Advisory Committee on the Medical Uses of Isotopes's Report on ^{137}CsCl Irradiators

Summary

After studying the issues, the Advisory Committee on the Medical Uses of Isotopes (ACMUI) came to the following conclusions:

1. Irradiators are necessary for medical practice and medical research.
2. It is not clear from the available data that x-ray sources are biologically equivalent to ^{137}CsCl irradiators.
3. Alternatives to the ^{137}CsCl irradiators currently in operation present greatly increased expense to programs that need the functionality and operational reliability of the irradiators.
4. The recommendation of the National Research Council (NRC) of the National Academies to eliminate the use of irradiators that employ ^{137}CsCl was based on the situation at the time of their study. Since that time, security of medical irradiators units has been substantially strengthened in three ways:
    a. Increased security of persons with access. The December 2005 NRC orders increased the security requirements for all persons having unescorted access to ^{137}CsCl irradiators, including background checks, personal reference checks, and fingerprinting checks against the FBI fingerprint database.
    b. Increased security of the facilities housing the units, including high-security locks on facility door, multiple doors with locks for access, motion sensors, video cameras monitored by facility security, preplanning with local law enforcement, database encryption, and secured facility schematics, and drawings.
    c. Increased security of the units themselves, including locks on source access panels and entry points.

    Given these changes, we found that the National Research Council concerns do not currently apply as previously stated, and have been superseded by increased safeguards as required by the Nuclear Regulatory Commission and state regulatory authorities. Well-secured ^{137}CsCl irradiators present little security hazard.

Practicality of Alternatives to ^{137}CsCl Self-Shielded Irradiators*

Blood and Blood-Product Irradiation

Based on our survey of the literature and other publicly available information sources, the only medical x-ray irradiator that the U.S. Food and Drug Administration (FDA) has cleared to irradiate blood and blood products to prevent graft-versus-host disease is the

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Raycell (Best Theratronics 2008) originally manufactured and sold by Rad Source (Rad Source 2007a) as the unit model RS 3000. Other manufacturers may also be developing plans for new irradiators.

The first question regarding practicality of an x-ray machine to irradiate blood or blood products is whether there are any technical issues. Although the photon energy of x-ray machines is lower than those of ^{137}Cs, Janatpour et al. (2005) demonstrated that x-ray machines can deliver the necessary 25 Gy dose with sufficient uniformity and stability to meet FDA guidelines. The typical x-ray irradiator generates a filtered energy spectrum with a peak energy of approximately 160 kVp, compared to the monoenergetic 662 keV gamma rays from ^{137}Cs. While a radiation weighting factor of 1 is applied to both gamma rays and x rays for radiation protection purposes (NCRP 1993), the biological effectiveness of low energy photons is approximately twice that of 662 keV ^{137}Cs gamma rays (ICRU 1986). Consequently, a dose of 25 Gy delivered by an x-ray irradiator will not produce the same biological effect as 25 Gy from ^{137}Cs gamma rays. The significance of this difference in radiation effectiveness relevant to transfusion medicine and immunological research is unknown.

Regarding costs, the NRC study (2008) quoted about $180,000 for a new x-ray irradiator and an annual service agreement cost of just over $10,000. However, the actual cost of the x-ray system has increased. In May 2008 this manufacturer quoted a purchase price of $250,0000 and $66,000 for a 3-year maintenance contract including a routine service call and one set of replacement parts as needed. While the purchase price might be about the same as a ^{137}Cs irradiator, the annual maintenance cost with a service agreement may be much greater unless the owner has engineering capabilities to provide service and maintenance in-house. Also, the service contract does not include physics services. Depending on the number of set-ups, calibration costs may exceed $10,000 per year if outside physics services are required. In addition, there would be a one-time cost of installing a 240 volt line to the room for most of the x-ray units replacing a cesium irradiator.

