



HAL
open science

Minimum reporting standards should be expected for preclinical radiobiology irradiators and dosimetry in the published literature

François Trompier, Larry Dewerd, Yannick Poirier, Morgane Dos Santos, Ke Sheng, Keith Kunugi, Thomas Winters, Andrea Dicarolo, Merriline Satyamitra

► To cite this version:

François Trompier, Larry Dewerd, Yannick Poirier, Morgane Dos Santos, Ke Sheng, et al.. Minimum reporting standards should be expected for preclinical radiobiology irradiators and dosimetry in the published literature. *International Journal of Radiation Biology*, 2023, pp.1-6. 10.1080/09553002.2023.2250848 . irsn-04207687

HAL Id: irsn-04207687

<https://irsn.hal.science/irsn-04207687>

Submitted on 14 Sep 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial - NoDerivatives 4.0 International License

1 **Commentary: Minimum Reporting Standards Should be Expected for Preclinical Radiobiology**

2 **Irradiators and Dosimetry in the Published Literature**

3 François Trompier¹⁽⁰⁰⁰⁰⁻⁰⁰⁰²⁻⁸⁷⁷⁶⁻⁶⁵⁷²⁾, Larry A. DeWerd²⁽⁰⁰⁰⁰⁻⁰⁰⁰³⁻²⁰⁰³⁻²³⁴⁴⁾, Yannick Poirier³⁽⁰⁰⁰⁰⁻⁰⁰⁰²⁻⁶⁵⁴⁸⁻⁸³²¹⁾,
4 Morgane Dos Santos⁴⁽⁰⁰⁰⁰⁻⁰⁰⁰³⁻²¹³⁹⁻²⁶⁷⁵⁾, Ke Sheng⁵⁽⁰⁰⁰⁰⁻⁰⁰⁰²⁻⁶⁶⁹⁶⁻⁵⁴⁰⁹⁾, Keith Kunugi²⁽⁰⁰⁰⁰⁻⁰⁰⁰¹⁻⁷⁶⁶⁶⁻⁵⁹⁰⁴⁾, Thomas
5 A. Winters⁶⁽⁰⁰⁰⁰⁻⁰⁰⁰³⁻⁴²⁰⁶⁻⁰⁰²⁰⁾, Andrea L. DiCarlo⁶⁽⁰⁰⁰⁰⁻⁰⁰⁰¹⁻⁸¹¹³⁻⁰⁰¹⁵⁾, Merriline M. Vedamony^{a6(0000-0003-2207-4636)}

6 ¹ Ionizing Radiation Dosimetry Laboratory (LDRI), Human Radiation Protection Unity, Institut de
7 Radioprotection et de Sûreté Nucléaire (IRSN), Fontenay-aux-Rose, France

8 ² Medical Radiation Research Center, Department of Medical Physics, University of Wisconsin School of
9 Medicine and Public Health, Madison, Wisconsin, USA

10 ³ Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland,
11 USA

12 ⁴ Department of Radiobiology and Regenerative Medicine (SERAMED), Radiobiology of Accidental
13 Exposure Laboratory (LRAcc), Institut de Radioprotection et de Sûreté Nucléaire (IRSN), Fontenay-
14 aux-Roses, France

15 ⁵ Department of Radiation Oncology, University of California San Francisco, San Francisco, California,
16 USA

17 ⁶ Radiation and Nuclear Countermeasures Program (RNCP), Division of Allergy, Immunology and
18 Transplantation (DAIT), National Institute of Allergy and Infectious Diseases (NIAID), National
19 Institutes of Health (NIH), Rockville, Maryland, USA

20 ^a Corresponding Author

21 5601 Fishers Lane, Room 7A67

22 Rockville, MD 20852

23 240-669-5432

24 Merriline.Satyamitra@nih.gov

25
26 **Disclosure of interest:** The authors declare that this work was conducted in the absence of any commercial or
27 financial relationships that could be construed as a potential conflict of interest.

