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Analysis of the principles of green chemistry in the radioiodination of metaiodobenzylguanidine compared to the principles already adopted for radiological protection

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Abstract: Environmental concerns have increasingly highlighted the importance of applying methodologies that prioritize safer waste treatments, the use of less toxic reagents, and milder synthesis conditions. In this context, radioiodinated metaiodobenzylguanidine (MIBG) stands out as a key radiopharmaceutical used in diagnostic scintigraphy and therapy of neural crest-derived tumors, such as pheochromocytoma and neuroblastoma, as well as in assessing sympathetic neuronal integrity after cardiac events. Halogenation reactions that avoid toxic reagents and hazardous conditions are essential for producing safe pharmaceutical compounds. Radioiodination, a specific type of halogenation, plays a critical role in the synthesis of radiopharmaceuticals—radioactive compounds formulated for diagnosing and treating human diseases. A major challenge in the production of radioiodinated MIBG is aligning the process with the principles of green chemistry, emphasizing the use of harmless substances and minimizing their quantities, while also meeting stringent nuclear, radiological protection, and pharmaceutical regulations. However, green chemistry considerations are often neglected in this process. This study quantitatively assesses the application of green chemistry principles to existing radioiodination methods for MIBG. The degree of compliance with each principle was expressed as a percentage. Additionally, a qualitative analysis was conducted to explore the alignment between green chemistry and radiological protection principles. Green chemistry is guided by twelve principles: Prevention, Atom Economy, Less Hazardous Chemical Syntheses, Designing Safer Chemicals, Safer Solvents and Auxiliaries, Energy Efficiency, Renewable Feedstocks, Reducing Derivatives, Catalysis, Design for Degradation, Real-Time Analysis for Pollution Prevention, and Inherently Safer Chemistry for Accident Prevention. This work

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examines how each principle applies to MIBG radioiodination, with some aspects also discussed in the broader context of radiopharmaceutical production. While radioiodinated MIBG complies fully with pharmaceutical requirements in its final medicinal formulation, its production currently incorporates about 68% of the green chemistry principles. As radiopharmaceutical production moves forward, greater attention should be given to eco-friendly practices. Investing time and resources into adopting green principles for MIBG radioiodination is a logical next step. This radiopharmaceutical holds well-established clinical importance, and future advances in its production should embrace sustainable, environmentally conscious methodologies.

Keywords: Green Chemistry, Radiological Protection, Radioiodination, Metaiodobenzylguanidine.

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Análise dos princípios da química verde na radioiodação da metaiodobenzilguanidina em comparação com os princípios já adotados para proteção radiológica

Resumo: Questões ambientais vêm direcionando atenção especial para métodos que promovam tratamentos adequados de descarte, uso de reagentes menos tóxicos e condições mais brandas nas rotas de síntese. A metaiodobenzilguanidina radioiodada (MIBG) é um radiofármaco de destaque na cintilografia diagnóstica e na terapia de tumores da crista neural, como feocromocitoma e neuroblastoma, além de contribuir para o prognóstico da integridade neuronal simpática após insuficiência cardíaca. Reações de halogenação que evitam substâncias tóxicas e condições perigosas geram compostos fundamentais para a indústria farmacêutica. Nesse contexto, a radioiodação é um exemplo específico de halogenação, essencial na síntese de radiofármacos — compostos radioativos empregados no diagnóstico e tratamento de doenças humanas. Do ponto de vista da química verde, a produção de MIBG radioiodada apresenta o desafio de priorizar o uso de substâncias inofensivas e de otimizar processos que minimizem o impacto ambiental, respeitando simultaneamente regulamentações nucleares, de proteção radiológica e farmacêuticas, embora, até o momento, tais processos pouco considerem uma abordagem ecológica. Este trabalho apresenta um estudo quantitativo da aplicação dos princípios da química verde aos métodos de radioiodação da MIBG. A conformidade com esses princípios foi expressa em porcentagem. Complementarmente, propõe-se uma análise qualitativa do alinhamento entre os princípios da proteção radiológica e os da química verde. A Química Verde baseia-se em 12 princípios: Prevenção; Economia Atômica; Sínteses Químicas Menos Perigosas; Desenho de Produtos Químicos Mais Seguros; Solventes e Auxiliares Mais Seguros; Eficiência Energética; Matérias-primas Renováveis; Redução de Derivados; Catálise; Desenho para Degradação; Análise em Tempo Real para Prevenção da Poluição; e Química Inerentemente Mais Segura. Este trabalho discute como cada princípio se relaciona com a radioiodação da MIBG, abordando também aspectos aplicáveis a radiofármacos em geral. Embora a produção da MIBG atenda integralmente aos requisitos farmacêuticos, atualmente cerca de 68 % dos princípios da química verde são contemplados. A incorporação de práticas sustentáveis representa o próximo passo na produção e controle de qualidade de radiofármacos, aliando segurança, eficácia e responsabilidade ambiental.

