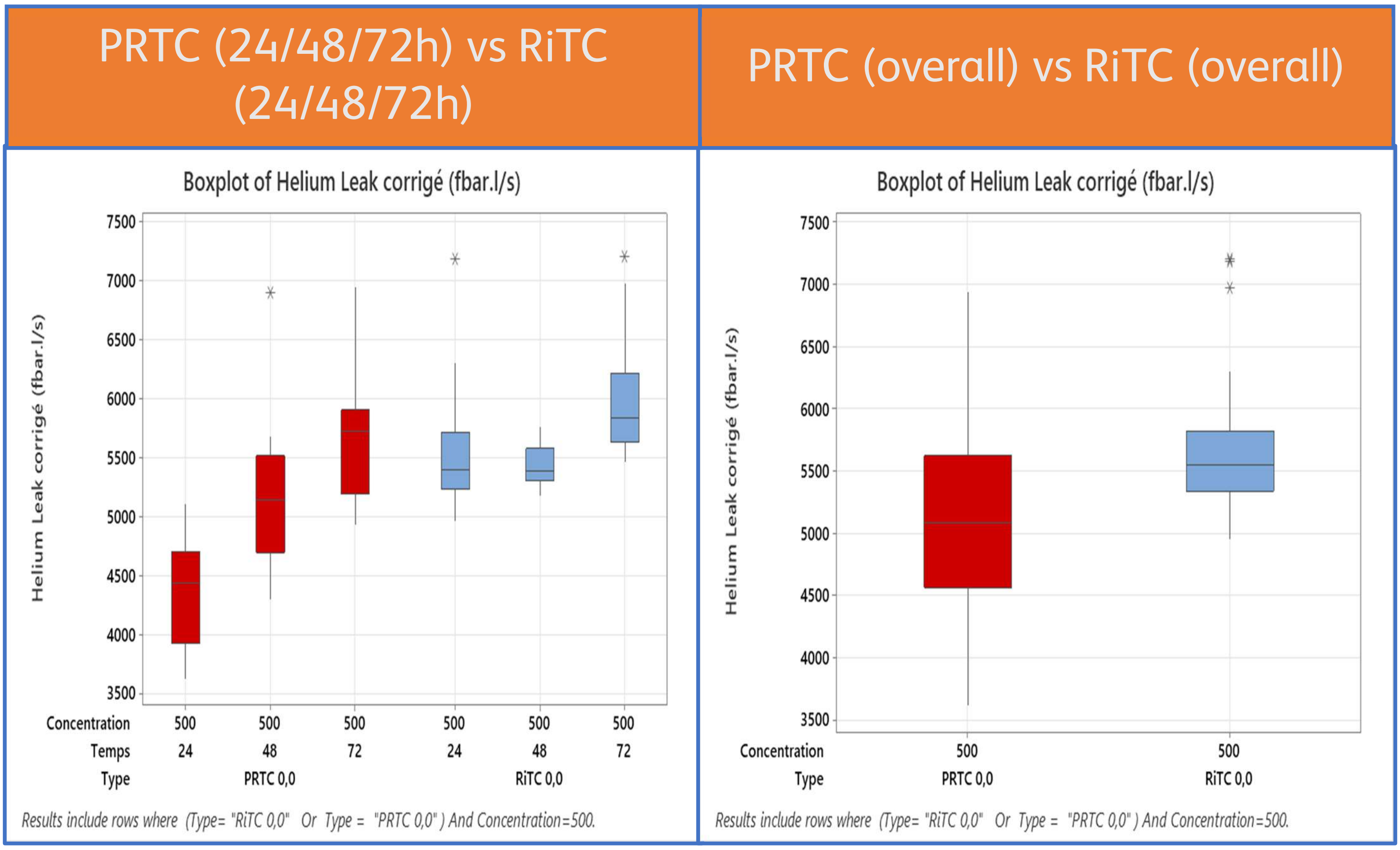


Figure 39 : Helium leak Protection comparison. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile

From these graphs, the more the sample is protected by plastic parts, the less it leaks.
Let’s summarize the foundlings regarding helium leak test:

Table 18 : Helium leak summary

Concentration	More concentration ≠ More leaks
Time	More time = More leaks
Stress	More stress = More leaks
Packaging	More packaging = Less leaks
Protection	More protection = Less leaks

All these elements helps to compare each configuration from one to another but the most important comparison is the one with the specification which is given by the Kirsh criteria and the ASM criteria which are respectively 6.10^{-6} mbar.l/s and 1.10^{-7} mbar.l/s. Figure 40 depicts this comparison.

