UNIVERSITY OF CALIFORNIA Office of the President

UNIVERSITY OF CALIFORNIA SYSTEMWIDE RADIOACTIVE SOURCE REPLACEMENT WORKGROUP RECOMMENDATIONS

APRIL 30, 2018

Radioactive Source Replacement Workgroup Members

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Executive Summary:

- The transition from cesium irradiators to X-ray irradiators should prove to be smooth, with some exceptions.
- X-ray irradiator outputs (energy, dose distributions) are more variable than for cesium irradiators.
- Standardization may be more difficult with X-ray than with cesium irradiators.
- Every established laboratory/investigator needs to empirically assess the effects to their studies of converting from cesium to X-rays specific to their replacement X-ray irradiator.
- Laboratories/investigators proposing to initiate use of ionizing radiation for their studies should seriously consider using X-rays from the outset.

Background:

Certain radioactive sources in large quantities have been identified as potential "dirty bomb" materials that could incapacitate a city for a long period if successfully distributed. Cesium 137, because of its powder form, has been considered of particular concern. It is commonly used in medical settings to sterilize blood, and in research settings to expose small animals, cells, chemicals, various materials and instruments to gamma radiation, resulting in the desired change to the item being exposed. Cobalt 60, in very large quantities, also presents some concerns for potential malevolent use, although it is in a metal form and therefore more difficult to distribute. Cobalt 60, in large quantities, is used in a medical setting for cancer treatment, and surgery as a gamma knife and in industrial settings for food irradiation.

The University of California owns 45 cesium or cobalt irradiators as follows:

- Cesium 137
  - Research-35
  - Medical-blood irradiators-6
- Cobalt 60
  - Research-1
  - Medical-gamma knives-3

These devices are found in 8 of the 10 campuses and 4 of the 5 medical centers and affiliated facilities.

Introduction:

David McCallen, Associate Vice President, Office of National Laboratories, sent a Decision Memo to President Napolitano dated 12/4/2017 recommending that the University of California consider partnering with the National Nuclear Security Administration (NNSA) on a cost-sharing program to replace UC-owned cesium irradiators with X-ray irradiators without adversely

impacting research or other critical operations. He noted that this replacement would significantly reduce the risk associated with the potential malevolent use of the cesium sources. The NNSA organized several meetings in California on this topic to raise awareness and to present an opportunity for risk reduction. The Decision Memo recommended that UC take full advantage of the NNSA incentive program where X-ray sources are deemed equivalent. It also recommended that a UC systemwide Radiation Source Replacement Workgroup be formed to explore whether a science-informed consensus could be reached on source equivalency for research applications. These recommended actions were approved by President Napolitano on 12/07/2017, and the Workgroup (WG) was appointed by UC Vice President of Research Art Ellis. Also, two technical conferences for the research community on ***Cesium Irradiators and Alternative Technologies*** were held at UCLA and UC San Francisco at the end of January. Researchers from a variety of institutions presented on their experience transitioning from cesium irradiators to X-ray irradiators and X-ray irradiator manufacturers discussed the capabilities of their machines. The WG members attended the conferences and participated in follow-up conference calls to discuss this topic.

Actions to Date:

On 2/16/2018, President Napolitano issued a letter to the Chancellors requesting that they work with their researchers to explore the systemwide effort to reduce risk by removing disused cesium irradiators and replacing those needed irradiators, where feasible, with X-ray irradiators through the NNSA Cesium Irradiator Replacement Program (CIRP). The University of California, Office of the President, signed a systemwide contract with Sandia to implement the CIRP program at UC facilities over a three year period, once individual researchers provide input on whether alternative technologies can meet the needs of their research. The President clarified the need for the campuses to fund the purchase of the new X-ray irradiators where appropriate. She requested an initial decision on each irradiator by 9/1/2018.

A Radioactive Source Replacement Workgroup was appointed by Vice President Arthur Ellis and Brian Smith, Associate Vice Chancellor for Infrastructure and Operations, UC San Francisco.

