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ASSESSMENT OF THE RISKS ASSOCIATED WITH IODINE-125 HANDLING PRODUCTION SOURCES FOR BRACHYTHERAPY

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ABSTRACT

In Brazil, prostate cancer is the second most frequent disease, with an estimated 68,800 new cases in 2013. This type of cancer can be treated with brachytherapy, which uses sealed sources of Iodine-125 implanted permanently in the prostate. These sources are currently imported at a high cost, making public treatment in large scale impractical. To reduce costs and to meet domestic demand, the laboratory for production of brachytherapy sources at the Nuclear and Energy Research Institute (IPEN) is currently nationalizing the production of this radioisotope. Iodine is quite volatile making the handling of its radioactive isotopes potentially dangerous. The aim of this paper is to evaluate the risks to which workers are exposed during the production and handling of the sources. The research method consisted initially of a literature review on the toxicity of iodine, intake limits, related physical risks, handling of accidents, generation of radioactive wastes, etc. The results allowed for establishing safety and radioprotection policies in order to ensure efficient and safe production in all stages and the implementation of good laboratory practices.

1. INTRODUCTIO

According to data from the International Agency for Research on Cancer (IARC), 27 million new cases of cancer are estimated in 2030 worldwide, with 17 million deaths from the disease. The estimated increase takes into account the expected, however slight, reduction in death rates for some cancers. This increase will have its greatest impact in low and middle income countries, and more than half of all cancer cases already occur in countries in South America and Asia [(1)].

In Brazil, the existence of the Population-Based (RCBP) and Hospital-Based (RHC) Cancer Registries and the recently released 2014 issue of Estimates of Cancer Incidence in Brazil(2) allows monitoring the development of cancer cases across the country. These registries showed for the years 2012 and 2013 an increase of 576,000 new cases of cancer, giving prominence to the magnitude of the problem in the country. Among all cases, prostate cancer is the second more frequent in Brazil, with estimated 68,800 new cases in 2013, followed by 57,120 cases of breast cancer(2;3). In relation to expenditures in patient care, in 2014 costs reached about R$ 4.5 billion (1.9 billion US Dollars) in 277 hospitals that perform diagnosis and treatment of cancer in Brazil(2).

Prostate cancer, when early diagnosed, can be treated by brachytherapy that uses radioactive sources of Iodine-125 permanently implanted in the prostate. Currently these sources are imported to Brazil at a unit cost of $ 40.00 and about 100 units are required for the treatment of each patient, making public treatment on a large scale impractical(2;4)

The treatment of prostate cancer by brachytherapy is done by placing the Iodine-125 ‘seeds’ in contact with the tumour. Radiation doses are delivered continuously to the tumour tissue during the radioactive decay of the source. Planting Iodine-125 seeds in this way classifies, the brachytherapy as low dose rate (LDR) with implanted sealed sources(8).

Its main advantages is a significant decrease in total dose delivered to the implant area, preservation of healthy tissues, lower incidence of side effects such as impotence and incontinence and fast recovery when compared with other approaches(9).

1.1 Laboratory for Production of Brachytherapy Iodine-125 Sources

A multidisciplinary team from the Center of Radiation Technology (CTR), at the Nuclear and Energy Research Institute (IPEN) was created to develop the production of Iodine-125 sources for brachytherapy treatments.

In the year 2012, approximately 38,000 ‘seeds’ were distributed for prostate cancer treatment in 19 clinics in Brazil. It is estimated that the domestic production will increase this to 8,000 seeds per month(5;6;7).

1.2 Production of Iodine-125 Seeds

The production process of these sources at IPEN consists of the deposition of Iodine-125 on a silver wire that is sealed in a titanium capsule. The capsule serves as a housing to the radioisotope, have a length of 4.5 mm length, 0.8 mm in diameter and have a 0.05 mm wall thickness. The silver wire is 3 mm in length and is 0.5 mm in diameter (FIG. 1)[10].

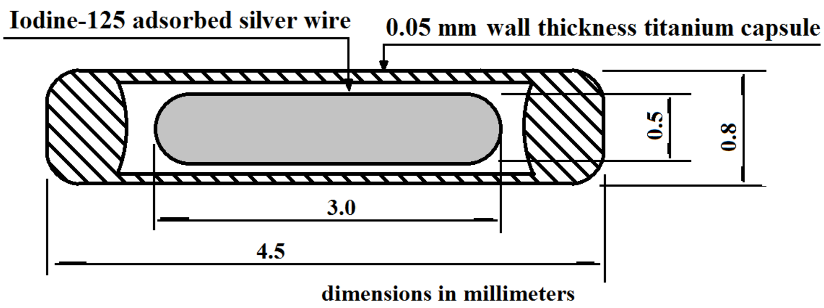

FIGURE 1: Schematic drawing of the Iodine-125 seed [10]

Iodine-125 seeds are produced in three main steps. First, Iodine-125 is deposited onto the silver wire by a chemical process. In the second step, the silver core with the absorbed radioisotope is placed in a titanium tube, which is sealed by a laser welding system. The third step is the quality control in which the seeds are subject to the leak test conditions and recommendations set forth by ISO-9978 standard for leak testing of sealed sources.[(7;11)]. After passing the quality control, the source are shielded, packaged and shipped to clinics making them available for the treatment of patients. Radioactive wastes generated in the production are isolated in order to decay [(7)].

