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Queiroz de Souza, Rafael; Uchikawa Graziano, Kazuko
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Compatibilities and incompatibilities between gamma rays and ethylene oxide as consecutive sterilization methods

COMPATIBILIDADES E INCOMPATIBILIDADES ENTRE RADIAÇÃO GAMA E ÓXIDO DE ETILENO COMO MÉTODOS SUCESSIVOS DE ESTERILIZAÇÃO

COMPATIBILIDADES E INCOMPATIBILIDADES ENTRE RAYOS GAMA Y ÓXIDO DE ETILENO COMO MÉTODOS SUCESIVOS DE ESTERILIZACIÓN

Rafael Queiroz de Souza[1], Kazuko Uchikawa Graziano[2]

ABSTRACT

The doubt regarding the re-sterilization of articles made of polyvinyl chloride (PVC) sterilized with gamma radiation (GR) and subsequently with ethylene oxide (EO) persists to date. Through a systematic literature review, this article analyzed studies that demonstrated compatibilities and incompatibilities between the sterilization processes with GR and EO, when used as consecutive sterilization methods. Seven studies were analyzed. It was verified that there is a multifactor influence regarding the safety of the procedure and that the chromatography analytical method employed by most studies yielded controversial results. This fact indicates the need for further studies on the issue, using more sensitive analytical methods than gas chromatography, such as the biological reactivity test in cell cultures, in an attempt to clarify the chronic doubt regarding the adequacy or inadequacy of sterilizing previously gamma-irradiated materials with EtO.

KEY WORDS

Gamma rays.
Ethylene oxide.
Sterilization.

RESUMO

A dúvida sobre a questão da re-esterilização de artigos confeccionados com cloreto de polivinila (PVC), esterilizados em radiação gama (RG) e posteriormente em óxido de etileno (EO) persiste até os dias atuais. Por meio da revisão integrativa da literatura, este artigo analisou estudos que evidenciaram compatibilidades e incompatibilidades entre os processos de esterilização com RG e EO quando utilizados como métodos sucessivos de esterilização. Foram analisados 7 estudos. Constatou-se que há influência multifatorial na segurança do procedimento e que o método analítico da cromatografia empregado na maioria dos estudos produziu resultados controversos. Esse fato indica a necessidade da realização de novos estudos sobre o assunto, utilizando-se métodos analíticos mais sensíveis do que a cromatografia gasosa, como o teste de reatividade biológica em culturas celulares, que poderá dirimir em nosso meio a crônica dúvida da compatibilidade ou incompatibilidade de se esterilizar em EO materiais previamente gamairradiados.

DESCRITORES

Raios gama.
Óxido de etileno.
Esterilização.

RESUMEN

La duda sobre la cuestión de la reesterilización de artículos confeccionados con policloruro de vinilo (PVC) esterilizados con Rayos Gamma (RG) y posteriormente en óxido de etileno (EO) persiste hasta la actualidad. A través de la revisión integradora de la literatura, este artículo analizó estudios que evidenciaron compatibilidades e incompatibilidades entre los procesos de esterilización con RG y EO, cuando se utilizan en forma sucesiva. Fueron analizados 7 estudios. Se constató que hay influencia multifactorial en la seguridad del procedimiento y que el método analítico de cromatografía empleado en la mayoría de los estudios generó resultados controversiales. Este hecho indica la necesidad de realizar nuevos estudios sobre el asunto, utilizando métodos analíticos más sensibles que la cromatografía gaseosa, tales como el test de reactividad biológica en cultivos celulares para dirimir en nuestro medio la crónica duda de la compatibilidad o incompatibilidad de esterilizar en EO materiales previamente irradiados con Rayos Gamma.

DESCRIPTORES

Rayos gamma.
Óxido de etileno.
Esterilización.

[1]Master's student, holder of a Grant by the Graduate Program in Adult Health Nursing at University of São Paulo School of Nursing. São Paulo, SP, Brazil. rafaelqsouza@usp.br [2]Full Professor of the Medical Surgical Nursing Department at University of São Paulo School of Nursing. São Paulo, SP, Brazil. kugrazia@usp.br

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INTRODUCTION

In 1967 a letter sent to the British Medical Journal reported that performing re-sterilization with Ethylene Oxide (EO) of health care material made of Polyvinyl Chloride (PVC) that had previously been sterilized with Gamma Rays (GR) produced *high concentrations* of a toxic EO byproduct - Ethylene Chlorohydrin (ETCH)[1]. In that letter, the authors did not mention the dosages they found, which would permit a comparison between the limits considered low or acceptable by official organizations. The report caused a series of debates among researchers.