29 **Introduction**

30 Preclinical researchers have long acknowledged the critical need for accurate dosimetry in the
31 conduct of radiation-exposure studies involving living systems. Although radiation dosimetry is required to
32 be National Institute for Standards and Technology (NIST)-traceable for human irradiation protocols, there
33 were previously only limited requirements stipulating accurate radiation exposures for preclinical radiation
34 studies funded by the National Institutes of Health (NIH). In one of the earliest identified publications
35 (1956) that addressed radiation dosimetry in murine studies, Hurst *et al.* (Hurst et al. 1956) discussed their
36 calculations surrounding estimating neutron responses, and “distribution of of absorbed energy versus
37 LET”. In 2009, Zoetelief *et al.* (Zoetelief et al. 2001) outlined European efforts to harmonize X-ray
38 dosimetry studies in radiation biology, which resulted in the establishment of a protocol to improve
39 dosimetry oversight and allow for better comparison of results across different institutions. It is, however,
40 unclear if these early efforts substantially changed the approach of biologists to ensuring accurate and
41 reproducible dosimetry in their radiation research.

42 The lack of consideration of dosimetry in *in vitro* and *in vivo* work was further explored in 2011
43 during the “Radiation Dose is More than a Number” workshop convened by NIST, and co-sponsored by the
44 National Institute of Allergy and Infectious Diseases (NIAID), and the National Cancer Institute (NCI). The
45 report that followed (Desrosiers et al. 2013) made nine recommendations that ranged from coordinating
46 with radiation physicists during the experimental design phase and including more setup and dosimetry
47 details in publications, to establishing working groups to develop protocols, and implementing formal
48 dosimetry intercomparison programs. In an attempt to address the latter suggestion, and ensure rigor and
49 reproducibility in their funded research portfolio consistent with NIH grants policy¹, the NIAID Radiation
50 and Nuclear Countermeasures Program (RNCP) released a request for proposals (NIAID-NIH-RFP-
51 NIHAI201800020²) in 2019, seeking to make a single contract award for “RNCP-Wide Dosimetry
52 Guidance & Monitoring of Sources and Irradiation Protocols”. This funding opportunity requested that
53 offerors develop a consistent means of dosimetry comparison and reproducibility, as well as provide the

¹ <https://grants.nih.gov/policy/reproducibility/index.htm>

² <https://sam.gov/opp/360d070bdf5d437f83e88c13442fa23f/view>

54 administrative foundation necessary to facilitate and coordinate dosimetry activities in partnership with the
55 NIAID. Respondents were asked to provide services, facilities, expertise, and capabilities to develop a
56 centralized dosimetry harmonization effort that fits the resources and circumstances of projects across the
57 funded RNCP portfolio. The contract award was made in 2020 to the University of Wisconsin (Principal
58 Investigator Larry DeWerd), who established a harmonization protocol to encompass all the irradiators in
59 use across the RNCP-funded portfolio of grants, contracts, and inter-agency agreements.

60 In 2019, the RNCP also became concerned with the specifics of establishing and reporting neutron
61 dosimetry and convened a “Neutron Radiobiology and Dosimetry Workshop” with presentations from 17
62 subject matter experts, planned in collaboration with the Department of Defense (DoD), Defense Threat
63 Reduction Agency (DTRA), and the National Aeronautics and Space Administration (NASA). The meeting
64 report that was published in 2021 (Stricklin et al. 2021) explored historical neutron exposure research and
65 highlighted the need for harmonized reporting of exposure and experimental parameters. The authors
66 concluded that efforts should be made to update computer coding for neutron dosimetry estimates,
67 government policies needed to be re-visited in terms of expected radiation energy spectrums, and funding
68 agencies must make key investments in consideration of neutron dosimetry, to improve science and ensure
69 radiation emergency preparedness.

70 All of these early attempts to ensure the use of accurate dosimetry in research laboratories
71 culminated in the current effort to take the next step and require that sufficient information be included in
72 published manuscripts, such that reviewers and editors can be assured that the irradiations were carried out
73 correctly, and readers can have the necessary information to replicate published experiments.

