



## Minireview

Lessons from the accident with  $^{137}\text{Cesium}$  in Goiania, Brazil: Contributions to biological dosimetry in case of human exposure to ionizing radiationElza Tiemi Sakamoto-Hojo<sup>a,b,\*</sup><sup>a</sup> Department of Biology, Faculty of Philosophy, Sciences and Letters at Ribeirão Preto, Brazil<sup>b</sup> Department of Genetics, Ribeirão Preto Medical School, University of São Paulo – USP, Av Bandeirantes 3900, 14040-901, Ribeirão Preto, SP, Brazil

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## ABSTRACT

Human exposure to ionizing radiation has increased over time, mainly due to medical applications, occupational and environmental exposure, as well as accidents involving radioactive materials. In September 1987, an accident with  $^{137}\text{Cesium}$  occurred in Goiânia city, Brazil; the accident started with the removal of a 50.9-TBq  $^{137}\text{Cesium}$  source from an abandoned radiotherapy unit. Among the radiation-exposed victims, at least 50 individuals showed symptoms of whole-body and local acute irradiation, and also external or internal contamination. In this report, the purpose was to review and summarize the main results of cytogenetic studies carried out with victims of  $^{137}\text{Cesium}$ , for blood collection performed shortly after the accident, and following several years post-exposure. The importance of dose estimates by biological dosimetry is highlighted, and also several lessons that were learned from the initial to follow-up (7–10 years after the accident) studies, mainly by applying the fluorescence in situ hybridization (FISH) method. A relevant aspect discussed on the basis of the results obtained in those studies refers to the incidence of chromosomal translocations, which were directly compared to the initial frequencies of dicentrics that were previously used to estimate the absorbed doses. In general, translocation frequencies were two to three times lower than the dicentric frequencies, and the differences were dose-dependent. Furthermore, regarding attempts to perform retrospective dosimetry (10 years post-accident), the dose estimates using translocation frequencies for victims of  $^{137}\text{Cesium}$  indicate the feasibility of this approach only for low level exposure (below 0.5 Gy), while for higher doses there are some limitations, and the requirement to apply appropriate correction factors, which were discussed on the basis of literature data. Apart of this, in general terms, important aspects to be mentioned refer to the need for better care and control of radioactive devices, as well as adequate education programs for professionals and also the population.

## 1. Introduction

## 1.1. Radiation exposure

Ionizing radiation (IR) has been extensively applied in diverse fields, especially in cancer therapy and diagnostic radiological procedures; apart from this, human exposure can occur due to several environmental exposures. Knowledge on the biological effects of radiation comes from studies of patients undergoing radiotherapy and those who received whole-body irradiation before bone-marrow transplantation, as well as from biomonitoring of exposed individuals in cases of nuclear accidents, such as the atomic A-bomb in Japan and the Chernobyl power plant accident [for review see Ref. [1]].

The biological effects of IR have been widely studied for several decades, and a body of evidence accumulated in the literature

demonstrates that acute or chronic exposure imposes a substantial risk to human health, mainly due to late effects associated with increased genomic instability [2,3]. The clastogenic potential of IR is well demonstrated in different cell types and organisms. For acute or chronic radiation exposure, chromosome aberrations are well accepted as a biological marker of IR exposure, and many cytogenetic studies in peripheral blood lymphocytes found increased frequencies of chromosomal aberrations at different levels of radiation exposure [2,4,5], even for radiation workers [6–10], for which accumulated absorbed doses calculated by personal physical dosimetry were available at the hospital and were found substantially lower than the permissible limits [10].

Estimates of radiation-induced malignancies come principally from studies with atomic (A)-bomb survivors; an elevated incidence of carcinomas was found linearly related to doses between 5 cGy and 2.5 Gy; nevertheless, above and below this range the shape of the dose-response

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relationship is not well-defined [11]. Actually, for very low levels, it has been difficult to evaluate biological effects; however, in spite of this, there is evidence that increased aberration frequencies are associated with cancer risks in addition to a wide variety of other health effects [3]. Epidemiological studies of atomic bomb survivors in Japan revealed high risks of cancer [2,12]. Thus, long-term follow-up studies of the A-bomb survivors have provided reliable information on health risks for the survivors and constitute the basis for setting radiation protection standards [12], which requires worldwide efforts and the interaction of international and national organizations that, in turn, entail the input of scientific and regulatory experts [13]. For this purpose, the identification of the most adequate biomarkers and bioassays that can be suitable to monitoring human exposure to radiation is of high importance [14]. Progress of this task requires the integration of biomarkers or bioassays of individual exposure, effects and susceptibility to IR [15].