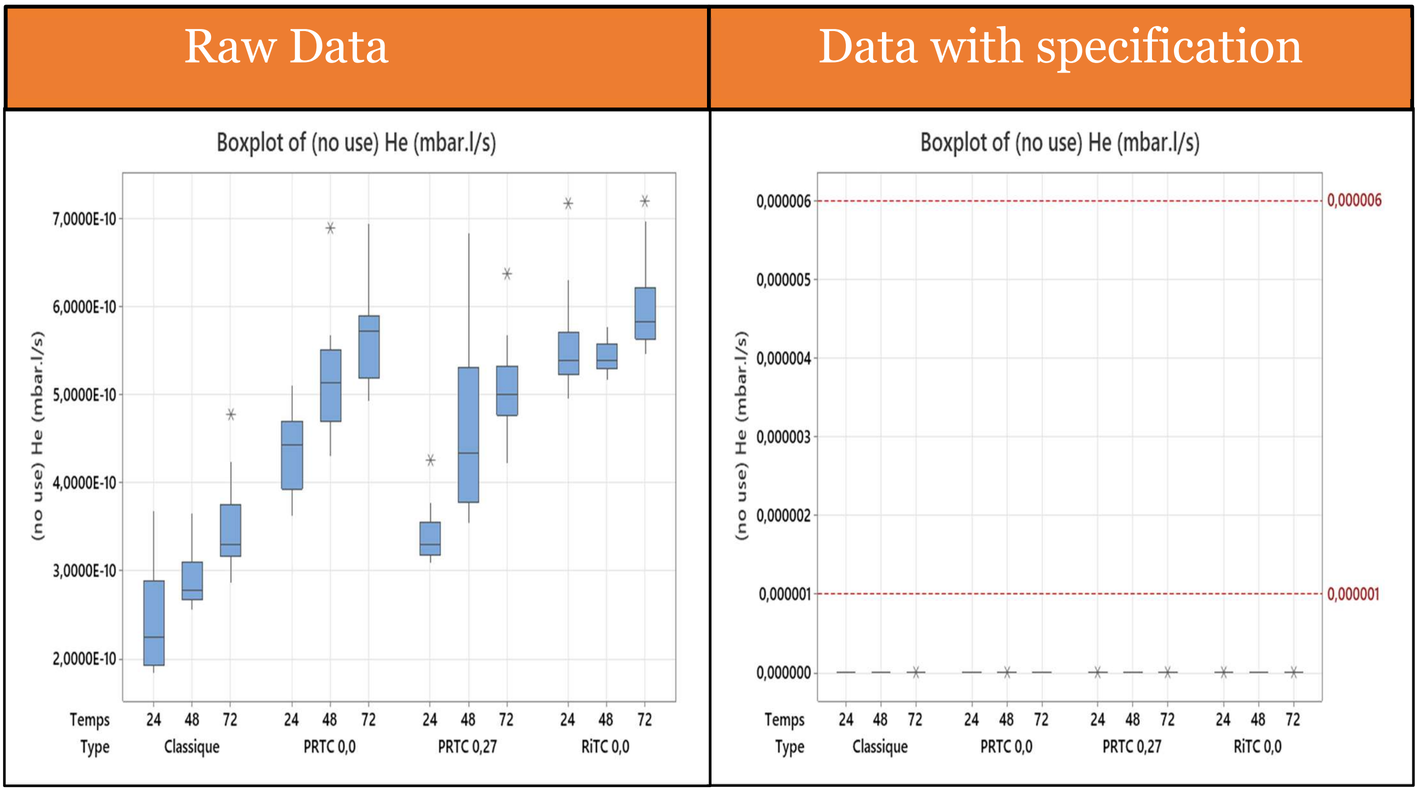


Figure 40 : Specification comparison. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile

Limitations can be given regarding these results.