Based on repair history of clinical x-ray machines, a user of an x-ray irradiator may experience a higher failure rate and require more service and down-time than a ^{137}CsCl irradiator. Since maintenance of an irradiated blood supply is important, purchasers of x-ray blood irradiators find it necessary to purchase an annual maintenance agreement. However, outside service can result in a facility being unable to perform life-saving irradiations for a time. For example, one owner experienced a service response and re-calibration time of two weeks. Both the upper and lower power supplies had to be replaced after a few years of operation. Therefore, blood banks and hospitals may need to plan for an alternative means of irradiation or an alternative supply of irradiated blood components to meet critical demand. Without ^{137}CsCl as an alternative, the facility may have to purchase two units to assure a continuous supply of irradiated blood.

Another factor to evaluate for practicality is the throughput of an x-ray irradiator. Two units of blood can be irradiated at one time with the Raycell, and irradiation time is about 5 min. This is sufficient for two blood centers contacted, which do about 30-100 units per month, and it is adequate for a clinic doing about 20 units per day. However, a significant workload like that at a large academic medical center with a throughput of 50-60 units per day may exceed the capabilities of a single x-ray unit. While it may seem that the exposure rate with the x-ray would keep up with the demand, the blood irradiation is not continually as with an assembly line. Rather, units are irradiated as needed based on the clinical demand, in irregular intervals. Thus, the duration required for the irradiation becomes an important limiting factor. One potential buyer stated that about 48,000 blood products could be irradiated within the x-ray tubes' 2000-h warranty period (Blood Bank Talk 2007). For a site processing 50 units per day and assuming that procedures requiring irradiated blood happen mostly during normal work days, that would imply the need for a new tube each 3.7 years, adding considerably to the cost of the operation.

Since ^{137}Cs has a half-life of 30 years, it is not financially practical to replace those units that were installed within the last 15 years. Ease of use is comparable between the ^{137}CsCl irradiator and the x-ray irradiator.

One issue that has not been investigated is whether all the operating cesium irradiators could afford to replace the units, or whether some facilities will cease operation, depriving patients of irradiated blood and researchers a source of radiation.

Biomedical and Small Animal Irradiators

Ten x-ray irradiators are commercially available for cell, tissues and small animals, eight from three U.S. manufacturers and two irradiators from outside the U.S. A few will be discussed as being representative of the issues.

The **RS 2000** (Rad Source 2007b) has been sold by Rad Source since 1999, with about 15-20 units placed in Europe and Asia and 50-60 placed in the USA. Several users contacted seem satisfied with the device. The purchase price is little over $100,000, and a service agreement is around $10,000 per year. Apparently reliability has been good; however, owners should expect to refurbish or replace the power supply about every 4-5 years.

The Rad Source RS 2400 (Rad Source 2007c), operating between 80 and 160 kV, delivers a higher dose rate using a new technology emitter. This 4-pi x-ray source may have the capability of eventually delivering about 300 Gy min^{-1}, but the two RS 2400s operated considerably lower than this. The International Atomic Energy Agency is testing one of these units for its sterile insect programs. The dose rate and irradiation volume of the RS 2400 are much larger than those for the RS 2000 and may allow five 450-ml blood bags to be irradiated simultaneously at a dose rate about 45 Gy min^{-1}. However, the canister loading methodology may need some redesign before it would be practical for irradiation of blood. Rad Source expects to submit its application for FDA approval for irradiation of blood products with this device in 2008. The RS 2400 is expected to sell for about $200,000 - 250,000 with an annual service contract of about $20,000. To ensure a high degree of reliability and minimal down time, the service agreement will include a tube replacement every 2000 h.

Faxitron (2008) sells two irradiation systems, the RX-650 and the CP-160, with prices around $43,000 and $87,000 respectively. The Faxitron RX-650 operates at a peak energy of only 130 kVp. To achieve adequate uniformity of dose, Kennedy et al. (2004) had to irradiate the mice from several directions because of the attenuation of the lower energy radiation in the bodies of the mice. Woo and Nordal (2006) concluded that the Faxitron CP-160 could be useful for small animal research if radiation was delivered carefully to ensure accurate and uniform radiation dose. The authors stated that at a distance of 33 cm the indicated beam diameter on the tray was 26 cm, whereas the part of the beam where the uniformity as within 10% was confined to a diameter of 16 cm.