In this context, the analysis of chromosomal aberrations has been widely applied in several kinds of radiation exposures (environmental, medical or occupational), since in general, it is possible to perform estimates of the risks of cancer development [16]. This concept is supported by the fact that IR exposure may lead to cancer, as reported for atomic bomb survivors [17,18], and also for cancer patients who received radiotherapy, for whom regular health care is required to detect adverse long-term outcomes, especially in children [19–22].

Furthermore, advances in investigative molecular approaches demonstrated the capacity of IR to cause alterations in gene expression profiles [23–25]. Significant changes in transcript expression levels were also reported for 78 genes (belonging to several biological classes) in lymphocytes of occupationally exposed individuals, for whom the exposure doses (accumulated along years) were determined with physical dosimetry by means of personal dosimeters, and varied from 0.696 to 39.088 mSv, which is below the admissible level for occupational exposure [26]. Interestingly, for low dose exposure, radiation specific mRNA transcript profile was also suggested as a biomarker in a recent report [15]. In spite of relevant findings obtained through molecular approaches, chromosomal aberrations still continue to be a suitable biomarker of IR exposure, especially in cases of radiation accidents involving human exposure.

## 1.2. Biological dosimetry

IR induces chromosomal exchanges (dicentric and translocations) in a dose-dependent manner [2], and the frequencies of exchanges in peripheral lymphocytes can be used to estimate the absorbed dose in cases of radiation accidents [5,27,28]. This method called ‘biological dosimetry’ was developed in the mid-1960s, and for more than 50 years, it was applied in thousands of cases of actual or suspected radiation exposures. Biological dosimetry is valuable when blood samples can be collected and analyzed early after an accident with radiation-exposed individuals [5], as it happened in the  $^{137}\text{Cesium}$  accident in Goiânia, Brazil [29,30].

Under the auspices of the International Atomic Energy Agency (IAEA), a technical report containing basic protocols on biological dosimetry was written by experts [5,27]; for several years, Prof. A.T. Natarajan and colleagues organized a series of IAEA workshops in different parts of the world, aiming to train professionals in the field of radiobiology and biological dosimetry. In 1983, Prof. AT Natarajan, under support of IAEA, established a “Biological Dosimetry” laboratory in the Brazilian Institute of Radioprotection and Dosimetry (IRD), which belongs to the National Commission on Nuclear Energy (CNEN), (Rio de Janeiro, Brazil). The main purpose was to use frequencies of radiation-induced dicentric to estimate the absorbed doses in victims of accidents involving ionizing radiation [28]. Few years later, in 1987, an accident with  $^{137}\text{Cesium}$  occurred in Goiânia, Brazil, and the newly established laboratory conducted initial dose estimates for exposed victims, a work developed under responsibility of Adriana Ramalho and

supervised by AT Natarajan. Remarkably, the accident in Goiânia was the first major radiation accident in which cytogenetic data could be generated under circumstances favorable to follow-up studies [28], in addition to the determination of absorbed doses.

In some circumstances, biological dosimetry can be performed in parallel with physical dosimetry, as reported by Kinoshita et al. [31]. In this study, the authors reinforce the validity and limitations of their results obtained with a radiation worker exposed to  $^{60}\text{Cobalt}$ , suggesting that in this particular case of partial-body exposure, the biological method can be valid but requires appropriate correction factors. Therefore, biological dosimetry combined with physical dosimetry may provide relevant results, but appropriate correction factors should be used for dose estimates.

Nevertheless, the interpretation of the results is complex in the field of biological dosimetry; either for acute or chronic exposure at different situations, there is a requirement of a basic knowledge on radiobiology and genetic effects of radiation exposure, but it is also of great importance to collect information about all details of exposure, which in general, mainly during the emergency, are poorly known.