74 75 ***Background and Rationale for Dosimetry Reporting***

76 Good science must be well described to be understood, compared, and replicated. For radiation
77 biology, this requires the combination of both biology and radiation physics – two very different expertises,
78 typically provided by different individuals with specialized training. While biological systems can be
79 difficult to control, particularly for *in vivo* models, radiation follows well-understood physical processes,

80 which can be controlled and measured to a very high level of accuracy, precision, and reproducibility.
81 Therefore, it is both feasible, and important, to require radiobiological studies to describe their irradiation
82 protocol.

83 Unfortunately, experimental irradiation protocols are currently not well described in the majority of
84 published radiobiology studies. This was already true in 2011, during the original NIST workshop
85 (Desrosiers et al. 2013), and has since been confirmed by multiple meta-studies showing no apparent
86 improvements in reporting since the original symposium (Draeger et al. 2020, Pedersen et al. 2016, Seed et
87 al. 2016, Stern et al. 2022, Stone et al. 2016). In a recent analysis of 1758 published pre-clinical studies
88 employing ionizing radiation, some parameters, such as radiation dose, are nearly always provided (>94%).
89 Many important details, such as the equipment producing the radiation, the radiation type, beam energy (or
90 quality), and dose rate, are usually, but not always, reported (>50-80%). Details pertaining to experimental
91 design, such as the number and geometry of the radiation fields, the use of shaping collimators, or rotating
92 tables to ensure uniform delivery to multiple animals, are seldom shared (>25%). Finally, details relating to
93 experimental validation of the delivered radiation dose through some form of dosimeter (ideally traceable to
94 national standards), are nearly always absent (<15%). Reference to published standards or protocols was as
95 low as 1.3% of published studies in Draeger *et al.* (Draeger et al. 2020).

96 As originally illustrated in the report following the NIST workshop, “investigators cannot report
97 what they have not considered.”(Desrosiers et al. 2013). When experiments are not described, a reviewer
98 cannot assess what an author might or might not have considered, or the soundness of the experimental
99 design at all. In some instances, metastudies reveal that certain publications contained glaring contradictions
100 in their irradiation protocols. These include descriptions of irradiators that would be incapable of producing
101 the experiment described in the methods, non-existent radionuclides, or typographical errors (e.g., kV to
102 MV), which translate into a thousand-fold difference in energy. These findings suggest that many studies
103 may be erroneously described, even in cases where there is no clear contradiction in the few details
104 available. For instance, irradiating multiple mice placed at varying distances from the center of the field will

105 often result in a different dose (and therefore a different biological effect) delivered to each, but this will not
106 be apparent in a manuscript that simply describes the source used and dose prescribed.

107 In a vacuum, a lack of rigor in describing experimental protocols might not imply anything, but
108 insufficient communication among authors, or a propensity to copy and combine old protocols without
109 sufficient rigor can be problematic. When combined with repeated reports outlining difficulties in
110 harmonizing radiation dosimetry across separate laboratories, (Pedersen et al. 2016, Seed et al. 2016,
111 Zoetelief et al. 2001) a more concerning picture emerges. As stated in the original NIST report, “Few
112 students or researchers using ionizing radiation in biological research have training in basic radiation
113 physics. This leads to the difficult situation that when ‘one does not know what one does not know’
114 dosimetry design and documentation go unaddressed”. And if it is not described, a journal or grant reviewer
115 cannot assess whether the experiment is sound.

116 One particular concept not initially addressed in the first NIST workshop concerns the definition of
117 radiation dose. Indeed – not all dose is created equal. An X-ray tube can be calibrated in terms of exposure,
118 air kerma, or adsorbed dose to water (D_w), depending on which correction factors are used. Reference
119 dosimetry can assume, or not, the presence of backscatter. Or, an investigator can refer to the radiation dose
120 being delivered to animals under experimental conditions. Each of these descriptions is scientifically sound,
121 and yet can lead to differences of up to 50% in reported doses. As described in the next section, the use of
122 Roentgen (exposure) vs dose for ^{137}Cs exposures will introduce an error of $\sim 11\%$. Without further
123 description, it is impossible to know which quantity an investigator is referring to. To address this, the
124 American Association of Physicists in Medicine (AAPM)’s Task Group 319 is developing new standards on
125 how to perform and report experimental dosimetry in kilovoltage cabinet irradiators. However, these new
126 guidelines have yet to be published, and their implementation will not be instantaneous. In the meantime,
127 investigators should be careful in how they describe their irradiation protocol in scientific communications.