Precision X-Ray Inc. (2005) sells four different biomedical and small animal x-ray irradiators with energies ranging from 160 kVp to 320 kVp. With 0.5 mm Cu and operating at 320 kV, the unit delivers a dose rate of 2 Gy/minute. The higher tube potential brings the RBE to the same value as the ^{137}Cs gamma ray beam. The price runs around $170,000, exclusive of the service contract.

Kimtron markets units similar to the Precision X-ray units, with four units operating between 160 kV and 450 kV. The prices appear comparable to similar units.

Gilardoni, an Italian company, sells the Radgil (Gilardoni 2000) with an energy of 200 kVp and a dose rate of about 1 Gy min^{-1} at a cost of about 94,000 Euros (~$146,000).

Hitachi (2008) manufactures the MBR-1520-3, which is a 150-kVp blood irradiator that can deliver doses from 15 to 35 Gy in 5-Gy increments. However, there is no indication of FDA approval for human use.

AAPM Survey of Users

The American Association of Physicists in Medicine (AAPM) conducted a survey of its members in August to assess their experience with irradiators. The results of the survey would be skewed toward hospital-based or university-based irradiators; however, for the information gathered, that should not affect the conclusions. The survey, since it was targeted at medical physicists and some health physicists, represents only a small part of the irradiators in use. Of the 363 respondents, 297 had irradiators, 84.6% of those used ^{137}Cs as the source, 9.3% used conventional x-ray units and 6% used medical linear accelerators (linacs). The ^{137}CsCl units represented the major vendors. Only 10% were purchased within the last two years, with 7% planning on replacing the units within the next 5 years.

A quarter of the ^{137}CsCl units had had some malfunction but most were repaired in less than 7 days. Of the x-ray units, 35% had malfunctions, with 44% being repaired within 7 days.

Only 40% of the cesium units were used for blood irradiation, with about 25% used for material irradiations and another 25% for animal irradiations. Of the x-ray units, half were for blood irradiation, while 19% were for material irradiation and 32% for animals. Forty percent of the medical linacs for the respondents were used predominantly for blood irradiation and 11% for animals.

This survey indicates that, while fairly reliable, conventional x-ray units and medical linacs account for a small minority of the irradiators in the field. They had slightly more downtime than ^{137}CsCl units. The cesium units have also been reliable and their users, in general, have no plans to replace them. Forced removal of the cesium irradiators would result in a very large loss of resources, both radiation sources and funds, not only for blood banks but research institutions as well.

Linear Accelerators

Medical linear accelerators (linacs) can and do provide irradiation for blood products and materials. While linacs can serve for animal irradiation, their use with mice presents some difficulties because of the build-up region in the dose that is on the order of the thickness of a mouse. Most facilities that use linacs for irradiation either are part of larger processing facilities (for example, medical product sterilization companies) or find time between patients (creating problems in scheduling and staffing) in a radiotherapy clinic because of the extremely large initial investment, about $2,000,000 for these units and the cost for maintenance of $200,000 per year. Night time irradiations pose additional staffing issues. Because of the costs, linacs are not a viable replacement for $^{137}CsCl$ irradiators for the vast majority of facilities.

Alternative Radionuclides

At the time of writing, the only reasonable alternative radionuclide source for irradiators would be ^{60}Co. This radionuclide is used in large industrial irradiators, but is not currently available for blood or research irradiators. The use of ^{60}Co would require frequent source change due to the much shorter half-life compared with ^{137}Cs (5.27 years compared with 30 years), and higher initial source activities to extend the useful life of the sources. The ^{60}Co also requires thicker shielding because of the higher energy (1.2 cm half-value layer in lead compared with 0.6 cm.) Since the half-value layer enters into shielding as an exponent, the difference in the thickness of shield required due to the differences in the values multiples rapidly. These two considerations would lead to high initial costs for a unit and frequent, repetitive costs for source replacement. Finally, there is no convincing evidence that the ^{60}Co sources of any form would pose less of a hazard than the $^{137}CsCl$.