Palavras-chave: Química Verde, Proteção Radiológica, Radioiodação, Metaiodobenzilguanidina.

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1. INTRODUCTION

Environmental requirements have been paying special attention to methodological applications regarding disposal treatments, the use of less toxic reagents and milder conditions of synthesis routes. Profound concerns over environmental issues as well as human exposure have been considered.

The concept of green chemistry emerged from 90's decade and it is becoming increasingly important to apply its principles to every area of science. Green chemistry goals are hazard minimization and prevention of chemical waste, which lead to redesigning some or every process stage of a product. This approach offers an ecological improvement for the process, while broad its sustainability [19] [25]. The basic idea of green organic synthesis involves reactions using water as preferable medium. The water solvent presents some advantages over traditional organic solvents such as non-toxicity and non flammability. Due to its low cost and abundance, water as a reaction medium fulfills the need for environmentally and economically acceptable processes. Bearing it in mind, it is also needed that the reactants used lead to the main substance and harmless products.

The halogenation reactions, for instance, are usually carried out with hazardous, toxic and corrosive molecular halogens or even performed in chlorinated solvents. Halogenated organic compounds are commonly used as starting substrates and synthetic intermediates for industrial chemicals and bioactive molecules. Its unquestionable usefulness has evaluated many alternative green halogenation routes' developments [24], [26], [28], [35]. An example of green and less toxic reaction is the iodination of aromatic compounds through the oxidation of I^- applying H2O2, NaClO or KIO3. The eletrophilic iodonium species formed attack the aromatic nucleous [1], [20],[27], [29], [31].

Radioiodination reactions represent a particular example of halogenation and are also extensively used for labelling biomedical compounds of interest. Triiodide, iodine

monochloride or chloramine-T are some substances used for this purpose [33]. The radioiodinated molecules obtained are then called Radiopharmaceuticals, which are radioactive compounds in medicinal formulations used for the diagnosis and for therapeutic treatment of human diseases.

Radiopharmaceuticals act as an important tool in Nuclear Medicine. Some of them are also used in Veterinary Medicine. Its composition allows metabolism tracking through a detectable radioactive signal that results in subsequent images mapping physiological function or metabolic activity of a specific organ [3], [7] [10],.[11]. [17]. [40]. They can be synthesized by nucleophilic and eletrophilic substitutions, isotopic exchange, quelanting methods or biosynthesis, for example [33]. Due to being a medicine, Radiopharmaceuticals synthesis must result in non toxic preparations. On the other hand, some routes consider the use of hazardous goods such as 18FDG synthesis that uses kryptofix, acetonitrile and ethanol. Therefore, further purification and quantification of these toxic substances in the final product are necessary [43].

The production of Radiopharmaceuticals involves radioactive substances handling and chemical processing, therefore exhibit some peculiarities such as small volumes, special plumbiferous shielding, remote operations, special treatment for liquid and volatile wastes, for example. Moreover, it involves pharmaceutical and nuclear regulations. The risks associated with their production depend on the types of radiation emitted and the radioisotopes half-lives. The retention of contaminated materials and waste disposal also requires special attention [42]. Bearing those specialties in mind, various aspects of metaiodobenzylguanidine radioiodination are presented below.