Workgroup Discussions:

The Workgroup (WG) held conference calls in February and March to discuss the presentations given at the conferences and the data collected on this topic. From user surveys, it was concluded that the uses of irradiators throughout the UC system are quite varied, but a majority are using the machines for cell and mice exposures. Others are using them for *C. elegans* (nematode worm) and *Drosophila melanogaster* (fruit fly) exposures, cancer vaccine trials, humanizing mice, blood irradiation, physical and chemical effects, food irradiation and degradation studies. The predominant purpose for irradiating cells is to expose feeder cells and to induce DNA damage responses in cell culture. In the case of animal irradiations, the most common use is for mouse bone marrow ablation. Therefore, in most cases, the irradiations are ablative in nature – to inactivate or kill the resident population of cells in preparation for subsequent procedures (e.g., feeder cell irradiation to prevent growth and crowding out of feeder-dependent cells, or bone marrow ablation to prevent GVHD).

Key Points:

The following points were gleaned from published papers, presentations and WG discussions as follows:

- With the exception of the surface dose, the depth dose curve for the 320 kVp X-ray irradiator was nearly identical to that of cesium down to a depth in tissue of 4 cm, while the 160 kVp X-ray machine could produce similar depth-dose as cesium only to a depth of less than 2 cm. The drop in dose from the top to the bottom of the mouse is relatively small with cesium, 220 kVp and 320 kVp machines compared to 160 kVp machines. Low energy machines are best used to irradiate thinner samples, such as cells.[3,4,7] Cesium can provide a high degree of skin sparing, with the surface dose less than half the maximum dose, with 320 kVp X-rays providing a surface dose only 20% lower than the maximum, and lower energy X-rays having very little if any skin sparing.[10] Higher energy machines in combination with appropriate filters to block the lower energy photons will permit decent penetration while sparing surface tissue.[9]

- X-ray irradiation is generally better than cesium for collimation, e.g., for partial body exposures, since it is easy to precisely collimate the x-ray point source with thin sheets of lead, whereas cesium requires thicker collimation and casts a broad penumbra from the extended line source; it also offers advanced features and imaging that may be needed for some experiments.[5]

- Different requirements for experiments may make it desirable to purchase different X-ray machines with different capabilities. For example, throughput will be crucial to some experiments, requiring an X-ray with a comparable or higher throughput as the cesium machine. As another example, lower energy machines may be sufficient for some experiments while also being less expensive to purchase, install, operate and maintain.[9]

- There are a wide variation of Relative Biological Effectiveness (RBE) values in the literature for X-rays compared to Cs-137 gamma rays used as the standard for comparison.[9, 11]

- In general, X-rays (energies equal to or below 320 keV) are more biologically effective than Cs-137 gamma rays, suggesting that lower doses of X-rays will be required to achieve the same biological endpoint as Cs-137 gamma rays.[1,4,6,7,9]

- Unlike the single gamma energy of cesium irradiators, X-ray irradiators produce different energies and spectra due to variations in X-ray tubes, energy settings and filtration utilized, with differences between manufacturers and even within the same model from the same manufacturer. This requires more detailed reporting to compare results from different X-ray machines; for example, in some cases, the quality of the beam (HVL) is not described. Cesium has substantially less machine-to-machine variation than X-ray machines, due to the reasons cited above.[9]

- It is difficult to provide a simple conversion factor for equating X-ray effects to Cesium-137 effects because RBE depends on multiple factors including X-ray peak energy, X-

ray energy spectrum (filtration), details of the experimental set-up such as distance of the specimen from the source and the field size, biological system, endpoint, etc.[9]

- Each experiment will need to be individually calibrated when converting from cesium irradiators to X-ray irradiators and the effort and resources required will depend on the precision of the effect desired. For example, in cases where inactivation of support cell proliferation or unwanted cell activity is desired – as in the case of production of feeders or irradiation of blood to prevent Graft-Versus-Host Disease (GVHD) following transfusions – the specificity of the absolute dose may not be as critical as ascertaining a tumoricidal dose or animal lethality dose.[9]

- The RBE is more important for tumor models and radiobiology studies that may be more sensitive. Feeder cell work and bone marrow work is generally less sensitive since the final goal is to inactivate proliferating cells.[9]

- Copper filtration (1-4 mm Cu) of the higher energy X-ray beams will change the spectrum by preferentially removing the lower energies and 'harden' the beam to only the higher energies. More copper filtration makes the radiation effect and energy closer to cesium. It also reduces the scatter radiation which can cause skin burns to animals. It also reduces the dose rate (for the same tube current), reducing throughput, for example. [9]