Further Considerations for Blood Irradiation

The subcommittee consulted 10 hematologists or oncologists and one clinical laboratory director. These included researchers at one of the nation's most prestigious blood disorder and hematologic cancer research centers having extensive use of $^{137}CsCl$ blood and small animal irradiators.

Most of the previous information, such as in the National Research Council report, focused use of irradiators at central blood banks.

Five of the 10 hematologists/oncologists reported that they regularly prescribe irradiated blood for transfusions. Of these, one said that up to 40% of all blood he prescribed was irradiated. The others estimated that 15% to 33% of all blood for transfusion was irradiated. They all mentioned that their patient population was the reason why they tended to prescribe more irradiated blood products than the nominal 10% that often is used for planning. Patients who are post transplant are one such category, although none of these physicians had many patients in this subset. The more common reason was the use of certain chemotherapeutics that severely affect the host immune system.

Although no surveyed physicians were aware of difference between ^{137}Cs irradiated blood vs. x-ray, all ten (including one physician who doesn't presently routinely give irradiated blood transfusions) stated a regulation to eliminate or reduce the availability of irradiated blood products, or access to $^{137}CsCl$ irradiators would represent a severe drawback in the hematology/oncology field of medical practice and research. One physician who prescribes irradiated blood 40% of the time said that hematologists and oncologist prescribe irradiated blood about 33% of the time and that figures which say that only around 10% of all transfused blood is irradiated are skewed by the trauma-related transfusions in hospital emergency rooms and for surgery-related transfusions. Oncologists might rely more on irradiated blood than other medical professionals.

One institution specializing in research on hematologic malignancies reported that four $^{137}CsCl$ irradiators are used by 250 authorized users at a frequency of about 30 to 40 times per day in support of about 20 research projects and eight active clinical trials. Although comparable x-ray systems could be obtained to replace the $^{137}CsCl$ irradiators, four physician/PhD researchers indicated that the change would require more than a year to develop the radiation response relationships between the radionuclide-source and x-ray source irradiators, and that impacts on ongoing funded research would be enormous.

None of the physicians or the lab director had knowledge of the radiobiological differences between samples irradiated by x-rays or monoenergetic photons from ^{137}Cs sources. Four of six hematologists had experience with both irradiator systems. Three also had experience also with linac irradiated blood before their institutions obtained dedicated blood irradiators.

^{137}Cesium Chloride Irradiator Security

Prior to the publication of the National Research Council report the U.S. Nuclear Regulatory Commission (NRC) has disseminated orders to licensees for increased controls on sources of radioactive material in quantities of concern. The "Orders Imposing Increased Controls" issued in December 2005 contain requirements based on the International Atomic Energy Agency Code of Conduct. These measures were required to safeguard radioactive sources from theft or other unauthorized use. These requirements include:

1. Limit access to approved individuals who need to use radioactive materials in performing work activities.
2. Perform background and trustworthiness checks on all employees with access.
3. Escort all service providers who need to access the radioactive source.
4. Document the monitoring of sources with means for detecting source removal.
5. Increase source monitoring during source delivery or shipment.
6. Respond immediately to any attempted theft, sabotage, or diversion of sources.
7. Develop a plan for assistance from supporting authorities in the event of theft, sabotage, or diversion.
8. Provide means for transmitting information between personnel and components used to detect an intrusion.
9. Notify the NRC Operations Center of any attempted theft of radioactive material.
10. Document any attempt at theft or diversion of radioactive material.

11. Use trusted carriers with package tracking systems, who maintain constant control during transit, and who maintain communication for response or assistance.
12. Notify the NRC 90 days prior to certain shipments.