2. MATERIALS AND METHODS

2.1. Radioiodination of metaiodobenzylguanidine (mIBG)

Since its introduction in 1980, radioiodinated metaiodobenzylguanidine still plays an important role in diagnostic scintigraphy and therapy of a neural crest derived tumors, such as pheocromocytoma and neuroblastoma, as well as for the prognostic of cardiac sympathetic neuronal integrity after heart failure [15], [16], [30], [38], [41]. Due to its structural resembling with noradrenaline, this compound emulates noradrenaline uptake and storage in adrenomedullary cells and sympathetic neurones [38].

mIBG can be labeled with 131I or 123I radioisotopes. The latter exhibits distinct advantages compared to 131I. Its 159 keV photon energy and 13.2 h half life allow higher quality images for single photon emission computed tomography (SPECT) and the absorbed dose for patients is lower than 131I [15]. However, 131mIBG is most widely used because of its higher shelf-life and use for therapy of several neuroendocrine tumors [6], [12], [16]. Some other analogues of mIBG, including labeled with alpha or positron emitters radioisotopes, besides arakilguanidines have been developed, which improved their aplication for other diseases, imaging quality and tumor uptake and retention [38].

Isotope exchange method is commonly used for the radioiodination of mIBG. This technique consists in the replacement of the stable iodine bonded in the aromatic ring for the radioiodine according to a nucleophilic substitution mechanism. The first extensive paper on this method for mIBG radioiodination was published by MANGNER *et al* (1982). This reaction is carried out in solid state; 0.22 mg of mIBG precursor and 25 mg of $(NH_4)_2SO_4$ are dissolved in 0.2-1.0 mL of water, then few microliters of radioidine in NaOH diluted solution are added. The mixture is heated at 140o C for 30 min leading in a 90-98% yield. Many modifications from this original route are described in the literature [41].

The radioiodination of mIBG can occur through several methods such as ammonium sulphate facilitated, copper (II) catalyzed or copper(I) assisted methods [41], as shown in

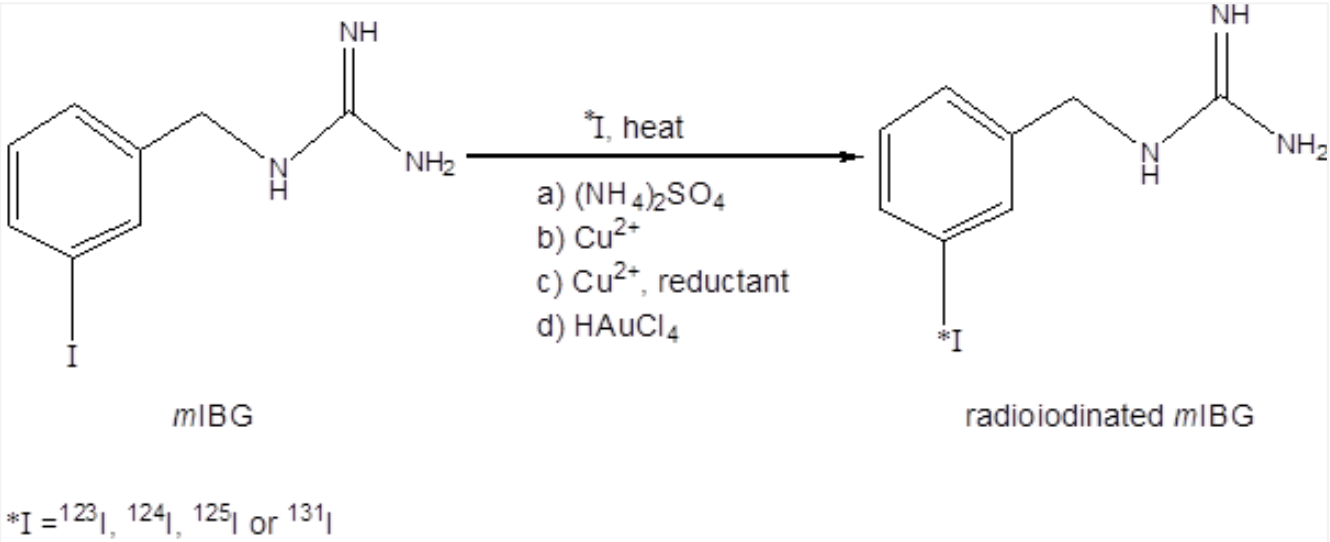
Table 1. The first mechanistic approach for the latter method was provided by MERTENS & GYSEMANS (1991). Figure 1 presents the illustration related to these methods.

