Why is Dosimetry and Standardization Important in Radiobiology? – The Physics Framework

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Proposed Topics for Discussion

- What are the requirements in RadBio research for PRECISION and ACCURACY?
- Accuracy of dose versus precision (or reproducibility) of dose.
- Are most institutions meeting these requirements for Accuracy and Precision?
- Typical uncertainties associated with dosimetry.
- Impact of today's increased resolution of measured biological endpoints, and the recent push for biologists to find highly dose dependent biomarkers?
- Is there a lack of dosimetry detail within publications?
- Is there a lack of reference to written standards within publications?
- Measured Dose versus Actual Dose to Shallow and Deep Depths
- Would this community benefit from a Dosimetry Comparison program, and/or dosimetry workshops?

What are the requirements in RadBio research for PRECISION and ACCURACY?

In order to determine whether increasing standardization of dosimetry in this field could significantly impact the field, the first question we need to answer is what are the current requirements in the field with regard to dosimetry PRECISION and ACCURACY for many of the biological endpoints for in vitro and in vivo irradiations. Examples are:

Survival Curves (e.g., LD50)
Apoptosis
Gene Expression (e.g., Low Dose)
Cell Transformation (normal to cancer)
Changes in reactive oxygen
Mutations
Protein Expression
Spinal Cord function
Epigenetics
Changes in Metabolites
Mechanisms in GI, Bone Marrow, Lung

What are the requirements in RadBio research for PRECISION and ACCURACY?

- Whether human or research animal, there are large biological differences that are influenced by genetic sensitivity.
- In addition there are environmental factors that change the background response to radiation.
- One study for example, for radon in homes the risk for lung cancer was calculated to be an excess of 21,000 for smokers and only 1700 for non-smokers. So if you have radon in your home you should really stop smoking to get a 10 fold decrease in radon induced cancer, while removal of the radon from the home has only a small impact.
- All this is documented in the new NCRP Report No. 167

What are the requirements in RadBio research for PRECISION and ACCURACY?

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- Another important factor that influences the background cancer frequency is life-style in general. The background rate of cancer ranges from 80-300 cancers per 100,000 depending on where you live.

- If you want to go to molecular responses, the data suggests that there are huge biological differences between tissues, between species, between strains and cell types.

- The bottom line is that biological dose response variability is very large.

What are the requirements in RadBio research for PRECISION and ACCURACY?

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- **<u>However</u>, there are some biological endpoints that have a very high dependency on radiation dose and, especially with tight species strain control, require <<10% precision in dose.**
- Examples are induction of myelopathy following spinal cord irradiation, as well as GI tract, bone marrow and lung responses.*
- This leads to Lethal Dose curves that can be steep as well, like that for the mouse and mini-pig.

* See R.P. Hill presentation in this same workshop

Accuracy of dose versus precision (or reproducibility) of dose.

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- Of course, when planning any RadBio study one should determine whether they will require just *precision* of dose across study group, or if they will also require *accuracy* in the dose.
- Most RadBio researchers focus more on ensuring REPRODUCIBILITY (precision) of dose across a study group than on accuracy of dose (traceability) because their main desire is for their biological endpoint data to have minimal size error bars.
- ACCURACY of dose should be important to them if they ever want to validly compare their data to other studies (or if others will ever want to compare to their data).

Are most institutions meeting these requirements for accuracy and precision?

- This is the second question that needs to be answered in order to be able to determine whether standardization should be increased.

- Only if the error bars for the dose response being studied are within the individual researcher's specific requirements can they conclude that the dose PRECISION was sufficient.

- This is because the magnitude of the error bars is due to much more than dose variation. So if the all variables result in sufficiently small error bars, you can be assured that the dose variation was small as well.

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Are most institutions meeting these requirements for accuracy and precision?

- Researchers can get a good idea if they are meeting their ACCURACY requirements only if their data compares well with a number of other researchers or, ideally, they compare well when they perform a Measurement Quality Assurance program with a primary (NIST) or secondary standards laboratory.

Typical uncertainties associated with dosimetry

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- Examples of available dosimetry for radiation biology research:
  - TLD and AlO OSL film = 0.005-10 Gy
  - Radiachromic Film = 0.1 to 200 Gy
  - Alanine = 2-200,000 Gy
  - Ionization chamber = 0 to limitless Gy
- Uncertainty in measured dose can easily range from approx 3% to 20% (95% C.L.), depending on how experienced the individual is that performs the dosimetry, and how well they account for influence quantities like post-irradiation growth/fade, energy, dose rate, temperature, humidity, non-linearity dose regions, TE depth differences between dosimetry and subject, etc.