Workers involved in the production are exposed to physical, chemical and radiological risks in all these steps. This aim of this paper is to analyze these risks and propose adequate safety measures and working processes.

2. METHODS

The method used in this study consists of the identification and assessment of the potential occupational hazards, the limits on intake of the radioactive substances and other radiation protection guidelines, associated with the handling of Iodine-125. These were based on the current regulations from the National Nuclear Energy Commission (CNEN) and recommendations of the International Atomic Energy Agency (IAEA). Data were obtained using web-based information systems as CAPES, DATA BASE, INIS etc. Data were screened according to the applicability to this study.

2.1 Physical Characteristics of Iodine-125

Iodine-125 emits gamma rays, X-rays, conversion- and Auger-electrons, but no beta-rays. Its main physicochemical and radiological characteristics are presented in Table 1.

TABLE 1: Properties of Iodine-125[12]

Gamma Energies	35.5 keV (7% abundance/93% internally converted, gamma) (No betas emitted) 27.0 keV (113%, x-ray) 27-32 keV (14%, x-ray) 31.0 keV (26%, x-ray)
Specific Gamma Ray Constant	0.27 to 0.70 mR/hr per mCi at 1 meter (Current literature indicates 0.27 mR/hr per mCi at 1 meter)
Physical Half-Life	60.1 days
Biological Half-Life	120-138 days (unbound iodine) - thyroid elimination
Effective Half-Life	42 days (unbound iodine) - thyroid gland
Specific Activity	17,400 Ci/gm (theoretical/carrier free)
Intrinsic Specific Activity	22.0 Ci/millimole
Lead foil or sheets (1/32 to 1/16 inch thick)	0.152 mm lead foil
Half Value Layer	0.02 mm Pb = 0.008 inches

Iodine-125 is produced in nuclear reactors by neutron activation of Xenon-124 through the reactions ^{124}Xe(n, γ)^{125m}Xe (57 s) → ^{125}I (59.4 d) or ^{124}Xe(n, γ)^{125g}Xe (19.9 h) → ^{125}I (59.4 d). It decays by electron capture to ^{125}Te, emitting photons with 35.5 keV (7% emitted and 93% internally converted) and X-rays with 27 keV (113%), 27-32 keV (14%) and 31 keV (26%) (FIG. 2). Due to the low energy and consequently low penetration of its photons, it has desirable characteristics as a source for brachytherapy as it does not penetrate deeply into the tissues, irradiating only the intended tissues[12].

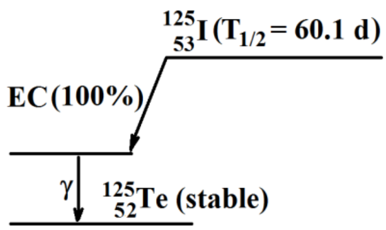

FIGURE 2: Decay of iodine-125 by electron capture.

Iodine is a volatile element and therefore ^{125}I presents a potential risk to workers through inhalation, thyroid being the most critical organ.

3. RESULTS AND DISCUSSSION

3.1 Physicochemical and radiological risks associated with ^{125}I

Iodine-125 has application not only in brachytherapy, but also as a radiopharmaceutical in radioimmunoassay. It is more dangerous than any other Iodine isotope mainly during manipulation steps. It displays both external irradiation risks (exposure to gamma rays) and contamination therefore internal exposure (since the active form of the product is volatile and can be absorbed by inhalation).

From a toxicological point of view there is great risk of damage to health, because the Thyroid gland concentrates very effectively radioactive Iodine absorbed by the body, becoming a significant source of internal radiation. Biologically too much Iodine by the Thyroid can inhibit the synthesis of Thyroid hormones (Wolff-Chaikoff effect). Thus, the iodine toxicity can eventually cause diseases such as iodide goiter, hypothyroidism or myxedema(13).

As both external and internal exposure and contamination are possible when handlingIodine-125 radiological risks should be taken into account when handling it. When exposed to Iodine-125, the most critical organ is the Thyroid gland. Exposure can occur by ingestion, inhalation, puncture, wound and skin absorption.

The risks associated with the handling of radioactive sources increases significantly due to the possibility of human errors caused by lack of work experience or awareness of the occupational risks to which the business is exposed.