Table 1: Methods references for the carrier-added (c.a.) radioiodinated *m*IBG.

Ammonium sulphate facilitated methods		
	Method reference	**Raw material (beyond mIBG, water and radioiodine)**
1	*Mangner et al, 1982	$(NH_4)_2SO_4$
2	*Mangner et al, 1983	$(NH_4)_2SO_4$, Acetic acid
Copper(II)-catalysed methods		
	Method reference	**Raw material (beyond mIBG, water and radioiodine)**
3	*van Dorelamen and Janssen, 1985	$Cu(NO_3)_2$
4	*Mertens et al, 1986	$CuSO_4$
5	*Mertens et al, 1986	$CuSO_4$, Acetic acid
6	Lambrecht et al, 1991	$Cu(NO_3)_2$, NaH_2PO_4
7	Carvalheira, 2008	$CuSO_4$, $(NH_4)_2SO_4$, Ethanol
Copper(I)-assisted methods		
	Method reference	**Raw material (beyond mIBG, water and radioiodine)**
8	*Mertens et al, 1986	$CuSO_4$, Ascorbic acid, $SnSO_4$
9	*Dougan et al, 1988	$CuSO_4$, Sulfuric acid, $SnSO_4$
10	*Neves et al, 1992	$CuSO_4$, Acetic acid, $Na_2S_2O_5$
11	*Franceschini et al, 1991	$CuSO_4$, Sulfuric acid, Ascorbic acid, $SnSO_4$
12	*Rossouw, 1992	$Cu(NO_3)_2$, Acetic acid, Ascorbic acid
13	Daming et al, 1996	$Cu(CH_3COO)_2$, Ascorbic acid, Acetic acid, Ethanol
Other assisted methods		
	Method reference	**Raw material (beyond *m*IBG, water and radioiodine)**
14	*Sinn et al, 1987	$HAuCl_4$, $CaCl_2$, Chloridric acid

* Source: Wafelman, A. R. et al., 1994.

Figure 1: Isotope exchange reaction for mIBG radioiodination: a) ammonium sulphate facilitated method, b) copper (II) catalysed method, c) copper(I) assisted method, d) tetrachlorogold acid assisted method. The radioiodine isotopes used are obtained in a diluted NaOH solution.



Isotope exchange results in a carrier added final product, e.g., the final product includes radioiodinated mIBG as well as the unlabeled mIBG. Large amounts of mIBG should be avoided in the final product because it may result in unwanted side effects for the diagnostic [8]. To surmount this problem, no carrier added (n.c.a.) radioidination of mIBG was evaluated (Table 2). However, a significant disadvantage of this radioiodination method is that chromatographic purification or filtration is required to remove the remaining starting chemicals, except the method which applies polymer supported technique [38].

