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## Dialyzers biocompatibility and efficiency determinants of sterilization method choice<sup>☆</sup>

Mise au point sur la stérilisation des dialyseurs :  
un des critères de choix à prendre en compte en 2012

B. Allard (Pharmacien gérant)<sup>a,\*</sup>, R. Begri (Pharmacien adjoint)<sup>a</sup>, J. Potier (Médecin praticien hospitalier)<sup>b</sup>, S. Coupel (Médecin adjoint centre formation)<sup>c</sup>

<sup>a</sup> ECHO, pharmacie à usage intérieur, 11, rue Félix-Éboué, BP55, 44401 Rezé, France

<sup>b</sup> Service d'hémodialyse, centre hospitalier du Cotentin, 46, rue du Val-de-Sair, 50102 Cherbourg, France

<sup>c</sup> ECHO, site du Confluent, 6, rue de la Gare, BP10095, 44402 Rezé cedex, France

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### Summary

**Introduction.** When selecting a dialyzer, the criteria of biocompatibility entering the choice of the dialyzer are based on the nature of the polymer constituting the membrane, but rarely on the dialyzer sterilization methods.

**Methods.** Thus, it seemed necessary to analyze the advantages and the disadvantages of the modes of sterilization and to analyze their impact on the performances and the biocompatibility of dialyzers to integrate this parameter to their investment choices for the kidney machine.

**Results.** Radiation sterilization induces structural modifications of the dialyzers components. Beta radiation causes fewer modifications than gamma radiation; these structural modifications can release cytotoxic components. Steam sterilization is a reference in terms of security for thermostable materials with an added benefit for steam process, which allows the removal of waste generated during the dialyzer's manufacturing.

**Discussion.** For the same membrane, performances of the dialyzers change according to the methods of sterilization, inducing different performances and different uses.

**Conclusion.** To conclude, beyond the choice of the polymer, the method of sterilization should consistently be taken into account in therapeutic choices and purchase of dialyzers. Considering its very high biocompatibility and considering the acquired experience,

### Résumé

**Introduction.** Les critères de biocompatibilité, entrant dans le choix du dialyseur, reposent avant tout sur la nature du polymère de la membrane, et rarement sur le mode de stérilisation du dialyseur.

**Méthodes.** Il est donc apparu nécessaire de définir les modes de stérilisation et analyser leurs impacts sur la biocompatibilité et les performances des dialyseurs, de façon à intégrer ce critère dans l'arbre décisionnel de choix du dialyseur.

**Résultats.** La stérilisation par irradiation s'accompagne de modifications structurales des constituants des dialyseurs, l'irradiation bêta-entraînant moins de modifications que l'irradiation gamma, ces modifications structurales pouvant amener la libération de composés cytotoxiques. Les modes de stérilisation par chaleur humide, autoclave ou vapeur fluente, restent une référence en terme de sécurité pour les matériaux non thermosensibles, avec un avantage supplémentaire pour la vapeur fluente, permettant un effet de chasse des résidus de fabrication.

**Discussion.** Pour une même membrane, les performances des dialyseurs sont modifiées en fonction du mode de stérilisation, entraînant des performances et possibilités d'utilisation différentes.

**Conclusion.** En conclusion, au-delà du choix du polymère, le mode de stérilisation devrait être systématiquement pris en compte dans

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\* Corresponding author.

e-mail : [ballard@echo-sante.com](mailto:ballard@echo-sante.com) (B. Allard).

moist heat sterilization is to be favored in the choice of dialyzers of equivalent performances. Furthermore, non-heat sensitive products have to be developed first and foremost with this mode of sterilization. © 2013 Elsevier Masson SAS. All rights reserved.

**Keywords:** Dialyzer, Sterilization, Biocompatibility, Dialyzer performance

les processus de choix thérapeutique et donc rentrer en compte dans le processus d'achat.

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**Mots clés :** Dialyseur, Stérilisation, Biocompatibilité, Performance

## Introduction

Dialyzers (so called kidney machine) are sterile medical devices that are made up of various polymers or cellulose acetate assembled between them in a synthetic polymer hull.