## 2. The accident with $^{137}\text{Cesium}$ in Goiânia, Brazil

The  $^{137}\text{Cesium}$  accident in Goiânia (Brazil) started with the removal of a 50.9-TBq  $^{137}\text{Cesium}$  source from an abandoned radiotherapy unit, giving rise to a radiological accident in September 1987. The sequence of events and details about the accident can be found in the IAEA report, 1988 [32]. Briefly, two persons removed the source assembly from the radiation head of a  $^{137}\text{Cesium}$  teletherapy unit, which was found in an abandoned and demolished house; the machine was formerly operating in a private radiotherapy institute, which moved to other location without notifying the licensing authority. The source assembly was taken home and dismantled, with a removal of the capsule containing  $^{137}\text{Cesium}$ . This capsule was ruptured and the remnants of the source assembly were sold to a junkyard owner. In the following days, the fragments of the source were distributed to several families, and after five days, a number of people were showing gastrointestinal symptoms; one of them, connected the illnesses with the source capsule, and took the remnants to the public health department of the city. This action began a sequence of events which led to the discovery of the radiological accident with  $^{137}\text{Cesium}$  [32].

Approximately 112,000 individuals were monitored in the Goiânia Olympic stadium, of which 249 were contaminated either internally or externally. At least 50 individuals showed symptoms of whole-body and local acute irradiation [32,33]. The management of patients and establishment of therapeutic strategies were problematic during the emergency period, due to the complex irradiation exposure and difficulties in obtaining credible information regarding exposure, such as source-to-object distance, duration of exposure, and source activity [34].

### 2.1. Cytogenetic analysis and dose estimates following the accident

Soon after the exposure, a cytogenetic study was carried out in peripheral lymphocytes taken from 129 victims, in order to estimate the absorbed radiation doses on the basis of the initial frequencies of dicentric and rings [29]; 21 subjects presented absorbed doses > 1.0 Gy, and in 8 of them the doses exceeded 4.0 Gy, with limit of 7.0 Gy; four victims died soon after exposure [30]. A calibration curve generated for  $^{60}\text{Cobalt}$  gamma-rays at a dose rate of  $0.12 \text{ Gy}\cdot\text{min}^{-1}$  was initially used, since a curve for  $^{137}\text{Cesium}$  was not available at that time; later on, the absorbed doses were adjusted for the calibration curve for  $^{137}\text{Cesium}$ . Estimates of absorbed doses for the victims supported the clinical management and appropriate treatments. The relevance of these results in the context of radiobiology and biodosimetry is well recognized, as the data could be applied in follow-up studies.

Few years after the accident, a follow-up study was conducted with



15 victims aiming to analyze the persistence of chromosomal aberrations by estimating the average half-time for the disappearance of dicentric plus rings [35]; in this study, the authors showed that the estimated average half-time of elimination of dicentric and rings among the highly exposed group (doses above 1 Gy) was 110 days for the initial period after the exposure (up to 470 days), while for absorbed doses < 1 Gy, they found 160 days (the disappearance of aberrations was slower). These results may reflect various subpopulations of human lymphocytes with different lifespans. The highly exposed individuals were of different ages, showed variation in the levels of leukopenia during the critical phase of the accident, and almost all subjects had internal contaminations with <sup>137</sup>Cesium. One of the purposes of this work was to deduce a correction factor to be applied in accident cases when there is a delay between exposure and blood sampling [35], since dicentric and rings are unstable and the lymphocytes carrying these aberrations are eliminated with time. The authors suggested that the mean value of 110 days for the half-time can be applied to a simple exponential function, whenever it is required to correct an observed frequency of aberrations, as long as the elapsed time is known and there is a realistic assessment of the dose received, which must be higher than 1 Gy. If the dose received is supposed to be less than 1 Gy, they suggested the value of 160 days.

An additional cytogenetic follow-up study was carried out for 12 individuals, 7.5 years after exposure to <sup>137</sup>Cesium in Goiânia [36]; for seven probands (absorbed doses: 0.3–4.6 Gy), the frequencies of dicentric were at least 10 times higher than the control value, and higher than expected, on the basis of the previous study [35], indicating that in some individuals, unstable aberrations may persist in a subpopulation of the lymphocytes. This could be a consequence of several factors, such as some degree of internal contamination (undetected at the time of the accident), health status and life style, in addition to age at exposure. In fact, individual variations regarding the elimination rate of unstable aberrations have been reported by Bender et al. (1988) [37], as several factors may influence the degree of turnover presented by the circulating lymphocytes.