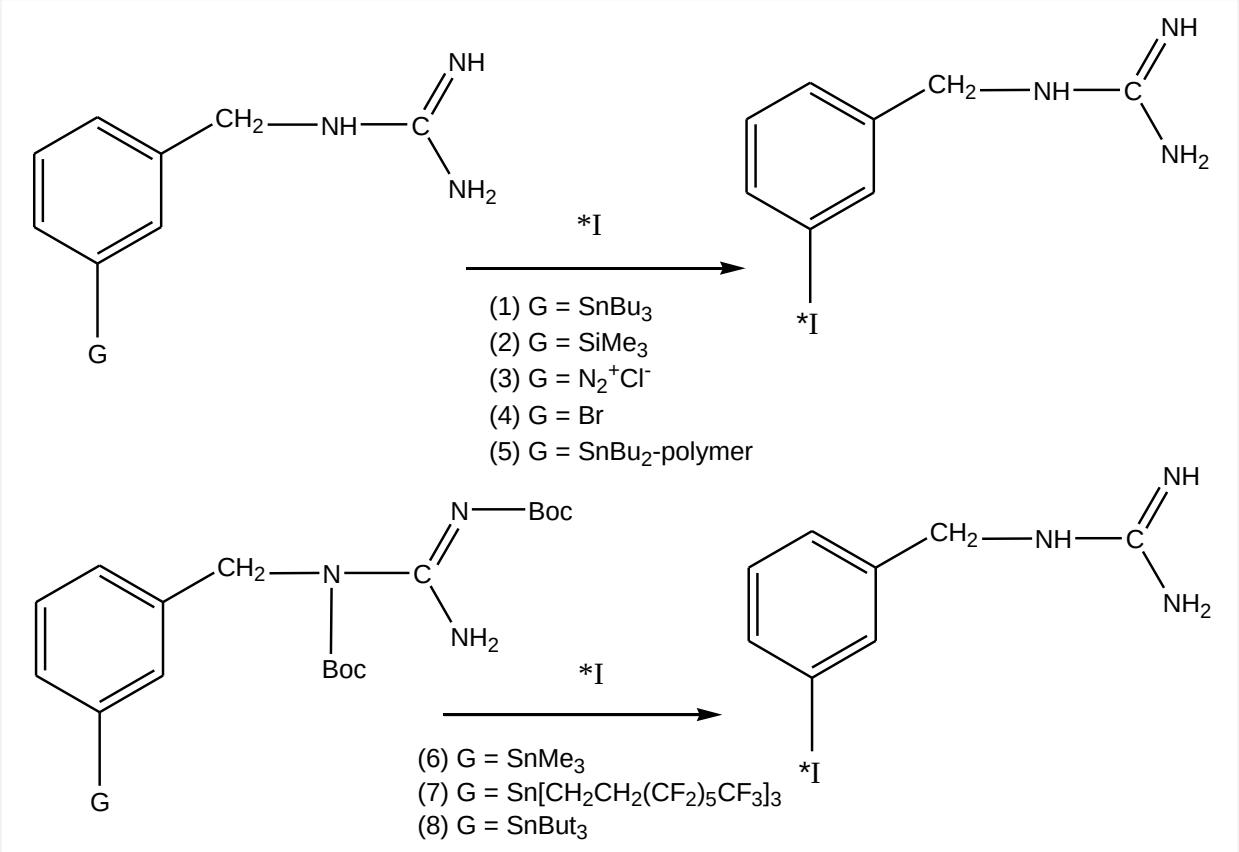
Figure 2 shows the use of different precursors for n.c.a. synthesis of radioiodinated mIBG.

Table 2: Methods references for the no-carrier-added (n.c.a.) radioiodinated mIBG **No-carrier-added (n.c.a.) synthesis methods**

	Method reference	Raw material (beyond radioiodine)
1	Vaidyanathan and Zalutsky, 1993	(1), Peracetic acid, Cyanamide, Chloroform, Methanol
2	Vaidyanathan and Zalutsky, 1993	(2), H_2O_2 , Acetic acid, Trifluoroacetic acid, N-chlorosuccinimide
3	Mairs et al, 1994	(2), Trifluoroacetic acid, N-chlorosuccinimide, Methanol
4	Mairs et al, 1994	(3)
5	Samnick, 1999	(4), $CuSO_4$, Sodium metabisulfite

	Method reference	Raw material (beyond radioiodine)
6	Hunter & Zhu, 1999	(5), Acetic acid, NaH_2PO_4, H_2O_2, Methanol
7	Katsifis et al, 2006	(2), Chloramine-T, NH_4OH, Trifluoroacetic acid, Ethanol
8	Vaidyanathan et al, 2007	(6), Acetic acid, N-chlorosuccinimide
9	Vaidyanathan et al, 2007	(6), Trifluoroacetic acid
10	Donovan & Valliant, 2008	(7), Iodogen, Acetic acid, Methanol, Sodium metabisulfite
11	Rossouw & Macheli, 2009	(8), Trifluoroacetic acid, N-chlorosuccinimide

Figure 2: Illustration of the precursors used for n.c.a. radioiodinated *m*IBG referred in Table 3.



(1) meta-tri-n-butylstannyl)benzylamine

(2) meta-trimethylsilylbenzylguanidine

(3) meta-diazobenzylguanidine

(4) meta-bromobenzylguanidine

(5) polymer-supported 3-benzylguanidinium

(6) N, N'-bis(tert-butyloxycarbonyl)-3-(trimethylstannyl)benzylguanidine

(7) meta-tris[2-perfluorohexylethyl]stannylbenzylguanidine

(8) N, N'-bis(tert-butyloxycarbonyl)-3-(tributylstannyl)benzylguanidine

Both carrier-added (c.a.) and no-carrier-added (n.c.a.) methodologies need special treatment concerning radioactive material manipulation and disposals.