The most relevant is the sensitivity of the measurement. Indeed, the device indicates a sensitivity of 5.10^{-9} mbar.l/s while most of the measurements are at 10^{-10} mbar.l/s magnitude. This is a crucial element which can helps to understand some differences between different results.

The other important limitation is the calibration of the device. Since it is a very precise tool, it needs to be calibrated every 24h and in the calibration test, there is a background value measured and which varies every day. As a result, from a measurement made one day and another the other day, results (especially low results) can vary quite largely. This is the case for the 250ppb/500ppb comparison. One of the measurements has been done on June 8th while the other one was performed on June 14th.

As a result, the comparison of two measures taken from two different calibration is not possible. Openings concerning this problem will be proposed further in the thesis.
Some results were indeed obtained relative to the functioning part. Let’s now look at the material characterizations that were performed.

4.3 Material characteristics

4.3.1 Tensile Strength

Tensile Strength tests were performed on the same configuration than those regarding the helium leak test. As a result, it is possible to obtain the same boxplots. Let’s see if the results follow the same patterns.
Figure 41 represents the time/concentration comparison on three configurations: Tub Syringes, PRTC 0.0 and PRTC 0.27.
Tensile strain at maximum load is the criteria used in this graph.

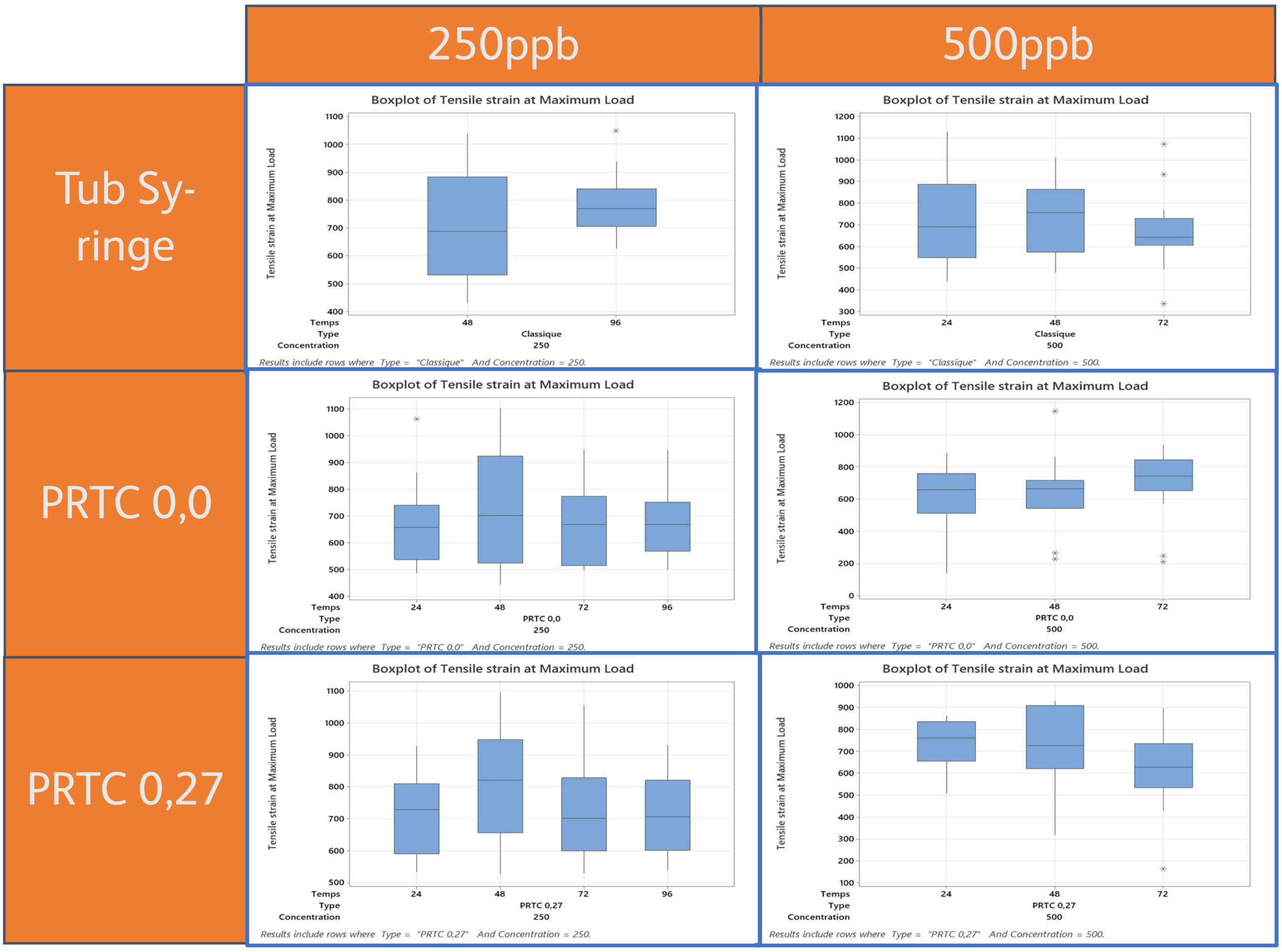


Figure 41 : Tensile Strain at maximum load on time/concentration comparison. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile

It can be understood that there is no change in the tensile strain at maximum load when exposure time grow or when the concentration is different.
These elements do not seem to be the one who influence this material behaviour.
Let's compare the configuration on all the available criteria: Tensile strain at maximum load, maximum load, stress at 100% strain, stress at 400% strain:

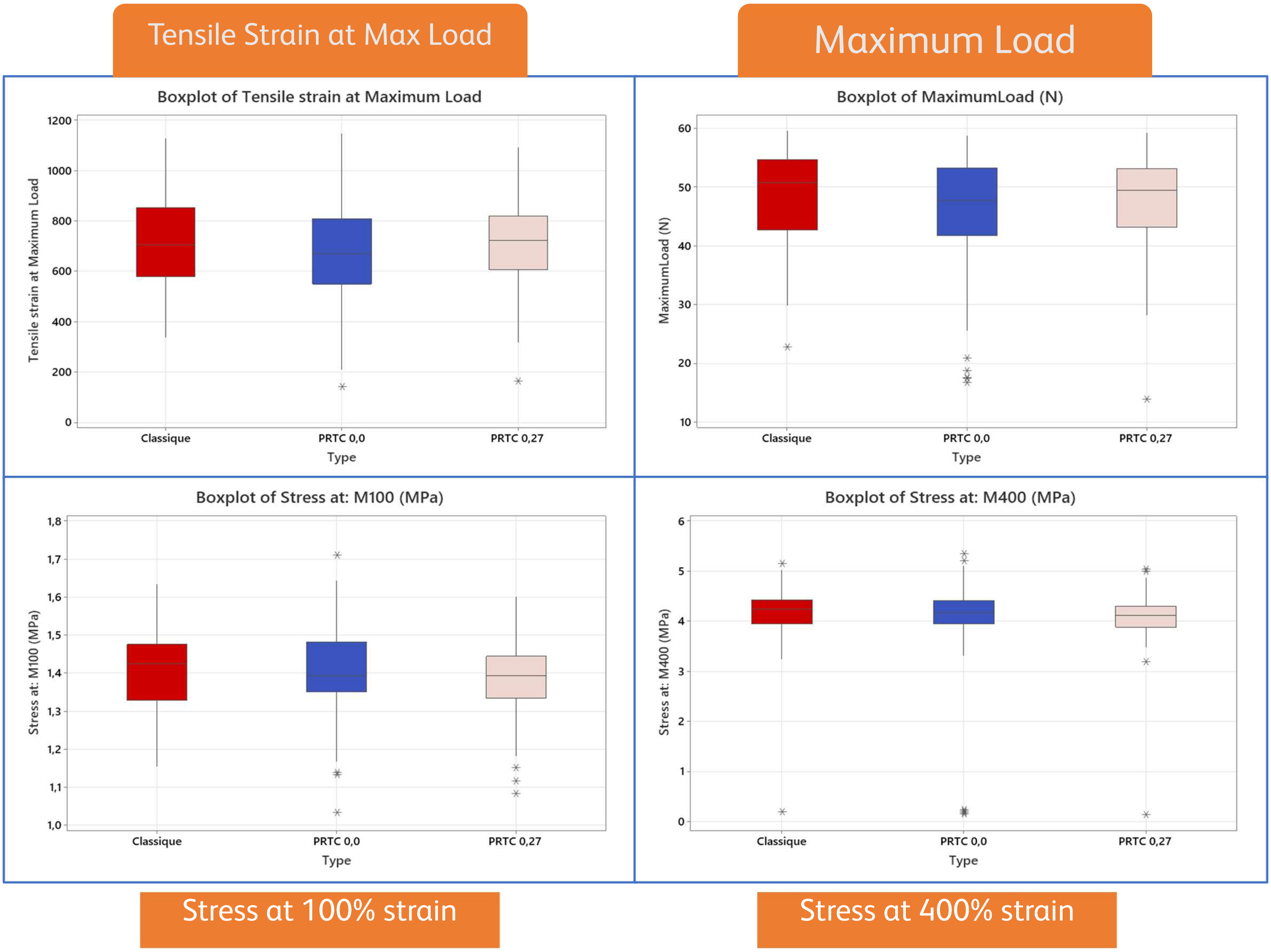


Figure 42 : Tensile strength on configuration comparison. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile

Here is the different configuration comparison: red boxplots represent tub syringes, blue one represents PRTC 0.0 and the white one stands for PRTC 0.27.
As it can be seen, there are no changes whether one criterion or another is studied, and the packaging seems to have no effect on these one.

One of the reasons that can explain the absence of changes from one configuration to another is the mechanism of the ozone attack. Indeed, it is mainly a surface attack while tensile strength as well as most of the other material characterisation depicts the