Other Drivers for Increased Precision and Accuracy

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- With the increase in hi-tech instrumentation and resulting increase in precision and resolution in measurement of biological endpoints, has this been another driver for higher precision and accuracy of radiation dose?

- The recent push for biologists to find highly dose dependent biomarkers (mass casualty triage) is also requiring more precise radiation dose delivery.

Is there a lack of dosimetry detail within publications?

Ideally, the following information should be included in RadBio publications:

- Animal type and dimensions
- Animal strain
- Irradiator Manufacturer/Model
- Source (nuclide, HVL, filter material)
- Radiation Energy
- Irradiation Geometry*
- Dosimetry Method (including depth)
- Dose (rel to water, tissue?)
- Dose Rate (fractionated?)
- Location of Detector
- Dose Reference Location
- Published Standards/Guides Used
- Uncertainty in Dose

* Source distance, field size, one-sided or two-sided?, bolus?, beam flattener?, backscatter?, containment material and thickness.

Is there a lack of dosimetry detail within publications?

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- Many of the publications in the area of radiation biology studies contain minimal detail in irradiation geometry, radiation spectrum, and dosimetry equipment and techniques.
- This can make it difficult for researchers to validly compare their radbio studies with other studies, design their study so it is a valid repeat of another study, and to determine how much of the discrepancy in biological response is due to dose delivered and how much to biology variation and analysis.
- I can present tables that show, what I perceive, as a lack of dosimetry info within published posters and journal articles in the radbio field.

Is there a lack of dosimetry detail within publications?

The following lists the approximate rate of occurrence of specific information within RRS Posters at 2010 Maui meeting:

Animal type 100%

Animal strain 95%

Irradiator Manufacturer/Model 70%

Source (nuclide, HVL, filtering) 75%

Radiation Energy 67%

Irradiation Geometry* 70%

Dosimetry Method 7%

Dose (rel to water, tissue?) 96%

Dose Rate (fractionated?) 52%

Location of Detector 7%

Dose Reference Location 4%

Published Standards/Guides Used 7%

Uncertainty in Dose 4%

* "TBI" or "WBI" was only given partial credit.

Is there a lack of dosimetry detail within publications?

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The following lists approximate rate of occurrence of specific information within previous 15 issues of Radiation Research journal:

Animal/Cell type 100%

Animal/Cell strain 100%

Irradiator Manufacturer/Model 80%

Source (nuclide, HVL, filtering) 100%

Radiation Energy 78%

Irradiation Geometry* 48%

Dosimetry Method 37%

Dose (rel to water, tissue?) 94%

Dose Rate (fractionated?) 81%

Location of Detector 20%

Dose Reference Location 7%

Published Standards/Guides Used 7%

Uncertainty in Dose 4%

* "TBI" or "WBI" was only given partial credit.

Is there a lack of reference to written standards within publications?

- The data from the previous slides indicate only ~7% of researchers cite written dosimetry standards/guides. Does this indicate that very few researchers *utilize* these standards?

- Is this is hurting the RadBio field?

- Can NIH and other funding agencies do more to enforce the use (and citing) of a dosimetry standard (ICRU 30, IAEA TR-398, AAPM Protocol for 40-300 kV X-ray, etc.)?