- The costs for a 36 animal comparison study of specialized mice could be as high as $5K.[9]

Conclusions and Recommendations:

The WG found that X-ray irradiators could replace cesium irradiators in many applications. There are likely some exceptions though, such as the need for very high radiation doses or radiation exposures over a period of days, which may best be achieved by other options, such as an unfiltered x-ray machine or with the use of a research reactor. Studies focused specifically on gamma exposure comparisons may also not be able to switch to X-rays. The transition to X-ray irradiators may be more straightforward in the case of biological experiments where the desired endpoint effect is killing cells in a weakly dose-dependent manner for the purpose of ablation. It is concluded that where a transition to X-ray appears possible:

- Each lab will have to do a comparison study to determine the difference with their experiments. Each study is unique and has to be customized depending on the energy of the source, the spectrum of the source (filtration), and the system (animal vs. cell), so it is not possible to have a standardized conversion factor for cesium versus X-ray irradiators.

- If a researcher has a year or less to complete their current experiments, they should continue with the cesium irradiator to complete those experiments. If their current studies require a longer time, they will need to perform comparison studies to determine if they can convert to X-ray. Thus, in some cases, a period of a few months to a year of X-ray and cesium irradiator overlap will be needed to allow for these comparison studies. If a

researcher has established that an X-ray irradiator will not produce equivalent results, they may benefit from having a cesium unit available until the study is completed, possibly a few years.

References

1. “Radiobiological Studies Using Gamma and X Rays”, Charles A Potter, et al, Sandia National Laboratory, SAND2013-0743, February 2013.

   Quote: “Conclusion: The effectiveness of X-rays was shown to vary with cell type.”

2. “Stochastic Threshold Exponential (TE) Model for Hematopoietic Tissue Reconstitution Deficient after Radiation Damage”, B. R. Scott, C.A. Potter, Dose-Response, 12:415-428, 2014.

   Quote: “Conclusion: The results obtained support the view that a 320 –kV-spectrum x-rays could be used in place of Cs-137 and Co-60 gamma rays in conducting hematopoietic tissue reconstitution studies.”

3. “Physical approach to depth dose distributions in a water phantom irradiated by a teleisotope photon beam”, Ahuja, et al, Med. Phys. 7, 120 (1980)

Quote: “Conclusion: Cs and X-ray (HVL 3mm Cu and 50 cm SSD) at up to 2 cm are equivalent.”

4. Presentation: “Gamma-ray and X-ray Irradiator Depth Dose Comparison –It’s Not Just About Energy Spectra”, Mark K. Murphy, PNNL-SA-131931, PNNL January 2018.

   Quotes- Conclusions:
   - “Our results indicate that using an RS2000 160 kVp X-ray irradiator instead of a Model 68-A Cs-137 irradiator, adds a maximum ~5% uncertainty for 25 gram rodents, and maximum ~8% uncertainty for ~50 gram rodents.“
   - “Our results indicate that using an Precision X-Ray XRAD 160 kVp X-ray irradiator instead of a PNNL custom Cs-137 irradiator, adds a maximum ~9% uncertainty for ~25 gram rodents, and maximum ~13% uncertainty for ~50 gram rodents.“
   - “Our results indicate that using an Precision X-Ray XRAD 320 kVp X-ray irradiator instead of a PNNL custom Cs-137 irradiator, adds a maximum ~5% uncertainty for ~25 gram rodents, ~5% for ~50 gram rodents, and ~9% for ~120 gram rodents.“

5. Presentation: Cesium and X-ray Irradiators- Core Operations Experiences at UC San Diego, Keith Jenne, DVM, UC San Diego, January 2018.

   Quote: Conclusions from UC San Diego users: “Cs is better for higher energy, experimental consistency and reproducibility and cost. X-ray is better for collimation, precision dosing, potentially better engraftment.”

6. Presentation: “Experiences with the Use of an X-ray Irradiator”, Colin Hill, Emeritus Professor, Radiation Oncology, USC, January 2018.