Good biocompatibility and performances for the clearance of uraemic toxin are the matters of vital concern. Key performance results considered are permeability, surface and uraemic toxin cleared according to the technique of dialysis used. Unlike the first three criteria, biocompatibility does not set the stage for manufacturers and prescribers performance reporting.

So, the criteria of biocompatibility entering the choice of the dialyzer are based on the nature of the polymer constituting the membrane, but rarely on the mode of sterilization of the dialyzer. The sterilization technology has evolved significantly over the past decades and has an influence on the biocompatibility of dialyzers as well as on their performances.

The table in [supplementary data, Appendix 1](#) summarizes the various ranges of Dialyzers, classified according to the manufacturers of membrane, and specifies the various methods of sterilization as well as the places of manufacturing and the type CE mark attached.

Thus, it seemed necessary to analyse the advantages and the disadvantages of the modes of sterilization and to analyse their impact on the performances and the biocompatibility of Dialyzers to integrate this parameter to their investment choices for the kidney machine.

## Various methods of sterilization

There are numerous methods of sterilization as specified in the plan below ([fig. 1](#)), but today, ethylene oxide sterilization gave way to radiation and heat sterilization ([fig. 1](#)).

### Radiation sterilization

#### Principle and implementation

Radiation sterilization bombard the medical device with very high energy ionizing particles altering microorganisms DNA/ RNA and producing very reactive free radicals.

The powerful ionizing radiation sources used for dialyzers are mainly generated by the gamma radiation of cobalt 60 or by electron-beam for the beta radiation equipment.

Dialyzers in their definitive packaging are exposed several hours for the gamma radiation, or few minutes only under the electron-beam for the beta brilliance. For short-term and surge requirements beta sterilization allows high productivity.

Nevertheless, beta radiation allows a more precise radiation. During the gamma radiation sterilization, dialyzers are dry (without an agent of filling) or filled with an aqueous solution in the blood and dialysate compartments. The name "gamma wet" (wet) or "gamma dry" (dry) results from the state of the dialyzer at the time of the sterilization up to its end use.

In the sterilization gamma, the agent by filing allows the distribution of the residues of manufacturing and products generated during the sterilization in the aqueous solution. Nonetheless, these dialyzers are much heavier and sensitive to the temperature.

#### Impact of the radiation on the dialyzer constituting materials

Depending on the dose, radiation induces structural modifications, splits and reticulations leading to a molecular rearrangement that can affect in a more or less important way polymers to be sterilized [1,2]. The absorbed energy is expressed in Gray unit.

Exposure to the beta radiation may induce fewer structural modifications due to a shorter duration and a more precise radiation dose. However, only scarce data are available [3]. The structural changes observed after gamma radiation, can arise even for microdoses. In the case of the polysulfone, these appear for a 1.66 KGy dose while the Pharmacopoeia sterilizing dose required is 25 KGy [4]. According to the sterilization method, these modifications may impact biocompatibility because of the new substances in the unknown toxicity generated and/or because of the alteration of performances of the dialyzer compared to the non-sterilized initial product [5]. Furthermore, the structural modifications continue even after the end of the radiation.

These changes would be due to the presence of free radicals [1] formed within the polymer during the radiation process that causes accelerated oxidation after the conclusion of the sterilization. The presence of these free radicals can be minimized by radiation without oxygen.

([tables 1a and 1b](#)), according to the works of Uhlenbusch-Körwer and Nyoman Ruspiasih, shows the main polymer

**Table Ia**  
Effects of the gamma radiation on polymers.  
*Effets de l'irradiation gamma sur les polymères.*

Monomer/Polymer	Gamma irradiation effect
Acrylic monomer (PAN membranes)	Increased permeability of high molecular weight molecules
Cellulose	Splitting of the molecular structure
Polymethylmethacrylate (PMMA)	Splitting of the molecular structure, decreased permeability of high molecular weight molecules ( $10^6$ to $10^5$ at 35 kGy)
Polysulfone (PSU)	Simultaneous chemical bridging and splitting reactions above 25 kGy
Polyethylene (EVAL <sup>®</sup> and hull)	Chemical bridging: hydrocarbon compounds producing aldehydes and organic acid
Polycarbonate (hull)	Browning
Polyvinylchloride (PVC Coque)	Splitting of the molecular structure, browning, hydrochloric acid release, possible infiltration of partially decomposed additives that is responsible for an unpleasant smell and accelerated aging process
Polyurethane (PUR)	Release of mutagenic compounds, especially from aromatic polyurethane

From Uhlenbusch-Körver et al. [2] and Nyoman Ruspasih et al. [4].

modifications known for dialyzers after gamma radiation [2,4].