To review the changes resulting from the NRC orders for increased controls, a site visit for one of the members of this subcommittee was arranged to a major medical center with four ^{137}CsCl blood irradiators. The visit found that the licensee maintained access control to the irradiators by the means required in the Order, including:

1. Allowing access only to approved personnel who had undergone a thorough FBI background check, fingerprinting, work history review, psychological review, and local law enforcement background check.
2. Allowing access only to persons needing and trained to use the irradiators properly.
3. Providing redundant enforced doors, locks, heavy walls, computer-coded key-card access, and continuous video monitoring of the halls, entry, and workspace occupied by the irradiator units.
4. Presenting documented procedures to ensure that authorized users support the institutions system to prevent unauthorized access and protect access information, drawings, schematics, maps, and facility floor plans from unauthorized use.
5. Coordinating with local law enforcement agencies for rapid response to any attempted intrusion or theft of radioactive material.

In addition, we found the irradiator systems to be outfitted with additional padlocks and security measures for preventing unauthorized access to radioactive sources inside the irradiators. The irradiators weigh 4000 to 5000 pounds and do not have wheels.

In summary, we found highly increased security of ^{137}CsCl irradiators and increased controls over access by authorized personnel at the institution. It would be very difficult, even for personnel with access permission, to attempt theft, diversion, or misuse of the ^{137}CsCl irradiator systems. The institution had implemented all requirements to enhance the security of ^{137}CsCl irradiator systems in a manner typical of such irradiators.

In addition to the increased security enhancements required by the NRC, an initiative by the Department of Energy (DOE), the Department of Homeland Security (DHS), and the Domestic Nuclear Detection Office will harden ^{137}CsCl irradiators throughout the United States to delay unauthorized access to ^{137}Cs sources. This has been a cooperative effort for the past 18 months. The demonstration project was completed in March of 2008 and the pilot project is currently being conducted in nine facilities. DOE and DHS anticipate that this pilot program will be completed later this year.

The pilot project is the actual enhancement of the irradiators in the field. The manufacturer will install additional material and make minor changes to the exterior of the irradiator to make it more difficult to remove the source(s). There are nine facilities that have volunteered to participate. The pilot will have two of the manufacturers visit the facility and add the enhancements to the irradiators. The pilot will demonstrate the ease and ability of performing these tasks in a “real world” environment. The pilot will also validate the costs to perform the retrofit. It is estimated that the cost will be \$2,000 to 4,000 for each device. The DHS and the DOE will pay the manufacturers for the enhancements. It is expected that the pilot will be successful and the project will be open to all of the devices currently licensed in the United States.

Alternative Forms for ^{137}Cesium Sources

The subcommittee considered whether this report should recommend to manufacturers of ^{137}CsCl irradiators that alternatives to the powder form of the source be pursued. However, as of this time, there is no convincing evidence that another form, particularly a solid form, would be safer. While a powder may be dispersed by a bomb, a solid poses a radiation hazard much greater than the dispersed powder. In addition, the manufacture of a solid source could pose a hazard to the workers making the sources.

Conclusions

1. Cesium-137 irradiators are used in a number of important medical and research applications. As the population of the United States ages, the use of irradiated blood products will escalate, producing an increased demand for the availability of this technology for patient safety. The need for medical irradiators is unquestionable.
2. Some investigators are concerned about the ways that differences in radiation quality between ^{137}CsCl irradiators and x-ray systems would affect experimental results on blood samples, small animals, separated T-cells and stem cells, and other biological media.
3. Alternatives to ^{137}CsCl irradiators are expensive, and forcing the switch to x-ray sources would place an unnecessary and great financial burden on blood banks and research institutions.
4. The ACMUI subcommittee believes that the ^{137}Cesium Chloride Irradiator Security Enhancements and Increased Controls and Security Inspections have provided strong measures for ensuring the safety and integrity of ^{137}CsCl sources in medical irradiators, have reduced the vulnerability of these devices as material suitable for malicious intent, and should prove to be acceptable as an alternative to removal or prohibition of these devices.

ACMUI ^{137}CsCl Irradiator Subcommittee

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