inner behaviour of the material. As a result, even id cracks are seen from the outer part, the inner part of the RiTC is most of the time totally safe and out of degradation.
Let's verify this hypothesis on the other material characterizations.

4.3.2 Swelling method

Swelling was performed on extreme configuration: RiTC 0.27 at 250ppb / 96h and RiTC 0.27 at 500ppb / 72h. They will compare with a T0 RiTC without any ozone exposure for comparison.
Here are the results summarized in Figure 43:

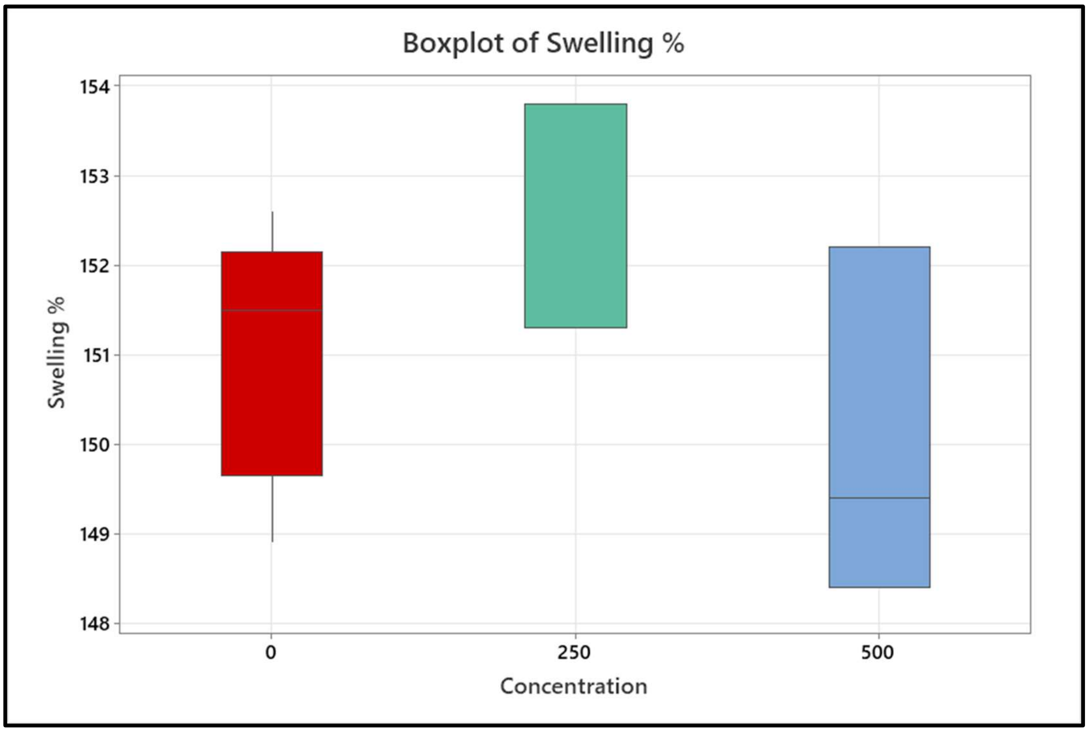


Figure 43 : Swelling results. The boxplot includes 50% of the results, the horizontal line represents the median value and is surrounded by the first and the third quartile