On empotage resins, mainly constituted by aromatic polyurethane, gamma radiation induces toxic molecule formation such as the carcinogenic and mutagenic MDA (4,4-methyl alcohol dianiline) molecule [6–9]. Conversely, polyurethanes of aliphatic origin that do not release MDA may be used. However, other carcinogenic compounds are formed in the rat, although the outcome is less pronounced than the aromatic polyurethane [7–12]. The cost of this raw material inhibits also its function.

### Moist heat sterilization processes

#### Principle and implementation

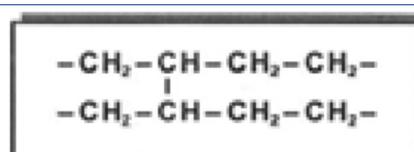
This sterilization mode is based on the heat denaturation of membranes and proteins of the infectious agents. For dialyzers, two moist heat sterilization strategies are implemented: autoclave or steam flow.

Autoclave: The vapor acts simply as coolant agent. The membrane of dialysis is not in direct contact with the sterilizing vapor. Sterilization consists of submitting the medical device to the heat action for a definite time (20–90 min), in a high

**Table Ib**  
Effects of the gamma radiation on polymers.  
*Effets de l'irradiation gamma sur les polymères.*

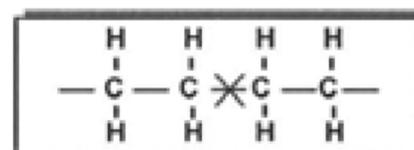
#### Preferential alteration of polymer induced by gamma irradiation

Chemical bridging



Polyamide  
Polyethylene  
Silicone elastomer

Splitting reaction



Polymethylmethacrylate  
Cellulose  
Polyvinyl chlorure

From Uhlenbusch-Körver et al. [2].

**Table II**  
Possible sterilization methods according to polymer membrane type.  
*Modes de stérilisation possibles selon la nature de la membrane.*

Types of polymer membrane		Gamma irradiation	Etylene oxide sterilization	Moist heat sterilization
Cellulosic polymer	Cellulose, cellulose derivatives (cellulose acetate excepted)	+	+	+
	Cellulose acetate	+	+	—
Polysulfone and polysulfone derivatives	Polysulfone	+	+	+
	Polyarylethersulfone (Arvlane <sup>®</sup> )	+	+	+
	PES (Diapes <sup>®</sup> )	+	+	+
	PolyamideS <sup>®</sup> /Polyamix <sup>®</sup>	+	+	+
	PEPA	+	+	+
Other synthetic polymers	PAN	+	+	—
	PMMA	+	—	—
	EVAL <sup>®</sup>	+	+	—
	Polycarbonate	+	+	—
	Polyamide	+	+	—

From Uhlenbusch-Körwer et al. [2].

temperature (superior to 121 °C) in a given time and in a pressure superior to the atmospheric pressure (1 in 2 Bars); there is a relation between the pressure and the temperature in the middle of saturated vapor (Regnault's table), as well as a conversely proportional correlation meanwhile and temperature [6,13,14].

The term “vapor” used by certain manufacturers should be replaced by “moist heat”.

Steam flow: dialyzers are individually sterilized by the passage of a continuous flow of vapor in all the compartments of the dialyzer (blood and dialysate) in a temperature of 121 °C during 15 minutes. Compared with the sterilization by the heat, the vapor fluente present the advantage to eliminate by the continuous flow of vapor inside and outside of the fibres of possible residues of manufacturing as well as the pyrogenic and the present endotoxins after the sterilization.