Measured Dose versus Actual Dose at Shallow and Deep Depths

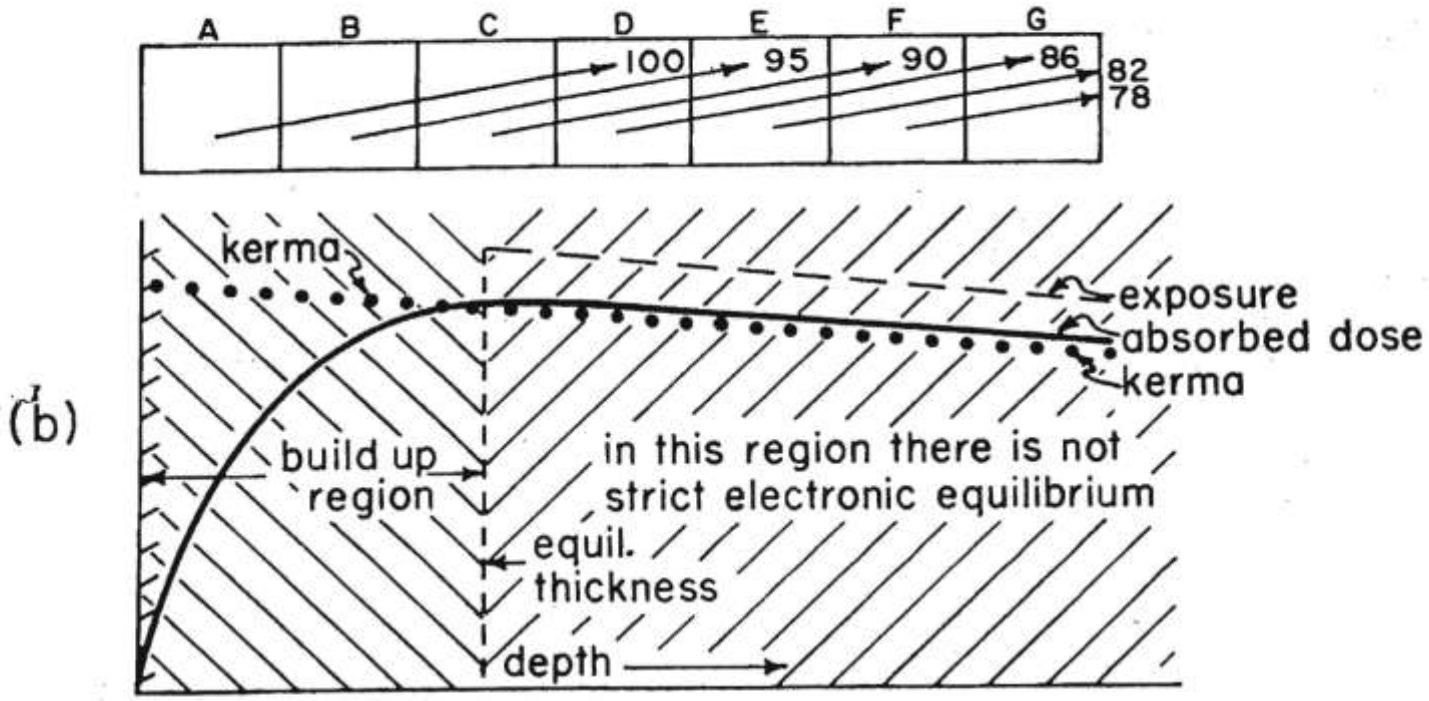

FIGURE IX-3.(a) Graph showing schematically why the absorbed dose increases wi depth and how electronic equilibrium is achieved when there is no attenuation of t primary. (b) Graph as (a) when attenuation of the primary occurs. Now electror equilibrium is not produced even at depths beyond the equilibrium thickness. Kerma a dose have the same units and so the curves are comparable; exposure is in different un and is not comparable.

Measured Dose versus Actual Dose at Shallow and Deep Depths

Figure showing potential portion of Cs-137 spectra **measured** versus that portion actually **contributing to dose** to subject.