Despite the importance and notoriety of radioiodinated *m*IBG applications, concerns about its eco-friendly routes of synthesis were not reported yet. To start an evaluation of the green approach for *m*IBG radioiodination methods presented previously, they will be discussed with special emphasis on the raw materials used, taking into account the twelve principles of green chemistry [19]. The philosophy of these principles is the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances, as shown in Table 3.

Table 3: The twelve principles of green chemistry.

1.	Waste prevention is preferable to waste treatment or clean up after it has been formed
2.	Wherever practical, synthetic methodologies should be designed to use or generate substances that exhibit little or no toxicity to human health and the environment
3.	Synthetic methodologies should be designed to maximize the incorporation of all materials used in the process into the final product.
4.	Raw material or feedstock should be renewable, rather than depleting, wherever technically and economically practical.
5.	Selective catalytic reagents are superior to stoichiometric reagents, all other factors being equal.
6.	Unnecessary derivatives (e.g., blocking groups, protecting groups, temporary modification of physical/chemical properties, etc.) should be avoided where possible.
7.	The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be eliminated wherever possible, and in cases where they are necessary, they should be innocuous.
8.	Energy requirements should be recognized for their environmental and economic impacts and correspondingly minimized.
9.	Chemical products should be designed to achieve efficacy of function while reducing toxicity.
10.	Chemical products should be designed so that, at the end of their functional life, they do not persist in the environment and break down into innocuous degradation products.
11.	Substances used in a chemical process, and the specific form of those substances, should minimize the potential for chemical accidents resulting from releases, explosions, and fires, for example.
12.	Analytical methodologies should be developed and used to allow for real-time, in-process monitoring and control to reduce or eliminate the formation of hazardous or unwanted substances.

The degree of compliance with each principle was expressed as a percentage. Additionally, a qualitative analysis was conducted to explore the alignment between green chemistry and radiological protection principles.

3. RESULTS AND DISCUSSIONS

3.1. The principles of green chemistry over mIBG radioiodination methods

This approach deals with the interpretation of each green chemistry principle and the peculiarities of mIBG radioiodination related to it, as presented as follow. Some aspects will be referred to in radiopharmaceuticals in general, as well.

The first principle is attended if the half-life of radioiodine is considered. After ten half-lives, most of the radiation is no longer present in the residual materials used in the synthesis like filters, vials or clamps. They are free of radiation and can be treated as common residue.

The second one is clearly suitable for radioiodinated mIBG once it is properly for human use. Radiopharmaceuticals, in general, are non toxic, but can exhibit low side effects for the patient [14], [36].

Atom economy concept is referred to as the third principle. This approach refers to the sustainable chemistry movement that represents a metric for quantification purposes [9]. The mass index (Equation 1) and the environmental factor (Equation 2) are auxiliary tools for the establishment of mass balance that integrate solvents, catalysts and other chemicals involved in the reaction [9].

$$\text{Mass index} = \sum \frac{RM(kg)}{P(kg)} \quad (1)$$

$$\text{Environmental factor} = \sum \frac{W(kg)}{P(kg)} \quad (2)$$

RM = raw material

W = waste

P = product

If this quantitative approach was applied for mIBG radioiodination, those equations should be rearranged in a manner that the radioactivity should be prior to the other chemicals masses once they are practically unmodified in the process – radiochemical raw material mass is around 10-17 g. For radiochemical synthesis, the yield is related to the fraction of radioiodine that labeled mIBG and the residual one. Any radiopharmaceutical labeling is designed to reach the maximum incorporation of the desired radioisotope into the molecule of interesting. For those methods that the final product obtained is carrier-added, the precursor amount is higher than the n.c.a. ones and consequently, the incorporation of radioiodine is low. Then, n.c.a. methods attain the third principle prior to the other ones.