#### Impact of moist heat on dialyzer constituents

This mode of sterilization by heat is not applicable for heat sensitive polymers, such as polymethylmetacrylate, polyacrylonitrile and cellulose triacetate. On the other hand, this effective and well-mastered process, is the gold standard in terms of safety, for non-heat sensitive materials [1,2,5] and should be recommended for dialyzers sterilization (table II).

### Influence of sterilization mode on dialyzers cytotoxicity

A number of studies tried to estimate the *in vitro* impact of the manufacturing/sterilization process on the cell toxicity. These works present the advantage to have used a “standardized” biological material, thus reducing the variability of the

host-cell response conditioned by the genetic heritage and the environmental conditions of the cell.

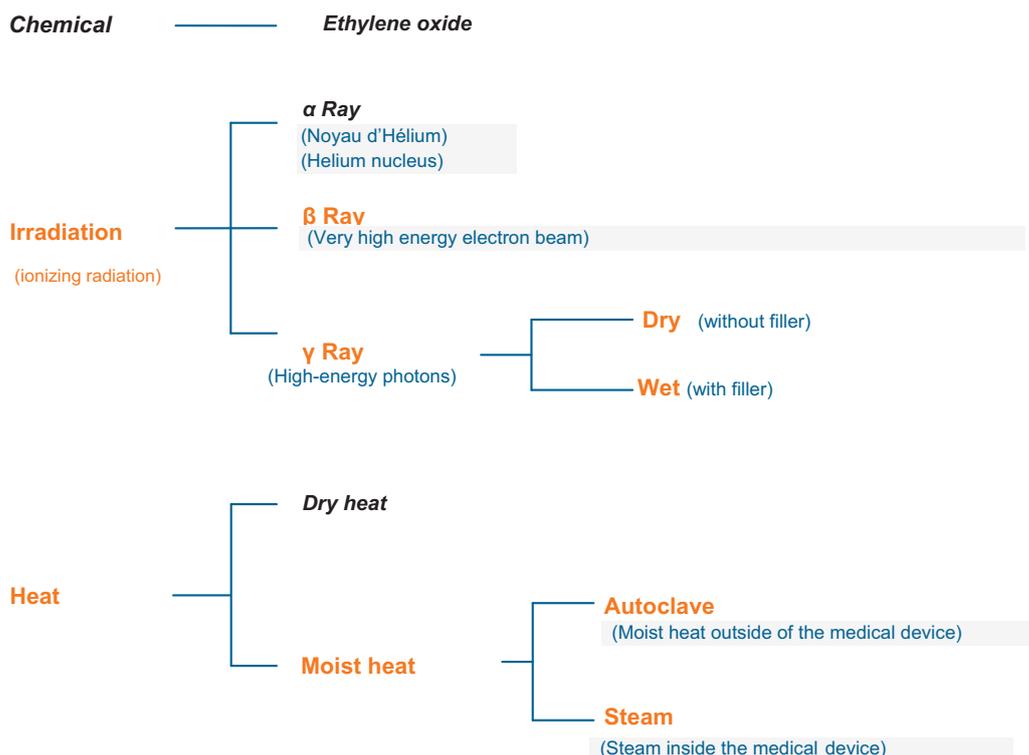
### Comparison of cell toxicity according to sterilization mode

In their biocompatibility and toxic risks analysis of the sterilization processes for dialysis devices, Guedri et al. [15] compared the fragmentation of the DNA of lymphocytes taken at the beginning, the middle and at the end of the dialysis session (by electrophoresis and spectrometry). The dosage in spectrometry of malondialdehyde stemming from samples leaving the fibres allowed estimating the production of free radicals. The results showed an increased fragmentation of the DNA and the production of free radicals after gamma sterilization. The method considered the most biocompatible being the moist heat sterilization.

During a cytotoxicity study considering the proliferative capacity of the V79/B2 cells of Chinese hamster, Bommer et al. [16] in contact with eluted samples of dialyzers cuprophane sterilized by moist heat or by increasing doses of gamma rays. The samples eluted from dialyzers sterilized by gamma radiation reduced the efficiency of the examination of cell culture by 30% compared with the control. Similar effects on the formation of colonies were observed. The cytotoxicity, minimal after moist heat sterilization, increases with the gamma radiation and depending the dose received. According to the authors, this phenomenon would be due to the presence of cytotoxic compounds after gamma sterilization (table III).