As well as for the Tensile Strength method, there are no significant changes whether the RiTC were cracked (RiTC 0.27) or not.
Let's analyse another method which is known to be more precise and can lead to important data such as forced aging behaviour, phase change temperature or viscoelasticity properties.

4.3.3 Dynamic Mechanical Analysis

Since it is a time-consuming method, only a few samples were tested. The most exploitables values were the one regarding T0 syringes and RiTC 0,27mm at 500ppb during a 72h exposure. Figure 44 represents the Young Modulus evolution over a strain change which varies between 0,1 to 20%. These values are the one seen by the elastomer when assembled on the barrel. Red curves represent the standard RiTC with no ozone exposure while the blue curves stand for RiTC 0,27.

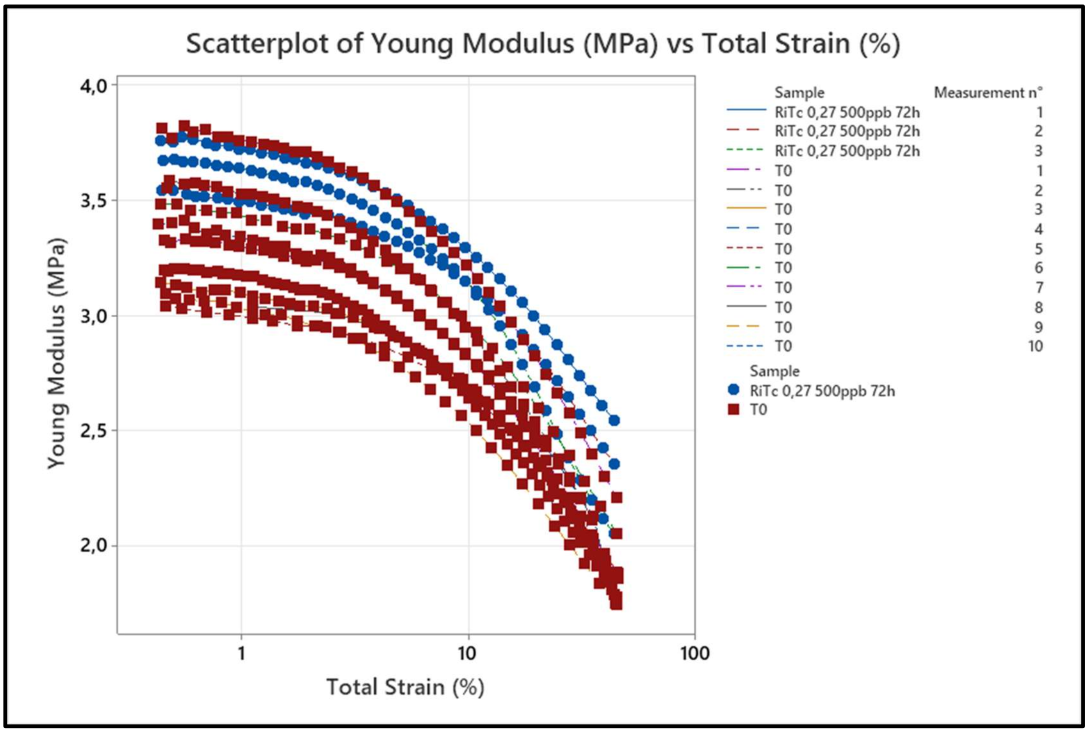


Figure 44 : DMA analysis

The Young Modulus decreases over the strain which means that the elastomer is crossing the viscoelastic boarder. When not strained, it behaves in the linear regime with no Young Modulus changes. At a certain point (1-5 strain %), the rubber reaches a nonlinear regime to go to a plastic regime with irreversible deformations.