In the years that followed, publications based exclusively on that letter recommended to not re-sterilize any previously irradiated material with EO[2-4], thus contributing with the dissemination of the alleged incompatibility between those two methods of sterilization.

In Brazil, the controversy emerged in 1982, in a book that states the following information:

> No previously gamma-irradiated PVC material should sterilized with ethylene oxide because there is a further reaction between the HCl (hydrochloric acid) residue set off by the irradiation and ethylene oxide, producing ethylene chlorohydrin, which has the same caustic properties of ethylene oxide, but is much more difficult to remove[5].

That statement is supported by the reference of a study performed in 1971[6], which evaluated the duration of EO retention in materials made of PVC, rubber, Teflon and Polyethylene, and the toxic level of the gas for the tissues by means of subcutaneous implants in rats. That study did not address the incompatibility between sterilization methods, so it could not have been cited as a support for the statements made by the author.

The author of another book, this one from 1987[7], states that if the times recommended for the aeration of PVC material are followed, previous irradiation from GR would not contraindicate consecutive sterilization with EO. That statement was based on a primary study from 1976[8], in which EO concentrations were dosed in endotracheal PVC tubes and its decrease rate over aeration time, and on a 1961 study[9], which consisted in evincing the harm to plastic after EO sterilization, without any reference to the previous use of GR. Another study, from 1997[10], presents the same statement followed by the same references.

It is observed that studies supporting the referred statement do not address the incompatibilities between sterilization methods. Therefore, they actually do not support the statements made by those authors.

In 1997, a bibliographic survey was performed on the subject and the author concluded that there were insufficient studies to solve the doubt and suggested that further experiments should be performed[11].

Nowadays, though there is no official recommendation prohibiting the procedure of re-sterilizing materials with an expired *sterilization date*, re-sterilization with EO is indicated for thermo-sensitive gamma-irradiated materials, despite the drawbacks of the method, such as adsorption and absorption of residual gas in the materials[12]. Nevertheless, studies that warn about the incompatibility of submitting materials that were previously gamma-irradiated, especially those made of PVC, to re-sterilization with EO leave doubts that must be solved.

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OBJECTIVE

To perform an analysis on scientific literature that evinced the compatibilities and incompatibilities between Gamma Radiation and Ethylene Oxide as consecutive sterilization methods.

METHOD

This is an integrative literature review, using a method that permits to include both empirical and theoretical literature, of which main advantages include the possibility of combining data obtained through different study designs[13].

The guiding question used in the present literature review was: *Is there any incompatibility or compatibility in the re-sterilization of materials consecutively sterilized with GR and EO?*

The material for the review was obtained through a search on the electronic databases: LILACS, PubMed/MEDLINE and SciELO. The following keywords were used: Gamma radiation, Ethylene Oxide and Sterilization. As a complementary strategy, a survey was performed on the archives of the following Libraries: Biblioteca da Escola de Enfermagem da Universidade de São Paulo, Biblioteca Central da Universidade Federal de São Paulo; and, also, a tree survey, which consists in searching for the references used to support the identified primary studied with the purpose of accessing the primary sources.

The survey included studies that performed experiments with the purpose to find incompatibilities or compatibilities of re-sterilizing with EO materials previously sterilized with GR.

A critical analysis of each study was performed based on the synoptic chart, which included a description of the methodological features obtained from the studies (Chart 2) and on the result synthesis chart (Chart 3).

RESULTS

With the purpose to facilitate the presentation of the results and the discussion, the selected studies were coded from E1 to E7. Chart 1 lists all studies per code, reference, and evidence.

Chart 2 lists the methodological aspects of the analyzed studies.

Chart 3 presents the synthesis of the results presented in the selected studies.