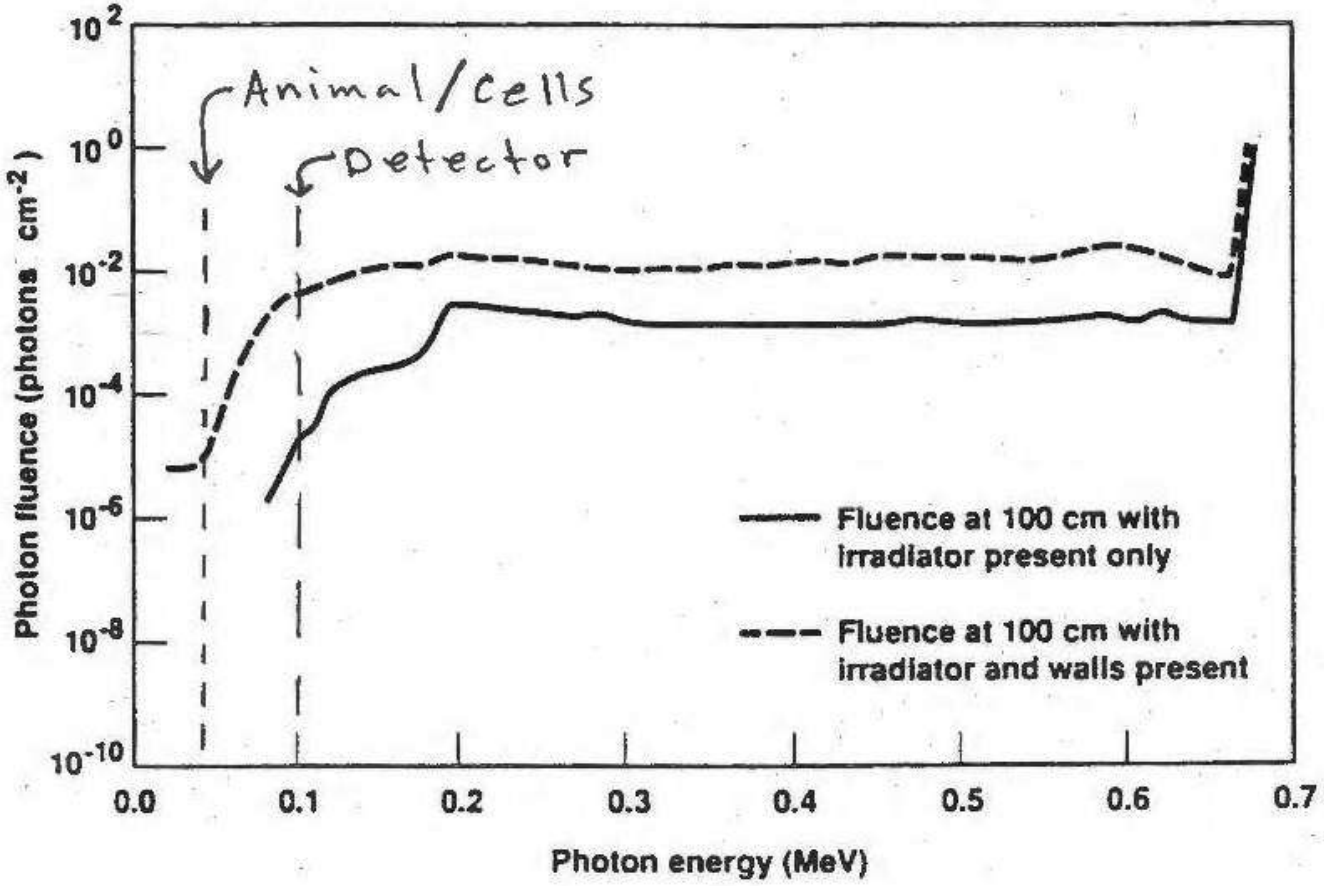

Fig. 5. Calculated photon energy spectra showing additional low-energy scatter contributed by the irradiator and the room walls.

Would this community benefit from a Dosimetry Comparison program?

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•Dosimetry “intercomparisons” are common in other fields that involve dosimetry.
• An example would be to take tissue-equivalent or water-equivalent phantom that is a crude shape of a rat or rabbit or pig (and which has cavities for passive dosimeters throughout), and send it as well as bag of dosimeters around to the various labs that perform radbio research using these animals.
•The participants would be instructed to insert the dosimeters and irradiate to a specific absorbed dose (relative to a 5-point average along anteroposterior axis perhaps), and send dosimeters and phantom back to program manager for readout.
•A comparison of cell culture irradiations using x-ray could also be performed.

Would this community benefit from a Dosimetry Comparison program?

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•Of course, these programs can be designed to not only look at the results of the detector readout, but also at the protocols used by the participant, the NIST traceability and uncertainties associated with their measurements, their understanding of the parameters that influence dose and dose distribution, how they interpret data, etc.

•Would it be beneficial to offer biologists and physicists a course on radiation dosimetry for radiobiology?

Conclusions

•The variability in biological dose response is so large that 10-20% uncertainty in delivered dose would not significantly impact most studies.

•For some studies (induction of myelopathy following spinal cord irradiation, as well as GI tract, bone marrow and lung funtions) there is a much higher dependency on dose, and the dose *precision* across study group needs to be kept to within about 5%, preferably within 3%.

• In order to have confidence in the comparison of these types of studies, the dose *accuracy* should be near the same magnitude as above.

•In order to answer whether the uncertainty in dose measurements across the RadBio community is large enough to negatively impact a significant number of studies, a study would need to be done. A dosimetry comparison program could help with this.

Conclusions cont. -

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•Currently, many RadBio publications lack **important dosimetry information** needed for researchers, and it would be very beneficial for journal editors and reviewers to require authors to list minimal info listed earlier.

•Currently, most all RadBio publications lack **reference to written standards/guides**, and it would be very beneficial for funding agencies, program managers, journal editors and reviewers to require authors to use and cite written standards like ICRU 30, IAEA TR-398, and AAPM Protocol for 40-300 kV X-ray.