For n.c.a. synthesis, the remaining chemicals should not be reused because after processing, the whole system must be cleaned up to keep its hygienic conditions. As for the carrier-added methods, the residual chemicals are part of the final product, which become fourth an unattainable principle.

Any radiochemical synthesis deals with substoichiometric quantities of the desired radioisotope. Besides, the mass used for the other reagents involved falls in the range of a few milligrams and few milliliters. The mIBG radioiodination, for instance, applies only 0.2 to 5.0 milligrams of the mIBG precursor. In addition, most of mIBG radioiodination methods also uses catalyst. These aspects, when completely considered, fulfill the fifth principal claim.

The sixth principal concerns secondary substances formation. Every method of radiopharmaceutical synthesis must result in neither modification nor side products, so, this point is also naturally attended.

The seventh one can be accepted for carrier added mIBG radioiodination (Table 1) because the main solvent used is water, a totally innocuous medium. For the n.c.a. methods (Table 2), the solvents are used in some very small quantities, but the waste formation is not avoided, refusing the acceptation of this principle.

Several methods of mIBG radioiodination occur under defined temperature. Because of this irreducible necessity, eighth principle is out of question for these methods. On the other hand, for some n.c.a. methods high temperatures are not necessary, so they fully accomplish this principle.

The ninth and the tenth principles of green chemistry are connected to the second one and are also naturally attended by any radiopharmaceutical production. During the designing of a radiopharmaceutical, high efficacy which is radiopharmaceutical maximum uptake by the target organ, and toxicity reduction are key parts of the whole project - more details about the design of radiopharmaceuticals are presented by Saha (2004). In addition, the radioisotopes used are short-lived ones and their decay products are neither toxic for the patient nor the environment. Specific rules for radioactive waste management are defined by the International Atomic Energy Agency.

The eleventh one concerns chemical accidents. The substances handled in the mIBG radioiodination minimizes the risks of it, even being used some flammable solvents and heating, due to their very small quantities in the reaction medium. The radioactive hazards were not clearly considered at this principle. For this reason, maybe some considerations should be made for those cases which deal simultaneously with radioactive and chemical substances.

The analytical methodologies were not evaluated herein. If they would, probably, the twelfth principle would not be part of the ones attained, once toxic chemicals such as

methanol are used in chromatographic techniques, for example. This means that quality control is an important tool for greener methodologies of mIBG radioiodination. An eco-friendly methodology for the 123I-mIBG analyses was developed to overcome the use of toxic solvents [4]. This work aimed at the optimization of the chromatographic method to decrease analysis time and mobile phase toxicity, applying ethanol as the organic modifier. Recently, it was selected as an alternative method to integrate the Brazilian Pharmacopoeia next version.

Aiming the assessment of this correspondence, these methods were related to those principles to evaluate quantitatively the green chemistry approach extension. The green principles achieved were highlighted for each method of c.a. and n.c.a. mIBG radioiodination. The twelfth principle was not considered because analytical methodologies were not evaluated in this work. Table 4 presents the results obtained for c.a. methods evaluated.

Table 4: Principles of green chemistry attained for the c.a. methods previously presented. These methods are displayed in Table 1.

	Principles of green chemistry											Percentage of green chemistry approach attained
C.a. methods	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
1	■	■				■	■		■	■	■	63,6
2	■	■				■	■		■	■	■	63,6
3	■	■			■	■	■		■	■	■	72,7
4	■	■			■	■	■		■	■	■	72,7
5	■	■			■	■	■		■	■	■	72,7
6	■	■			■	■	■		■	■	■	72,7
7	■	■			■	■	■		■	■	■	72,7
8	■	■			■	■	■		■	■	■	72,7
9	■	■			■	■	■		■	■	■	72,7

C.a. methods	Principles of green chemistry											Percentage of green chemistry approach attained
	1	2	3	4	5	6	7	8	9	10	11	
10	■	■			■	■	■		■	■	■	72,7
11	■	■			■	■	■		■	■	■	72,7
12	■	■			■	■	■		■	■	■	72,7
13	■	■			■	■	■		■	■	■	72,7
14	■	■				■	■		■	■	■	63,6

As described above, only a part of the whole green chemistry principles is attended by mIBG radioiodination methods presented herein.