A study in 2009 by Strahlentherapie und Onkologie oncology institute in Switzerland, followed four physicians with little work experience and responsible for performing a lot of therapeutic procedures using dosimeters finger TLD. The results indicated that professional experience was crucial in reducing occupational exposure. For the more experienced professionals, about 400 applications per year could be carried out without exceeding the annual dose limit for the extremities (hand), 500 mSv/y. For less experienced professionals only 200 applications per year could be carried outshowing the importance of professional experience of the personnel at the clinic, but also in the production and handling of radioactive sources(14).

In relation to the perception of risk associated with professional practice, a work performed by a group of psychologists addressed the issue of risks related to occupational exposure to iodine. The study evaluated how professionals view the risk and what they do to protect themselves. The main results indicated the need for a deeper understanding of the work process, to minimize risks and uncertainties with regard to workers[15].

In another study involving workers who manipulated iodine (iodine-131) [16;17], 11% had at least one result above the limit and some kind of internal contamination. Initial results indicated the need for a retrospective epidemiological study to investigate the relationship between incidence of cancer and occupational exposure to ionizing radiation from dose records extracted from the National Dose Registry of Canada from 1951 to 1988 and incidence data cancer of the Canadian cancer Data Base from 1969 to 1988. The results showed a high risk of manifestation of various cancers, particularly the incidence of thyroid cancer. But the authors indicate the need for further research to better assess this possible connection[16;17].

3.2 Radioprotection in the production and handling of Iodine-125

In order to conform to dose limitations, internal safety policies in handling iodine-125, should be established in departments that handle this type of source. Below is a proposal of what such a policy should contain:

- All workers should be certified (have received training to carry out the manipulation), as well as having individual dosimeters.
- If not certified they should not manipulate source without proper supervision.
- In order to identify potential sources of difficulty during handling they must conduct a exercise with an inactive material, such as assay the standard procedure that use to radioactive sources.
- Do not eat, drink, smoke, use makeup, etc, in order to avoid contaminations
- Injuries in regions vulnerable to contamination should be covered preferably by waterproof materials.
- Continous cleaning procedures should be adopted to avoid contamination or even initial spread of contamination.
- Radioactive liquids should only be handled in areas where there is tissue paper, (Radioactive liquids should always be handled over a suitable tray lined with absorbent paper or a disposable liner. Work bench should also be covered with absorbent paper with a non-porous backing).
- For handling small quantities of material it is recommended to use automatic pipettes.

- Paper tissues must be used instead of Handkerchiefs. They should be disposed as low activity waste.
- Materials that are not used in a particular experiment should be removed from the work area in order to avoid accidental contamination.
- Radioactive liquids should always be handled with an appropriate safety barrier, according to the risk conditions that are relevant for the handling i.e. physical condition of the source, steams, gases, dust or similar states.
- Conditions of temperature and pressure of glove boxes must be carefully administered to prevent, contamination due to pressure difference, saturated filters among other things.
- All radioactive samples should be clearly identified, placed in suitable containers and stored in a clean, safe place. A record must be kept with a list of names and dates for each stored sample.
- At the end of each work session, all working areas should be checked for contamination and in case of any surface contamination it should be removed and the area checked so that it can be declared free of contamination.
- Coats used during the procedure and all protective clothing should be removed before leaving the laboratory, and left to decay if they have any contamination
- The radioactive waste generated must be properly segregated and stored for decay in accordance with regulations of the country.

Regarding the care of the direct manipulation of unsealed sources containing iodine 125; attention should be paid to various safety aspects. This should include: care in opening capsules in order to prevent the formation of bubbles or droplets in the radioactive package; using at least two pairs of gloves, since iodine may penetrate surgical gloves; manipulation of materials with activities below 370 kBq can be handled in work bench. For activities above this value, exhaust Capel with exhaust system should be used and direct manipulation always avoided. Tweezers can be used(18).

To accomplish this survey the personnel must use portable type scintillator detectors during the work. In addition to this, it is recommended to periodically survey all working areas in order to find contamination. The results are to be stored for subsequent surveys, if needed. Thyroid survey routine should be performed on all workers involved in the manipulation of Iodine-125.

FIGURE 3: Iodine-125 in handling safety cabin and personal protective equipment (highlighted double-layer gloves on lead gloves).

3.3 Limits of incorporation and Monitoring

Handling of radioactive materials in general is harmful. The risk rating associated with iodine 125 is divided into three categories A, B and C. As the: high hazard > 10mCi ($3.7x10^8$ Bq); B: moderate hazard > 100µCi to 10 mCi ($3.7x10^6$ Bq) and C: low hazard to 100 µCi ($3.7x10^6$ Bq) [19].