Quote: Conclusions: “Recommend use RBE of 1 for cesium and then compare same doses of 250 KVP with filtration (2mm aluminum) for biological effect.”

- “There can be small differences due to a number of factors: chamber size and materials, type of animal and depth of target cells, tissues.”
- “Relative dose rate must be similar or in the high dose rate effect range of dose rate.”
- “Endpoint sensitivity should be checked. Irradiating for survival as an endpoint is different than for tumor induction or mutation induction in some tissues.”
- “Very low doses generally less than 50 cGy can present unique problems and unexpected results.”
- “The biological variation is generally larger than physical difference causing variance in RBE.”

7. Poster: Regional Microdosimetric Variations in Bone Marrow for Photon Irradiation at Different Energies Matthew Belley, et al, Duke.
   Quote: Conclusions:
   - “To obtain biological effects that best model exposures from either clinical radiotherapy or nuclear incidences, X-rays of highest potential energy and filtration should be used.“
   - “Absorption in bone at low effective radiation energies and the consequent high doses to neighboring bone marrow due to the photoelectric effect is especially problematic in studies involving radiation effects on the hematopoietic system.”
   - “For the Precision XRAD 320 machine, the F8 filter (1.50 mm Al + 0.25mm Cu + 0.80 mm Sn) has an HVL of ~4.0 mm Cu at 320 kVp and is close to effects of 137Cs or 60Co γ-rays.”

8. “Comparison of Cesium-137 and X-ray Irradiators by Using Bone Marrow Transplant Reconstitution in C57BL/6J Mice”, Brian W. Gibson, et al, Comparative Medicine Vol. 65, June 2015, pages 165-172.

   Quote: “We concluded that although both sources ablated endogenous bone marrow sufficiently to enable stem cell engraftment, there are distinct physiologic responses that should be considered when choosing the optimal source for use in a study and that irradiation from the *137* Cs source was associated with lower overall morbidity due to opportunistic infection.”

9. Radioactive Source Replacement Workgroup (WG) opinion.

10. Results of Monte Carlo simulations by Workgroup member Bruce Faddegon for a 10 cm diameter mono-energetic beam of 50-662 keV incident on water at 10 cm and 50 cm from a point source.

11. RBE Comparison Table created by Workgroup member Kei Iwamoto, UCLA

X-ray energy	RBE to Cs-137	Relative dose increase	System	Endpoint	Citation	Notes	Model
320 kV (1mm Cu HVL)		1.16	Bone marrow	Clonogenic growth post in vivo IR	Belley et al. 2015		animals
320 V (4mm Cu HVL)		1.07	Bone marrow	Clonogenic growth post in vivo IR	Belley et al. 2015		animals
320 kV	0.763		Splenocytes TBI	cytotoxicity	Scott et al. 2013		animals
320 kV	1.346		Bone marrow TBI	cytotoxicity	Scott et al. 2013		animals
160 kV	See note		Bone marrow	Bone marrow transplant reconstitution	Gibson et al. 2015	We conclude that although both sources were efficient at ablating endogenous bone marrow sufficiently to enable stem cell engraftment, there are distinct physiologic responses that should be considered prior to choosing the optimal source for use in a study.	animals
300 kV (1.65mm Cu HVL)	1.11		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 100 cells/circumference ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.08		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 10 cells/circumference for ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.07		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 1 cells/circumference for ten 1.56 Gy fractions	animals
300 kV (1.65mm Cu HVL)	1.00		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 100 cells/circumference for a single fraction of 11.36 Gy	animals
300 kV (1.65mm Cu HVL)	1.00		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 10 cells/circumference for a single fraction of 11.36 Gy	animals
300 kV (1.65mm Cu HVL)	1.08		Gut	Jejunal crypt assay	Fu et al. 1979	Survival of 1 cells/circumference for a single fraction of 11.36 Gy	animals
320 kV (HVL 1mm Cu)	1.5		HBEC-13	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 1mm Cu)	1.6		HBEC-2	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 3.7mm Cu)	1.2		HeLa	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
320 kV (HVL 3.7mm Cu)	1.5		A549	Cytotoxicity via MTT	LRRI (Scott et al. 2013)		cells
300 kV (HVL 3mm Cu)	Approx 1.23		C57BL/6	LD50/30	UCLA radonc		animals