As seen in Table 4, the methods ranging from 3 to 13 exhibit the highest percentage of the green approach just because of the fifth principle. One can consider that this slight difference in quantitative terms means no great significance, however, this principle is also related to the use of catalysts. Catalysts are responsible for saving time in reactions. As shown in table 4, most of c.a. methods adopt the use of it. The time expended in the radiosynthesis is a critical parameter due to the radioisotopes half lives. The Radiopharmaceuticals production logistical is severally guided by the radioisotope decay, final product delivery and clinical exam duration. Hence, these methods can be considered greener and prior to the other c.a. methods. The results obtained for n.c.a. methods are presented in Table 5.

Table 5: Principles of green chemistry attained for the n.c.a. methods previously presented. These methods are displayed in Table 2.

N.c.a. methods	Principles of green chemistry											Percentage of green chemistry approach attained
	1	2	3	4	5	6	7	8	9	10	11	
1	■	■	■			■			■	■	■	63,6
2	■	■	■			■			■	■	■	63,6

N.c.a. methods	Principles of green chemistry											Percentage of green chemistry approach attained
	1	2	3	4	5	6	7	8	9	10	11	
3	■	■	■			■		■	■	■	■	72,7
4	■	■	■			■			■	■	■	63,6
5	■	■	■			■			■	■	■	63,6
6	■	■	■			■		■	■	■	■	72,7
7	■	■	■			■		■	■	■	■	72,7
8	■	■	■			■			■	■	■	63,6
9	■	■	■			■			■	■	■	63,6
10	■	■	■			■		■	■	■	■	72,7
11	■	■	■			■			■	■	■	63,6

The examination of Table 5 shows that for n.c.a. methods, the greenest ones are 3, 6, 7 and 10. The eighth principle clearly has become them superior once the use of heating is not necessary. Nowadays, saving energy is an eminent claim, which is remarkably considered in synthesis rout planning.

Some interesting points can be noticed when crossing both Tables 4 and 5 results. Differing from c.a. methods, the fifth principle is absent for n.c.a. ones, because the use of catalysts is not necessary, while the third one is only attended by the n.c.a. methods which are more selective. The fourth principle is not attended by both ones due to technical singularities which were explained previously. Only four n.c.a. methods fulfill the eighth principle, which indicates that the consumption of energy should be reviewed for mIBG radioiodination. Less toxic solvents should be used for n.c.a. methods to attain seventh principal requirements.

Still observing Tables 4 and 5, one can see that the fulfilment of green principles is extremely dependent on the synthesis route. On the other hand, the principles 1, 2, 6, 9, 10 and 11 are in common for c.a. and n.c.a. mIBG radioiodination methods and can be extended for any other Radiopharmaceutical synthesis.

One can also realize that both c.a. and n.c.a. methods attend seven to eight principles. None of them has fulfilled high or low principles. If the twelfth principle could be attained, the green approach would be rising from 72,7 to 75%. This small increase does not seem worthwhile, nevertheless, a routine analysis method should consider the waste production and its treatment, as well as the toxic substances exposure to the analysts.

Higher levels of green acceptance could be reachable if some improvements should be made. For instance, the third and the eight principles would be attended if further optimization studies could be done to minimize the heating and the consumption of mIBG precursor mass for c.a. methods. These refinements would result in 90,9% of green approach achievement, which is an unquestionable ascension in the green chemical principles agreement.

4. CONCLUSIONS

Radioiodinated mIBG is a medicinal formulation which completely fulfils radiopharmaceuticals requirements; however, it only attends, approximately, 63 to 73% of green chemistry principles. The n.c.a. radioiodinated mIBG shows the disadvantage of possible side effects or reduction of organ uptake, but it exhibits the higher quality of methods in agreement with the principles of green chemistry. However, the carrier-added preparations are preferred than the n.c.a. ones for some studies or clinical applications. The method which will be selected depends on the technology requirements, the radiochemical yield and the final product application.

Radiopharmaceuticals production should pay attention to the green concerns. Time and capital can be invested to fulfill green principles for the radioiodination of mIBG. This radiopharmaceutical has recognized and established importance on its usefulness in Nuclear Medicine. The next step for production and quality control of Radiopharmaceuticals is the accomplishment of eco-friendly concepts.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

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