Chart 1 - Presentation of the selected studies by their evidence

Code	Complete reference	Evidence
E1	Cunliffe AC, Wesley F. Hazards from plastics sterilized by ethylene oxide. **Br Med J**. 1967	Incompatibility
E2	Lipton B, Gutierrez R, Blaugrund S, Litwak RS, Rendell-Baker L. Irradiated PVC plastic and gas in the production of tracheal stenosis following tracheostomy. **Anesth Analg**. 1971	Incompatibility
E3	Handlos V. Ethylene chlorohydrin formation in radiation and ethylene oxide-sterilized poly(vinyl chloride). **Biomaterials**. 1984	Incompatibility
E4	De Seille JM, Delattre L, Meurice L, Jaminet F. Etude de l'effet d'une sterilisation A l'oxyde d'ethylene sur les teneurs residuelles en chlorhydrine du glycol et en ethyleneglycol dans des articles medico-chirurgicaux a base de pvc, prealablement irradies au cobalt 60. **J Pharm Belg**. 1985	Incompatibility
E5	Bogdansky S, Lehn J. Effects of y-Irradiation on 2-chloroethanol formation in ethylene oxide-sterilized polyvinyl chloride. **J Pharm Sci**. 1974	Compatibility
E6	Star EG. Gamma-Strahlen und Äthylenoxid-sterilisation. **Zentralbl Bakteriol Mikrobiol Hyg**. 1980	Compatibility
E7	Ceribelli MIPF, Cruz AS, Toledo, HHB. Raios gama e óxido de etileno II: esterilizações incompatíveis? (Análise piloto). Acta Paul Enferm. 1998	Compatibility

Chart 2 - Presentation of the studies per raw-material, sterilization parameters and the analytical methods used

Code	Materials / Raw-material	GR Sterilization	EO Sterilization	Analytical methods	Type/Time of aeration
E1	PVC	Not informed	Not informed	Extraction in distilled water, blood and/or saline solution (Detection methods not informed)	The texts suggests that the residue was detected on a daily basis up to the sixth day after sterilization with EO
E2	PVC tubes	Performed by the manufacturer	120°C and 6 h of exposure	Chromatography	3 air washes and 6, 7, 8 and 9 weeks on shelves
E3	PVC with the several stabilizers	32 kGy	EO 0,5 g l^{-1}, 45°C	Chromatography	Not performed
E4	Rigid and flexible PVC tubes and PVC powder with different intervals between sterilizations	0, 15 and 30 kGy	EO 12% / Freon 88%, 55,6°C, 60% humidity, pressure of 7 psi, 9 h of exposure	Chromatography	0, 1, 5, 12, 20, 34, 61, 91 days
E5	PVC tubes	2,5 and 5,0 Mrads.	EO 12% / Freon 88%, concentration of 1099 mg/l, 55°C, 50 % humidity, pressure of 15 psi and 4,5 h of exposure	Chromatography	Environment for 0, 2 and 4 days
E6	PVC tubes	Performed by the manufacturer (2,5 Mrads)	Pure EO, 55°C and 90 min of exposure	Chromatography / Cytotoxicity	0, 4 and 21 days for Gas chromatography /5 and 7 days for cytotoxicity
E7	Surgical gloves and surgical cotton threads	Performed by the manufacturer	210 minutes of exposure	Cytotoxicity	127 minutes, hiperventilation for 60 min under pressure of 0.50 kgf/cm^2 with intermittent vacuum of up to -0,50 kgf/cm^2.

Chart 3- Synthesis of the selected studies results

Code	Synthesis of the results
E1	A small amount of chloride was found in the distilled water used to wash the PVC tubes that had previously been sterilized with GR. Nevertheless, a considerable amount of ETCH was found when those tubes were re-sterilized with EO.
E2	It was evinced that "significant" amounts of ETCH were present in all samples, even after nine weeks of aeration.
E3	It was found that the ETCH concentration formed on the pre-irradiated flexible PVC was small compared to that formed on the rigid PVC, due to the smaller intensity at heating, responsible for the emission of Chlorine during its manufacture and better conditions for diffusion. The amounts of ETCH residue also ranged according to the stabilizers used in the polymer.
E4	It was observed that ETCH concentrations increased significantly with higher doses of GR. Regarding the flexible tubes, the initial ETCH levels were higher, but the deabsorption kinematics is similar including in higher GR doses. Regarding the rigid tubes, raher than eliminating ETCH with time, it was observed that its concentration increased. In general, a smaller interval between sterilizations resulted in greater amounts of residue.
E5	About 350 ppm of ETCH was observed in the non-aerated materials, which, according to the authors, is a non-toxic amount.
E6	It was observed that the re-sterilization of previously gamma-irradiated PVC with EO actually increases the levels of ETCH formed. Those levels, however, decreased with time of aeration. The cytotoxicity test showed that, in some cases, after 5 days of aeration, the material did not cause cellular hazards, thus permitting to state that pre-irradiated PVC material could be re-sterilized with EO provided that the recommended aeration time was followed.
E7	The results showed that all surgical glove sample presented a cytotoxic effect, regardless of their being re-sterilized with EO. Regarding the surgical thread samples, it was shown that the original cytotoxicity levels of the threads was limited to the sample area, and no surounding lesions were observed, and the same occurred after their exposition to the two sterilization processes, thus revealig there was no cytotoxicity.