128
129 *U.S. Efforts in Dosimetry Harmonization*

130 Inconsistent dosimetry was first outlined by the 2011 NIST panel³, and follow-up publications in
131 2016 by Seed, *et al.*, (Seed et al. 2016) and Pedersen, *et al.* (Pedersen et al. 2016) suggested that only one in
132 five laboratories deliver dose within 5% of a specified target level, with variations up to 42% observed.
133 From 1971 to 1999, the EULEP-EURADOS initiative performed 8 similar intercomparisons and
134 consistently found errors of up to ~20%, and found the majority of institutions could not satisfy a $\leq 10\%$
135 homogeneity requirement (Zoetelief et al. 1997). Radiation biology research often employs orthovoltage X-
136 ray systems and ¹³⁷Cs sources where dosimetry is based on manufacturer recommendations. For X-rays,
137 results may not be traceable to NIST standard beams because of the differing maximum beam energy and
138 the filtration used for a certain energy. In addition to traceability issues, low-energy X-rays introduce
139 variability in dosimetry and radiobiological response in multiple ways. First, low energy bremsstrahlung
140 radiation is more readily absorbed in tissues than are higher energy photons from isotope irradiators.
141 Second, low-energy X-rays are more readily absorbed by cortical bone, inducing differential biological
142 effects in bone marrow and different biological responses (Bell et al. 2022, DeWerd et al. 2021, Poirier et al.
143 2020).

144 From 2020 to 2023, The NIAID/RNCP program for harmonization of radiation dose evaluated >30
145 irradiators (X-ray and cesium), and found that upon initial survey, 50% of machines were outside of $\pm 5\%$ of
146 the targeted 4 Gy dose, the benchmark for acceptable irradiation, as is shown in Figure 1[Figure 1 near
147 here]. Traceable NIST beams for X-ray beams were used for cabinet X-ray systems by matching half value
148 layers (HVL) for radiobiological X-ray beams, although kVp and second HVL are much different.
149 Phantoms for total-body, and partial-body irradiation were established, and dose was measured using
150 LiF:Mg,Ti thermoluminescent dosimeters (TLDs) calibrated using the NIST-traceable HVL matched X-ray
151 beams.

152 Variations from the 4 Gy target dose ranged from +/-12% to 25%. After consultations and retesting,
153 results for nearly all institutions were brought within the required 5% of target dose, and doses were
154 resolved for the remaining institutions after consideration of physics issues. Also, precision mapping of the

³ <https://www.nist.gov/programs-projects/medical-archive-workshop-radiobiology-dosimetry-standardization>.

155 radiation field using multiple TLDs was important and permitted the resolution of dose discrepancies that
156 aligned with variations in dose. To summarize, there are three problems that are frequently encountered at
157 institutions that must be addressed. First, the correct physics dose quantity and other characterizations
158 should be employed, especially for X-ray machines. An example of this that was found with some
159 radionuclide sources involving a dose discrepancy of ~11 %. The institutions in question were using the
160 manufacturer-supplied radiation exposure quantity in Roentgens, rather than the absorbed dose to water; and
161 the correction needed to achieve absorbed dose to water was 11% - matching the observed error perfectly. A
162 second problem is not understanding the physics or the measurements given; consultation with a medical
163 physicist would be of great benefit, but not all sites conducting radiation biology research have access to the
164 support of a certified medical physicist. Of note, not all certified medical physicists are familiar with
165 irradiation conditions and calibration protocols of preclinical systems, which can be vastly different than
166 clinical systems. Finally, an inadequate understanding of dose distribution within the radiation field,
167 especially in cabinet-style orthovoltage X-ray irradiators, is a significant problem. It is important to
168 understand the isodose plot of the field, and in many cases, rotation of the subject animals is necessary to
169 average out the dose. The goal of this NIAID-funded program is the harmonization of dose among
170 institutions regardless of the source used to establish the radiation.