### Effects of manufacturing and sterilization residues on mitochondrial oxidative phosphorylation

The presence of manufacturing and sterilization residues in dialyzer is not often analysed with regard to the



**Figure 1.** Dialyzers sterilization methods.  
*Méthodes de stérilisation des dialyseurs.*

biocompatibility in hemodialysis. Brunet et al. [17,18] estimated the effect of manufacturing residues of the dialyzer extracted from the rinsing liquid in an in vitro model using isolated rat liver mitochondria.

The study of the oxidative phosphorylation was realized on the third rinsing liter of a cellulosic dialyzer and two dialyzers polysulfone, one sterilized by fluente steam (FX) and the other one by gamma radiation (APS) [17].

The results showed differences in the capacity of mitochondria to synthesize ATP and respiratory control (capacity to activate the phosphorylation and in the presence of ADP). The most noxious effect was observed with the dialyzer with cellulosic membrane. Among both membranes it polysulfone, the FX obtained a better score than the APS. According to the author's hypothesis, the flushing effect of vapor fluente sterilization on the manufacturing residues may explain this difference.

**Table III**  
**Comparative study of cytotoxicity according to the dialyzers sterilization method.**  
*Étude comparative de cytotoxicité selon le mode de stérilisation des dialyseurs.*

	1 h	4 h	6 h
Ethylene Oxide sterilization	–	–	–
Vapor	–	–	–
27 kGy	+	+	+
56 kGy	++	++	++

Bommer et al. [16].  
*Eluates effects after circulation of culture medium (500 mL during 1 h, 4 h and 6 h) in dialyzers sterilized by different methods [ethylene oxide (EtO) and steam gamma irradiation (56 kGy and 27 kGy)] on the proliferative capacity of Chinese hamster cells V79/B2. –: absence of cytotoxicity; +: moderate toxicity; ++: greater toxicity. Effets des éluats obtenus après circulation d'un milieu de culture (500 mL pendant 1 h, 4 h et 6 h) dans des dialyseurs stérilisés selon différentes méthodes [oxyde d'éthylène (EtO), vapeur et irradiation gamma (27 kGy et 56 kGy)] sur la capacité proliférative des cellules V79/B2 de hamster chinois. – : absence de cytotoxicité ; + : toxicité modérée ; ++ : toxicité plus importante.*

**Environmental studies on the hemocompatibility**

In a study of Erlenkotter et al. [19], two polysulfone membranes, one sterilized by gamma radiation, and the other by the moist heat, presented different scores of hemocompatibility. This study is based on the analysis of a score of hemocompatibility regarding the factor C5a of the complement, complex thrombin–antithrombin III, the release of the platelet factor 4, the synthesis and the release of elastase from polynuclears and platelet count. The polysulfone membrane sterilized by gamma radiation presented a score of hemocompatibility inferior to that of the moist heat sterilized polysulfone membrane.

Because of the more recent and less widespread use, there are few data concerning the hemocompatibility of dialyzers sterilized by radiation beta.

Table IV

Effect of the sterilization method on the performance of the Purema membrane.

*Impact du mode de stérilisation sur les performances de la membrane Purema.*

Name	Manufacturer	Polymer	Membrane	Sterilization mode	Beta2-Microglobulin clearance		Albumin losses (g/4 h)	
					Le Roy et al. [23] (%)	Potier et al. [24] (%)	Le Roy et al. [23]	Potier et al. [24]
XENIUM 210	Membrana	Polyethersulfone	PUREMA (polyether sulfone)	Gamma irradiation	80.0	80.8	0.59	< 3 g
PHYLTER 22S				Moist heat sterilization	82.4	82.4	6.14	5–10 g

In 2011, Kiaii et al. reported [20] a thrombocytopenia risk associated with the use of dialyzers sterilized by beta radiation from a 22 months retrospective cohort study of 1832 patients. The relative risk of thrombocytopenia – defined by a rate of platelets lower than  $100 \times 10^{-3}/\mu\text{L}$  and a reduction in more than 15% by the platelet number at the end of dialysis – was significantly more elevated with beta sterilized dialyzers (OR: 3.57; CI 95%: 2.54–5.04,  $P < 0.001$ ). However, this publication was very controversial [21,22], since mechanisms bringing to a thrombocytopenia were many, multifactorial and with difficult to analyse through retrospective data. The possible role of the sterilization by beta radiation beta in thrombocytopenia is still to be confirmed by more thorough studies.