## 2.2. Translocation analysis and retrospective dosimetry

The introduction of the fluorescent *in situ* hybridization (FISH) technique using chromosome-specific DNA probes (chromosome painting) allowed improvements in the resolution of detecting and evaluating structural chromosomal aberrations, especially translocations in human [38] and rodent cells [39,40]. In addition, advances of the FISH method and its application in the mutagenesis field generate a great knowledge on the nature of spontaneous or radiation- or chemical-induced chromosome damage in several cell types [4,16,41,42]. It is noteworthy that the use of chromosome painting became a promising tool in radiation biodosimetry, since its suitability to study various types of chromosome rearrangements, and also the persistence of such rearrangements into cells along time following exposure. With the aim to standardize the classification of chromosome aberrations, by efforts of several experts in the field, a nomenclature for chromosome aberrations detected by painting (Protocol for Aberration Identification and Nomenclature Terminology, 'PAINT') was published, which has been used to classify different types of aberrations [43]. In addition, another nomenclature, called the 'S&S system', was developed due to the recognition that most of the anomalous painting patterns were the result of complex exchanges, such as those arising from the interaction of 3 (or more) breaks in 2, or more chromosomes [44]. The S&S system is particularly suitable if a mechanistic interpretation of aberration origins is required [45].

Translocations were previously considered as stable aberrations, and under this assumption, their frequencies could hypothetically be used to retrospectively estimate past radiation exposures; attempts have been reported to estimating absorbed doses for Chernobyl clean-up workers [46,47], and atomic bomb survivors of Hiroshima and

Nagasaki [48]. A good correlation was reported between the frequencies of translocations observed in the lymphocytes of the atomic bomb victims and the *in vitro*-induced frequencies [48]; however, in these studies, information on the initial yield of dicentric was absent, making it difficult to validate retrospective biodosimetry by performing translocation analyses several years, or decades after radiation exposure.

Along almost 30 years, the quality of rearrangement analysis by the FISH method has substantially improved although difficulties to perform dose estimates in case of human exposure to radiation still remain. However, if blood samples can be collected shortly after the exposure to radiation, dose estimates by dicentric analysis are the best choice when there are large numbers of victims.

In biodosimetry studies, the information about the kinetics of the elimination of dicentric and translocations after irradiation, and how and to which extent translocations persist is very important [49]. The authors found in experiments with mice an equal induction of dicentric and translocations immediately following irradiation of splenocytes, but along 14 days, the frequencies of dicentric declined very fast, while the fall was slower at later times; differently, the frequencies of translocations were constant up to 7 days and declined linearly with time, reaching a 50% reduction at day 112. These results clearly demonstrate that the frequencies of radiation-induced translocations do not remain constant *in vivo* over time [49]. The results obtained for victims of <sup>137</sup>Cesium in Goiânia are in agreement with these findings, since for certain dose levels, the frequencies of translocations were found lower than the initial frequencies of dicentric determined shortly after the exposure [4].

With the aim to confirm the above information, and to find out if translocation frequencies determined retrospectively reflect the initial frequencies of dicentric obtained by Ramalho et al. for the victims of <sup>137</sup>Cesium in Goiânia [30], Natarajan et al. performed an extensive study in blood samples collected 8 years after the accident [50]. By applying FISH for most of human chromosomes, the authors analyzed translocation frequencies for ~80% of the genome, and the results could be directly compared to the baseline frequencies of dicentric. They found that frequencies of translocations analyzed 8 years after the radiation exposure were two to three times lower than the initial dicentric frequencies, and larger differences were found at higher doses (> 1 Gy); however, at lower doses (0.1–0.4 Gy), the frequencies of translocations were higher than those of the dicentric. One of the most important factors pointed out by the authors is the persistence of translocation, which is time and dose-dependent in lymphocytes; this factor potentially causes a bias in retrospective dose estimates, and should be taken into consideration.