171

172 ***French Efforts in Dosimetry Harmonization***

173 In France, the Institute of Radiological Protection and Nuclear Safety (IRSN) has a long tradition of
174 collaboration between dosimetrists and radiobiology researchers. Technical support has always been
175 provided to define the best irradiation conditions and reference dose rates, whether for gamma irradiators,
176 conventional X-ray facilities, or for irradiation at reactors (e.g., the SILENE facility in Valduc, France) with
177 a concern for the traceability of these data. A dose rate in the most appropriate dosimetric quantity and a
178 homogeneity level are defined for each irradiation configuration. For example, for cell irradiations, a
179 configuration is defined for a given container, filling volume, and number of containers. It is not only a
180 question of defining a reference rate in D_w or in air kerma according to the reference protocols in use (such

181 as the AAPM's TG-61 or the IAEA TRS-398), but also taking into account factors that can affect the dose
182 rate, and defining it at the level of the biological material of interest (Dos Santos et al. 2021). For small
183 animals, whether for total-body or localized irradiations, specific phantoms are produced using molds. For
184 programs involving study of bone tissue, electron paramagnetic resonance (EPR) spectroscopy, which
185 enables the dose actually delivered to the bone to be estimated, has been introduced (Guillou et al. 2022).
186 These skills have been regularly made available to other national or European research institutes, private
187 companies, and European projects such as RENE (Figure 2) (Trompier et al. 2017). In Figure 2 [Figure 2
188 near here], the accuracy of the reference dosimetry of beams use to established calibration curves in
189 biological dosimetry was evaluated with alanine dosimeters calibrated in Dw. Deviations from reference
190 dose (10 Gy) range from a few % up to 50%, with about 50% of results within +/- 5%. Dose quantities used,
191 when known by participants, were either air kerma or Dw. The impact of using different dose quantities
192 and/or beam quality was noticeable in dicentric assays, but had not been accounted for when analysing
193 results of biological dosimetry for this inter-laboratory comparison. With the arrival of more complex new
194 small animal X-ray conformal irradiation platforms to the IRSN (SARRP, Xstrahl), and the increased use of
195 a linear accelerator (LINAC), the need to have a dedicated physicist on a full-time basis was felt to be
196 important, due to the greater complexity of use and dosimetry aspects. This recommendation has also
197 resulted in a dedicated research program at IRSN on the latter aspect, notably to develop new dosimetry
198 approaches (e.g., for small fields), new protocols for dose rate measurement at biological sites, verification
199 of manufacturer data, and quality control. A similar need among other users of SARRP type of X-ray
200 platforms has resulted in hiring additional physicists to ensure the optimal performance of these machines.
201 This small community quickly organized itself to share experiences, protocols, and methods, and
202 endeavored to set up a program to verify manufacturer data, and provide intercomparison and technical
203 assistance for physicist-orphaned machines, notably in the framework of a new French national network of
204 irradiation platforms for radiobiology studies (Réseau des Plateformes National d'Irradiation; ResPlanDir)⁴.
205

⁴ <https://www.france-hadron.fr/en/platforms/features-modalities.html>

206 **Proposed New Instructions for Authors for Dosimetry Reporting**

207 Given the concerns outlined above regarding accuracy and reproducibility of radiation dosimetry in
208 radiobiological research, and in the interest in ensuring rigor and reproducibility of irradiation experiments,
209 the authors of this commentary, in agreement with another recent commentary on this subject by Marcu et
210 al. (Marcu et al. 2022), propose that journals engaged in publishing radiobiology research introduce new
211 ‘Instructions for Authors’ addressing minimum standards for reporting radiation dosimetry information.
212 Implementing the recommendations below would also address issues sometimes encountered in successful
213 study replication. Therefore, the following minimum irradiation parameters are suggested:

- 214 • Name of the irradiator (company, country, model)
- 215 • Type of source (radionuclide (e.g. cesium, cobalt), X-ray)
- 216 • Energy (kVp, mA; for X-ray systems)
- 217 • Filtration (for kV X-ray systems, half value layer if known)
- 218 • Radiation dose and dose rate, source to surface distance (SSD), field size,
- 219 • Sample being irradiated, and
- 220 • Irradiation geometry (nature of animal restraint (e.g., pie or other jig), the material of the sample
221 holder, shielding (if appropriate), orientation to the source, any animal(s)/sample rotation)
- 222 • Dose quantity (e.g., how radiation dose was measured - D_w , air kerma, midline tissue, etc.)
- 223 • Pre-use, device calibration method used
- 224 • Planning and dose calculation method (required for multiple field conformal dose delivery,
225 particularly orthovoltage small animal conformal dose delivery systems, optional otherwise)
- 226 • Reporting of any in-run dose measurements (if applicable)

227

228

REFERENCES

1. Bell BI, Vercellino J, Brodin NP, Velten C, Nanduri LSY, Nagesh PKB, Tanaka KE, Fang Y, Wang Y, Macedo R, English J, Schumacher MM, Duddempudi PK, Asp P, Koba W, Shajahan S, Liu L, Tomé WA, Yang WL, Kolesnick R, Guha C. Orthovoltage x-rays exhibit increased efficacy compared with γ -rays in preclinical irradiation. *Cancer Res.* 2022;82(15):2678-91.
2. Desrosiers M, DeWerd L, Deye J, Lindsay P, Murphy MK, Mitch M, Macchiarini F, Stojadinovic S, Stone H. The importance of dosimetry standardization in radiobiology. *J Res Natl Inst Stan.* 2013;118.
3. DeWerd LA, Kunugi K. Accurate dosimetry for radiobiology. *Int J Radiat Oncol Biol Phys.* 2021;111(5):e75-e81.
4. Dos Santos M, Paget V, Trompier F, Gruel G, Milliat F. Dosimetry for cell irradiation using orthovoltage (40-300 kv) x-ray facilities. *J Vis Exp.* 2021;10.3791/61645(168).
5. Draeger E, Sawant A, Johnstone C, Koger B, Becker S, Vujaskovic Z, Jackson IL, Poirier Y. A dose of reality: How 20 years of incomplete physics and dosimetry reporting in radiobiology studies may have contributed to the reproducibility crisis. *Int J Radiat Oncol Biol Phys.* 2020;106(2):243-52.
6. Guillou M, L'Homme B, Trompier F, Gruel G, Prezado Y, Dos Santos M. Preclinical modeling of low energy x-rays radiological burn: Dosimetry study by monte carlo simulations and epr spectroscopy. *Front Physiol.* 2022;13:1075665.
7. Hurst GS, Mills WA, Conte FP, Upton AC. Principles and techniques of mixed radiation dosimetry; application to acute lethality studies of mice with the cyclotron. *Radiat Res.* 1956;4(1):49-64.
8. Marcu LG, Bezak E, Sykes PJ. Radiation research journals need to stipulate minimal dosimetry requirements for publishing research using x-radiation exposures. *Radiat Res.* 2022;198(2):204-6.
9. Pedersen KH, Kunugi KA, Hammer CG, Culberson WS, DeWerd LA. Radiation biology irradiator dose verification survey. *Radiation Research.* 2016;185(2):163-8, 6.
10. Poirier Y, Belley MD, Dewhirst MW, Yoshizumic TT, Down JD. Transitioning from gamma rays to x-rays for comparable biomedical research irradiations: Energy matters. *Radiat Res.* 2020;193(6):506-11.