DISCUSSION

From the methodological perspective, study E1 (original 1967 letter that initiated the polemic) is fragile because there is insufficient details to make it reproducible. Therefore, its results are questionable. Furthermore, no quantitative experimental data was presented. The referred study presented a 1965 study[14] as reference, which evinced the formation of toxic chlorohydrins in food, when fumigated with EO, due to the presence of Chlorine on its surface. There is no report on previous exposition of samples to GR: therefore, this study does not offer solid support to the statements made by the authors.

Study E2 does not present reference doses, which would permit to classify the amounts founds as *significant*. The dose of radiation used was not specified, neither was the concentration of the sterilizing agent, thus compromising the reproducibility of the study.

Study E3 did not include the aeration time after the re-sterilization with OE before the analyses, which is determinant for safety when using these materials. The study did, however, present in detail the composition of the PVC used, showing that it interferes on the residual concentrations of EO and its byproducts. Furthermore, it highlighted the differences of gas elimination on rigid and flexible PVC.

Study E4 presented in detail the parameters used for sterilization. One important variable controlled in the study was the interval between sterilizations. The authors concluded that it would be sensible to wait a few days for the material to *recover* before submitting it to re-sterilization with EO. That variable should be further investigated. Another important aspect considered in the study was the presentation of the material: rigid, flexible and powder, which was determinant for the safety of re-sterilization with EO.

Study E5 was meticulous regarding the description of the parameters used for sterilization. In addition, it was the first study that contested study E1, generating the polemic of incompatibility between sterilization methods. The result permitted that, in 1976, another study ensured that provided the recommended aeration time for PVC materials is followed, their previous irradiation does not represent a contraindication to their re-sterilization with EO[15].

Study E6 used cell culture toxicity and residue quantification methods. Though pure EO was used for sterilization, results showed there was compatibility between sterilization methods. Though it used gas chromatography to quantify the residues of EO and its byproducts, the authors concluded the results based on cellular toxicity tests.

Study E7, opposed from the other studies, used latex and cotton as samples. Though it did not use PVC materials, this study draws our attention to the cytotoxicity of the materials used in health care even when those are not exposed to EO. This factor calls for further studies. Other characteristics that should be highlighted are the use and specification of forced aeration used to eliminate residues from EO and its byproducts, which is essential to guarantee safety when using material sterilized by this method.

Controversies exist regarding the results of studies that used gas chromatography as an analytical method. This fact may indicate that the method is questionable in terms of its sensitivity to evince the answer to the guiding questions in the studies. On the other hand, the analysis of cellular

toxicity used in two studies proved to be a method that could verify cellular death at the presence of toxic substances in materials submitted to sterilization using those agents, because the samples are tested directly in live cells, thus simulating the contact of the material containing toxic residue with human subjects, as it would occur in health care practice.

CONCLUSION

The analysis of the evidence presented in the studies showed that there is no specific situation in which these procedures are totally safe, because, based on the performed experiments, the safety of the procedure could be affected my several factors, including: the type of raw-material, whether the material is flexible or rigid, conformation with the product, the addictives (stabilizers) used, besides the aeration time of the material after sterilization with EO. Nevertheless, these factors were found base on studies that used, namely, gas chromatography as the analytical method, which is currently questioned by experts.

The final statement points at the need for further studies that use analytical methods more sensitive than gas chromatography, e.g. the biological reactivity test in cellular cultures, to solve the chronic doubt that exists in our field of study, concerning the compatibility or incompatibility of sterilizing with EO materials that have been previously gamma-irradiated.

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Correspondence addressed to: Kazuko Uchikawa Graziano
Av. Dr. Enéas de Carvalho Aguiar, 419 - Cerqueira César
CEP 05403-000 - São Paulo, SP, Brazil