Similar results were obtained for 12 individuals, 7.5 years after exposure to <sup>137</sup>Cesium in Goiânia [36], for whom the frequencies of translocations were determined by FISH, using two cocktails of chromosome probes: #1,6,11 and #3,4,8 (~36% of the genome) and ranges of 0.5–9.7 and zero to 4.2 translocations per 100 cells were found, respectively. The mean genomic translocation frequencies were  $5.15 \pm 1.11$ ;  $8.84 \pm 1.63$ ; and  $22.58$  translocations/100 cells for different levels of absorbed doses presented by the probands: < 1.0; 1.5–2.0; and 4.6 Gy, respectively, indicating a 10–45 fold increase compared to the control value. The dicentric/translocation ratios calculated for groups of individuals classified at different levels of absorbed doses were found to be dose-dependent, with average values ranging from 0.24 (0.5 Gy) to 4.56 (4.6 Gy) depending on the level of the absorbed dose. In spite of the low number of individuals enrolled in this study, the relevance of the data regarding the translocation analysis for a certain percentage of the genome could be discussed in the context of its application in retrospective radiation dosimetry; since in the Goiânia accident the initial dicentric frequencies were available, it was possible to compare the dose estimates obtained by using the two methods (dicentric and translocation analyses). Taken together, the results indicate that the initial induction of dicentric does not

correspond to the frequencies of translocations observed later, and seems to be dose-dependent, a conclusion that is in agreement with the previous report [50]. Actually, a reduction in translocation frequencies observed for certain dose range reflects a limiting aspect in validating the use of FISH chromosome painting to estimate individual absorbed doses in retrospective biological dosimetry, as it has already been demonstrated in victims of Chernobyl [46,51,52]. Indeed, in these reports, several limitations were also pointed out for the application of retrospective dosimetry to estimating individual absorbed doses for radiation-exposed individuals in Chernobyl. Unfortunately, in all these studies, initial estimates of aberrations (dicentric) were absent, making impossible to perform comparisons with the translocation frequencies which were observed later.

Again, taking the advantage that in the Goiânia accident, the initial frequencies of dicentrics are available for more than one hundred individuals exposed to  $^{137}\text{Cesium}$ , we carried out another follow-up study with blood samples collected 10 years after the exposure, considering the hypothesis that estimates of translocation frequencies one decade after the accident would allow to study the feasibility of retrospective dosimetry [53]. In this work, we applied the FISH method using probes for chromosomes #1, 4 and 12 (~19% of the genome), and the dose assessment was performed based on the frequency of translocations obtained from a calibration curve (equation:  $Y = 0.0243 \times 2 + 0.0556X$ ) generated in our laboratory, by *in vitro* irradiation of human lymphocytes with  $\gamma$ -rays, following cytogenetic procedures according to IAEA (1986) [27]. The calibration curve was constructed on the basis of genomic frequencies (FGs) extrapolated for the whole genome [54]. Translocation frequencies for chromosomes 1, 4 and 12 varied from  $1.9 \pm 0.0014$  to  $18.8 \pm 0.0042$  per 1000 cells for the individuals exposed to different doses (0.3–1.9 Gy) of  $^{137}\text{Cesium}$ , and the FGs were in the range of 0.0058–0.0591. For individuals for whom the initial estimates were lower than 0.3 Gy, the calculated values using the calibration curve for translocations were similar. However, for exposures in the range between 1.5 and 1.9 Gy, the decline on the translocation frequencies led to dose estimates in the range of 0.4–1.0 Gy, which are approximately two- to five-fold lower than the initial absorbed doses. Therefore, these results indicate a decrease in the translocation frequencies along with time (10 years).

Overall, the results indicated that the application of retrospective dosimetry can be feasible only for low level exposure (below 0.5 Gy), while above 0.5 Gy, the doses can be underestimated, due to the tendency of decline in the frequencies of translocations; these results indicate a requirement to apply appropriate correction factors, which take into consideration the persistence of translocations along with time, and the influence of endogenous and exogenous factors determining the inter-individual variability [53]. In this context, it is very important to take into consideration that complex aberrations may be induced by high radiation doses, and lymphocytes carrying simultaneously translocations and other aberration types could be eliminated faster. In fact, by studying *in vitro* irradiated human lymphocytes, Matsumoto et al. suggested that dicentrics may contribute to a decline of the translocation frequencies with time, and that some translocations are not completely persistent [55]. Furthermore, *in vivo* experiments carried out in mouse cells showed reduced frequencies of translocations due to the presence of cells with multiple aberrations [56]. Therefore, retrospective dosimetry in case of exposure to high doses of radiation presents serious limitations, due to uncertainty concerning the stability of translocations, which can be reduced in heavily damaged cells of exposed individuals. To minimize this problem, translocations can be scored only in stable cells, excluding those carrying unstable aberrations. Most probably, a decade after radiation exposure, a high percentage of heavily damaged cells could be eliminated, thus remaining predominantly cells carrying stable aberrations.