11. Seed TM, Xiao S, Manley N, Nikolich-Zugich J, Pugh J, Van den Brink M, Hirabayashi Y, Yasutomo K, Iwama A, Koyasu S, Shterev I, Sempowski G, Macchiarini F, Nakachi K, Kunugi KC, Hammer CG, Dewerd LA. An interlaboratory comparison of dosimetry for a multi-institutional radiobiological research project: Observations, problems, solutions and lessons learned. *Int J Radiat Biol.* 2016;92(2):59-70.
12. Stern W, Zira S, Boyd C, Iliopoulos I, Peiris P, Fedurin M. Alternative technologies meta study report. Laboratory BN: U.S. Department of Energy, Office of Nuclear Energy. 2022; Report No.: BNL-223583-2022-FORE. <https://doi.org/10.2172/1895064>
13. Stone HB, Bernhard EJ, Coleman CN, Deye J, Capala J, Mitchell JB, Brown JM. Preclinical data on efficacy of 10 drug-radiation combinations: Evaluations, concerns, and recommendations. *Transl Oncol.* 2016;9(1):46-56.
14. Stricklin DL, VanHorne-Sealy J, Rios CI, Scott Carnell LA, Taliaferro LP. Neutron radiobiology and dosimetry. *Radiat Res.* 2021;195(5):480-96.
15. Trompier F, Baumann M, Barrios L, Gregoire E, Abend M, Ainsbury E, Barnard S, Barquinero JF, Bautista JA, Brzozowska B, Perez-Calatayud J, De Angelis C, Domínguez I, Hadjidekova V, Kulka U, Mateos JC, Meschini R, Monteiro Gil O, Moquet J, Oestreicher U, Montoro Pastor A, Quintens R, Sebastià N, Sommer S, Stoyanov O, Thierens H, Terzoudi G, Villaescusa JJ, Vral A, Wojcik A, Zafiropoulos D, Roy L. Investigation of the influence of calibration practices on cytogenetic laboratory performance for dose estimation. *Int J Radiat Biol.* 2017;93(1):118-26.
16. Zoetelief J, Broerse JJ, Busscher FA, Hiestand WP, Julius HW, Jansen JT. Recent eulep dosimetry intercomparisons for whole body irradiation of mice. European late effects project group. *Int J Radiat Biol.* 1997;72(5):627-32.
17. Zoetelief J, Broerse JJ, Davies RW, Octave-Prignot M, Rezvani M, Vergara JC, Toni MP. Protocol for x-ray dosimetry in radiobiology. *Int J Radiat Biol.* 2001;77(7):817-35.