As it can be seen, these patterns are quite the same whether it deals with T0 rubbers or degraded ones.

As explained above, the ozone attack is mainly at the surface of the material which justify the fact that the inner behaviour of the rubber is not changed.

Now that all the different measurements have been analysed, there is a need to summarize everything and to give all the limitations or possible improvements regarding either the method or next steps to lead to a more global knowledge concerning ozone exposure on syringe rubbers.

5 Summary/Conclusions

The work that is done in this thesis aimed to understand the impact of ozone on a specific formulation of polymer which was called FRM1. It was a polymer made of SBR material whose goal was to guarantee the container closure integrity of a syringe for medical use. First, some theoretical aspects were studied such as information about ozone and elastomers. Then, methods to characterize rubbers that were exposed to ozone were explained. Eventually, the results obtained were put into perspectives and compared one to another. It is now time to write conclusions about this work and think about alternatives and openings regarding this subject.

5.1 Conclusions regarding the research problem

Multiple elements were tested in this experiment including the effect of time, temperature, stress, protection, and packaging on the impact of ozone on rubbers. Three types of characterization were performed, visual, functional, and material tests. These characterizations gave different results. Here are the main results obtained.

The stress applied on the rubber has a significant impact on its ability to resist to ozone exposure. Indeed, by imagining enlarged tips to increase the stress applied on the tip caps, more cracks were observed, and the functional aspect of the syringe was challenge. It was the case with the helium leak test. However, the stress had no impact on the material properties tested with tensile strength test, swelling test and dynamic mechanical analysis.

Time and concentration correlation was also an important factor of discrimination over different configurations. In fact, the more the samples were exposed to ozone, the more cracks were present, and the more leaks were measured through the helium leak test. It was globally the same conclusion when the concentration of ozone increased. However, some limitations regarding helium leak test did not permit to observe this tendency.

Eventually, the packaging made of different plastic or paper layers showed an important impact. More precisely, the ‘tub’ packaging led to a complete protection regarding the visual, functional, and material tests while ‘rondos’ and ‘bags’ let the ozone penetrate the rubber and degrade it.

If the focus is made on the initial reason of this thesis which is the possible extension of shelf life of SYR1 syringes, no elements justify the impossibility of an extension of this shelf life. In fact, SYR1 syringes are sold and stored in tubs with protection that are, as it is showed in this thesis, resistant enough to resist to high concentrations such as 500ppb during 72h.

However, the correlation between high concentrations during short times and low concentrations during long periods is not so easy. Even if extrapolation of curves has been tried, there are uncertainties remaining on the mechanism of the ozone impact whether it deals with high or low concentrations. As a result, here are some limitations and future experiments to lead to the required answer.

5.2 Sub problems and hypotheses for further research

A lot of openings on different methods can be suggested to improve the quality of the results.
As it was showed, the helium leak detector made some interesting measurements, but the calibration is a staggering issue. To counter it, some alternatives exist such as the understanding of the blank measurement. Indeed, the calibration enlighten the fact that there is a background noise that is sometimes higher than the results obtained. However, the subtraction of this value does not solve the problem. One of the solutions is to perform a blank measurement through the help of what is called a master which is a metallic syringe which is 'not' leaking normally. The measurement of this master at each calibration and its subtraction to the value obtain can lead to comparable measurements from one series to another.
Another opening regarding the methods used is the understanding of the crack penetration. In fact, pictures taken of cracked RiTC showed that the cracks seem to penetrate at the edge of the RiTC while the inner parts are not degraded. It can be a solution to flip the RiTC to look at the inside of the rubber and understand to what extent does the cracks are transversal.
A chemical analysis of the surface of the rubbers is also a possibility to acquire more knowledge on the bonds that are broken during the ozonolysis and what king of elements such as antioxidants or small molecules are present on the outer layer of the RiTC. It can be either InfraRed or Raman spectroscopy.
Finally, a more complete comprehension on the aftermath of ozone exposure can be reached by measuring the concentration seen by the rubbers inside the packaging. In fact, as it is shown, the packaging has an important impact, and it is quite difficult to quantify it precisely yet.

A lot of work was done to understand the impact of ozone on SYR1 rubbers, and the results are promising. Yet, some research and experiments can follow to complete this thesis.

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