## Influence of sterilization mode on performances of dialyzers

### Differences of performances for same membrane, according to sterilization mode

Studies comparing the efficiency of the membranes of dialysis for online hemodiafiltration (HDF) reported differences for the same polyethersulfone membrane according to its sterilization mode by moist heat or gamma. The two criteria compared were: the  $\beta_2$ -microglobulin (PM: 11,800 Da) reduction coefficient and the loss of albumin (PM: 66,000 Da).

The study of Le Roy et al., realized in HDF compared eleven membranes of high permeability with a surface superior to 2 m<sup>2</sup> with regard to the clearance of the small molecules, of the  $\beta_2$ -microglobulin and the losses of albumin during 4 hours dialysis sessions [23].

Each of the dialyzers was tested on three patients during three successive sessions by the patient. Among them, two dialyzers resulting from the same manufacturer, but from two different distributors, presented the same membrane Purema<sup>®</sup> with this difference that one was moist heat sterilized (Phylther S) and the other one of the gamma radiation (Xenium).

The losses of albumin hemodiafiltration with the heat sterilized membrane was 6.14 g/4 h while that of the gamma sterilized membrane was only 0.59 g/4 h.

These results confirmed the survey carried out in Cherbourg on the same membranes from ten trials [24]. Depending the

sterilization mode, the Purema membrane exhibited different albumin permeability.

The sterilization mode evidenced an effect on the structure and the permeability of the membrane to solute (and thus to a toxin). There are also more marked differences depending on the dialysis methods used (HD or HDF pre-dilution, post-dilution, and according to the convective volume), in particular transmembrane pressures (PTM). The impact of the sterilization mode of the structure of the membrane makes some laboratories to propose dialyzers more adapted to the dialysis methods (table IV).

The moist heat sterilization Phylther (Phylther SD) was eliminated on a gamma sterilization mode (Phylther G) to defeat the two important permeability of Phylther SD in HDF. Conversely, the heat sterilization version must be exclusively reserved for a use in conventional HD.

### Performances stability over time for gamma sterilized dialyzers

It is probable that the dialysis membranes sterilized by gamma radiation are altered over time [1]. Indeed, the Cotentin Hospital in Cherbourg studied the losses of albumin in HDF of a polysulfone derived membrane as a function of time since sterilization of the dialyzer. This dialyzer exhibited first normal loss of albumin (< 3 g by dialysis session). However, 4 months later, exactly the same dialyzer taken from the same batch and secondary packaging (box) stored according to the manufacturer recommendations, exhibited losses of albumin exceeding 5 g by dialysis session. The tests were made on several dialyzers of the same batch with the same result.

As far as we conceive that the polymerization process of the membrane is stable in the medium-term, this fortuitous observation questions performance stability over the time of the radiation sterilized products. We are conducting a prospective cohort study on this topic.

## Conclusion

In the decision tree for dialyzers choice, criteria that should be taken in account are:

- performances regarding therapeutic objectives for clearance of uraemic toxin;
- practical implementation, established according to the techniques used, to the equipment and to the patients population;
- biocompatibility, more difficult to circumscribe for a heterogeneous population of polypathologic patients.

Nonetheless, the sterilization mode may have a major impact on materials used in the manufacturing of dialyzers. With regard to the cytotoxicity of some sterilization modes and because of the exposure, three times a week in standard dialysis to six times a week for the daily dialysis, this criterion must be taken into account in the decision tree of choice of the dialyzer.

Considering its very high biocompatibility and considering the acquired experience, moist heat sterilization is to be favoured in the choice of dialyzers of equivalent performances. Furthermore, non-heat sensitive products have to be developed first and foremost with this mode of sterilization.

## Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.phclin.2013.10.071](https://doi.org/10.1016/j.phclin.2013.10.071).

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