Figure 1

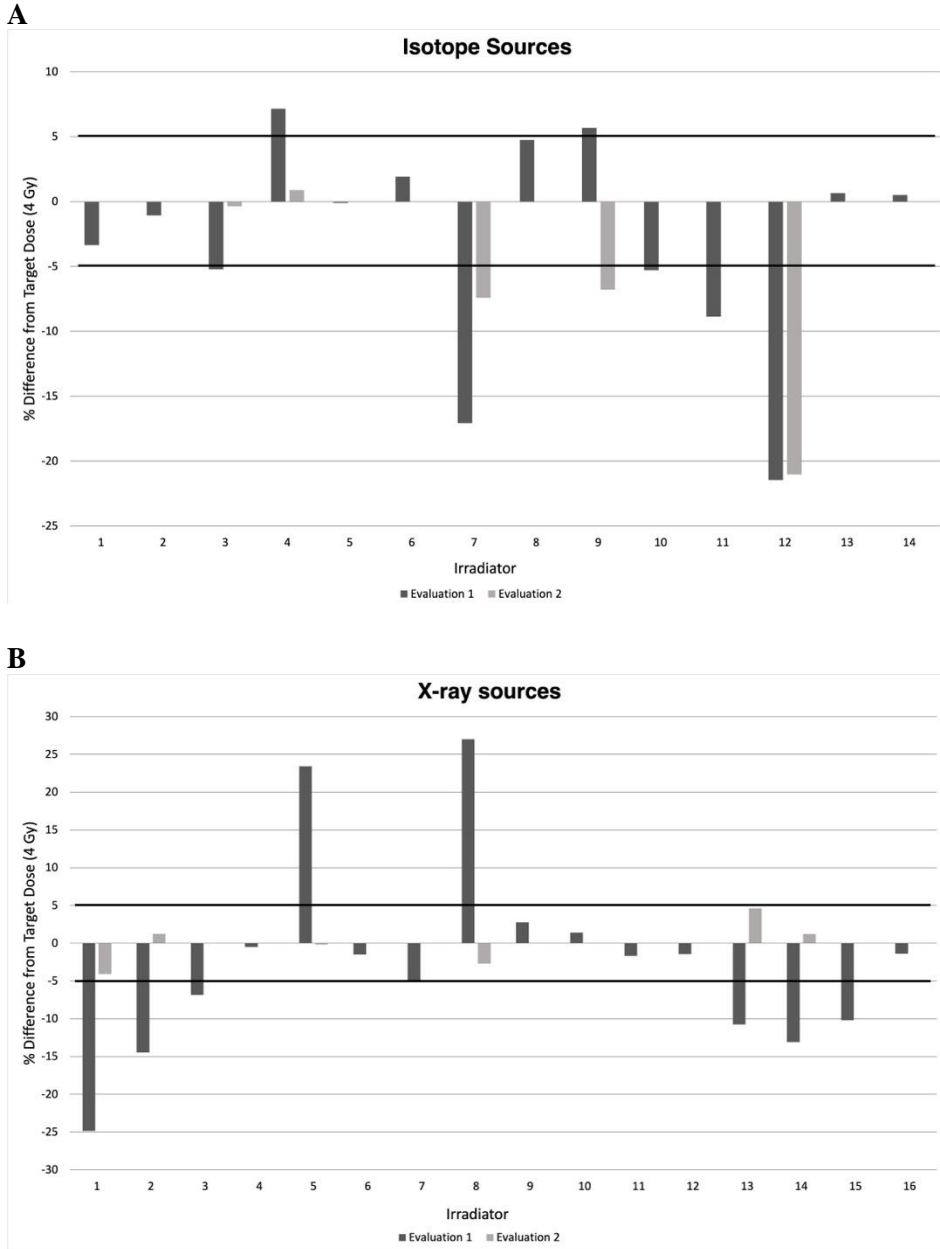


Figure 1. A) Performance of U.S. institutions with isotope irradiators within NIAID-supported sites; B) Performance of institutions with orthovoltage X-ray irradiators within NIAID-supported sites. The bold horizontal lines in each panel represent the $\pm 5\%$ cutoffs for acceptable variance from the 4 Gy target dose. Gray bars indicate paired final retesting results for irradiators with initial test doses that were $\geq \pm 5\%$ of the target dose.

Figure 2

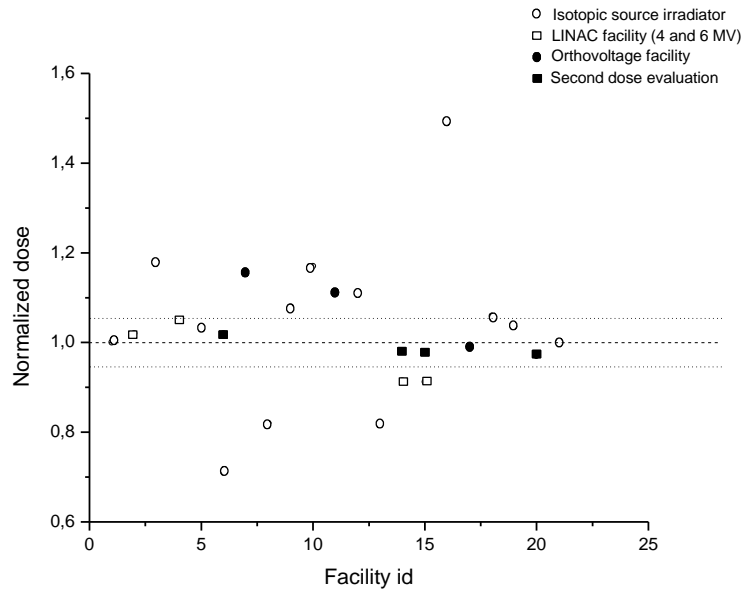


Figure 2: Doses measured at 21 European facilities with alanine with a calibration in terms of dose in water and normalized to the dose delivered at the French primary laboratory (modified and used with permission from (Trompier et al. 2017)).