Regarding retrospective biodosimetry for cases with partial-body exposures or large dose inhomogeneity, the FISH chromosome painting method also has limitation in assessing initial absorbed doses in terms

of stable translocations [57], and a correction factor should be applied to overcome the problem of non-uniform irradiation.

In studies using FISH and chromosome-specific DNA libraries, it is assumed that the radiation-induced chromosome damage occurs randomly among the chromosomes. However, there are reports in the literature indicating that some of them could be more involved than others in chromosomal aberrations [58,59]. Certain chromosomes may also be preferentially involved in rearrangements in cancer, and this has been observed for example, for chromosome 16 in different types of malignancies [60–62]. We have carried out a study with seven victims of  $^{137}\text{Cs}$  exposure (absorbed doses: 0.8–4.6 Gy), with blood samples collected 10 years after exposure, aiming to study this approach. The results indicate that chromosome 16p is more prone to radiation-induced chromosome breaks, and demonstrated a non-random distribution of induced aberrations, *in vivo* (in  $^{137}\text{Cesium}$ -exposed victims), but also *in vitro* (irradiated-lymphocyte cultures) [63]. These results indicate another limiting factor to be considered in retrospective dosimetry, when a subset of chromosomes is chosen for the detection of translocations. A possibility to overcome this limitation is to standardize a set of chromosomes, but the choice may require a detailed investigation on the breakage-sensitivity of each chromosome encompassing the human genome.

### 3. Conclusions

Biological dosimetry is an important approach in the monitoring of radiation-exposed individuals, and this method can be applied in several circumstances of human exposure to IR. However, the precision of the dose estimates may vary depending on several factors that are related to the nature of exposure (such as acute or chronic, partial or whole body, internal and external contamination), distance to the source, duration of exposure, and source activity. The cytogenetic analysis of unstable aberrations (dicentrics and rings) in peripheral blood lymphocytes has been successfully applied for acute exposure, in the case of blood samples collected from victims of the  $^{137}\text{Cesium}$  accident in Goiânia, shortly after the radiation exposure. However, this is not always possible, for example, when an accident involves a large number of individuals, consequently, the cytogenetic analysis becomes extremely laborious, and often unfeasible, thus requiring other kind of analysis. Follow-up studies (7–10 years after the accident) of the  $^{137}\text{Cesium}$  accident in Goiânia provided important lessons to characterize the elimination of unstable chromosomal aberrations, and the persistence of translocations, as well as the proportions of both kinds of aberrations at a certain time.

In several radiological accidents, mainly those with high magnitude of human exposure, retrospective dosimetry is often a unique possibility for dose estimates, since the unfeasibility to carry out blood sample collection by the time of the accident. In order to test this approach in a context of the Goiânia accident, attempts have been made to perform a retrospective dosimetry by using the analysis of translocations detected by the FISH method. The application of this approach generated valuable information regarding several aspects, mainly due to the availability of initial frequencies of dicentrics. Although some limitations could also be pointed out, the results show that the methods are useful for low-level exposure (below 0.5 Gy). In contrast, for higher doses, there is a need to apply appropriate correction factors, which take into consideration the persistence of translocations along with time and the influence of endogenous and exogenous factors determining the inter-individual variability. Furthermore, for the interpretation of the data, many aspects should be taken in account, such as the nature of exposure, individual radiosensitivity, sampling time, the kinetics of elimination of damaged cells (including those carrying dicentrics and translocations simultaneously) as a function of time and dose, as well as the set of chromosomes to be analyzed for translocation scoring.

Overall, the  $^{137}\text{Cesium}$  accident in Goiânia is an example of a complex accident, which led to numerous serious consequences for the



exposed individuals, and the environment. Furthermore, the entire population of the Goiânia city suffered discrimination for a long time, there was a significant economic loss and burden, a substantial psychological impact, and the waste repository is still a matter of concern in the village of Abadia, Goiás state [32]. All kinds of consequences to human and environment requires several actions, and like other serious accidents, these consequences also demonstrate the need for better care and control of radioactive devices, as well as adequate education programs for professionals and also the population.

### Conflict of interest

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