The limits for annual ingestion of iodine are provided based on studies of the International Commission on Radiological Protection ICRP[20]. Assuming deposition homogeneously throughout the body, a biological half-life of 12 days annual limit for intake would give a dose of 700µCi the dose to the whole body in intake would be 0.7 µCi ($2.59x10^4$ Bq). In accordance with NCRP the annual limit for intake of nuclides in ways that are incorporated into the genetic material is 170µCi (6.3×10^6 Bq) [21]. Table 2 shows the dose limits for critical organs in the case of ingestion.

TABLE 2: Committed Dose Equivalent and Annual Limit on Intake[22]

Organ	Committed Dose Equivalent	Annual Limit on Intake (ALI)
Thyroid/inhalation class “D”	814 mrem/mCi	60 µCi (2,2MBq)
Thyroid/ingestion/NaI	1185 mrem/mCi	40 µCi (1,5 MBq)
Any organ/puncture/puncture/adult	1258 mrem/mCi	------
Thyroid/inhalation	910 mrem/mCi	------
Whole body/inhalation*	24 mrem/mCi	200 µCi

* Committed Effective Dose Equivalent(CEDE).

In case of ingestion or inhalation, potassium iodide pills (200mg) should be administered. When administered up to two hours after ingestion uptake of Iodine by the Thyroid can be reduced by 80%. It is worth noting that the thyroid accumulates 30% of soluble radioactive iodine collected by the body; the remaining 70% is excreted very quickly through urine [14;17].

Brazilian law that regulates the use and application of radioactive material, CNEN NN 3.01 [23], sets out the rules and regulations that radiological services must follow. Monitoring of occupational, environmental, and local area must be performed. Different procedures must be applied for each type of monitoring. Occupational monitoring TLD should be used and evaluated on a monthly basis. For personal monitoring (visitor), electronic dosimeters or pen dosimeter are used. In monitoring the working environment, TLD detectors can be used in different reading points, one being recommended as a warning detector to monitor the laboratory output. Environmental detectors will control the dose output of air and water.

FIGURE 4: External monitoring being carried out at the end of working in the laboratory.

The dose limits established and currently obtained the sources of production laboratory at Ipen are in agreement. The value of annual personal dose has been given around 0,20 mSv / month (restriction of dose 10 mSv/year); being effective dose 6mSv/year for investigation level. Equivalent dose (skin/hands and feet): 150mSv/year and 50 mSv dose equivalent crystalline/year [23].

3.4 Radioactive waste containing Iodine-125

All radioactive facilities are subjected to licensing process by the National Nuclear Energy Commission (CNEN). In order to ensure the radiation protection of, the radioactive waste management process can starts with determining the type of installation in which the waste will be generated. Currently, Resolution No. 112 [24] of CNEN subdivide the radioactive installations: installations using sealed sources; installations using unsealed sources; plants using ionizing radiation generating equipment; and facilities for the production of radioisotopes. This same resolution classifies radioactive facilities in groups of 1 to 8, according to the level of radiation worked. As the group 6, referres to facilities that handle, store or use or store radioactive unsealed sources with a total activity exceeding 20 thousand times the exemption value for Iodine -125, is 10^3 Bq/g or 10^6 Bq[24].

After being segregation step, the waste radioactive is classified and then should be disposed of according to their classification. Regarding the physical state of the waste generated, the values set out in standard for remission are: Dismissal of solid waste can only be performed in a municipal waste collection system and must have a specific or overall activity limited to amounts established for each radionuclide. The table 3 shows values for iodine - 125[25].

TABLE 3: Dispenses level of liquid and gaseous wastes containing Iodine - 125[25]

Dispenses level liquid waste	Dispenses level of gaseous waste	Liquid waste exemption levels in the network of sanitary sewage
Bq/m^3	Bq/m^3	Bq/year
3,7E+04	5,6E+00	1,0E+8

Care must be taken that liquids and gaseous waste are properly absorbed on a suitable matrix and solid wastes packed properly. Both kinds of waste properly labelled (date, origin, alleged amount of activity) and only discarded following the rules of CNEN [24;25;26].

4. CONCLUSIONS

The implementation of best practices of to the routine of the Iodine-125 seed production is an effective means of ensuring the safety of laboratory activities. However, continuous training is required, and can be done through periodic meetings in order to provide adequate knowledge of the laboratory routine for new professionals and maintaining the knowledge of more experienced professionals. Use of protective equipment should be mandatory as part of the professional routine. Monitoring after each experiment or after doing work in production is also already a part of the routine in pre-production and should be extended to working in the lab. The waste management system will also be a part of all stages of production sources. The system is already being deployed in accordance with the steps already completed in the lab deployment. In future work, data from monitoring the professional staff should be analysed to see if the suggested radiation protection measures are being effectively used, and also data on the radioactivity of the waste generated by production lot.

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