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Review of Deterministic Neutron RBEs for Survivable Personnel Radiation Exposures from Nuclear Detonation Simulations

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14. ABSTRACT

To improve current casualty estimations for nuclear detonation scenarios, an approach to account for the relative biological effectiveness (RBE) of neutrons from prompt radiation exposures is required. This report details a series of efforts to address this need. The energies and radiation doses of neutrons that might be encountered in surviving populations are presented using urban radiation transport studies. The radiobiology of neutrons is reviewed, and a selection of whole animal experiments providing insight on the lethality dose response from mixed field exposures (neutron and photon) were identified. An approach for estimating dose-dependent neutron RBEs was developed. Currently used neutron RBEs are examined. Based on the collective findings , we suggest a dose-dependent neutron RBE function based on non-human primate data or a single neutron RBE of 2 which we expect to be adequate for casualty estimation purposes. As new data are made available, these estimates should be revisited.

15. SUBJECT TERMS

Neutrons, Relative Biological Effectiveness, RBE, Radiation Dose Response, LD50, Casualty Estimation

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UNIT CONVERSION TABLE

U.S. customary units to and from international units of measurement*

U.S. Customary Units	Multiply by → / ← Divide by†		International Units
Length/Area/Volume			
inch (in)	2.54	$\times 10^{-2}$	meter (m)
foot (ft)	3.048	$\times 10^{-1}$	meter (m)
yard (yd)	9.144	$\times 10^{-1}$	meter (m)
mile (mi, international)	1.609 344	$\times 10^{3}$	meter (m)
mile (nmi, nautical, U.S.)	1.852	$\times 10^{3}$	meter (m)
barn (b)	1	$\times 10^{-28}$	square meter (m^2)
gallon (gal, U.S. liquid)	3.785 412	$\times 10^{-3}$	cubic meter (m^3)
cubic foot (ft^3)	2.831 685	$\times 10^{-2}$	cubic meter (m^3)
Mass/Density			
pound (lb)	4.535 924	$\times 10^{-1}$	kilogram (kg)
atomic mass unit (AMU)	1.660 539	$\times 10^{-27}$	kilogram (kg)
pound-mass per cubic foot ($lb\ ft^{-3}$)	1.601 846	$\times 10^{1}$	kilogram per cubic meter ($kg\ m^{-3}$)
Pound-force (lbf avoirdupois)	4.448 222		Newton (N)
Energy/Work/Power			
electron volt (eV)	1.602 177	$\times 10^{-19}$	joule (J)
erg	1	$\times 10^{-7}$	joule (J)
kiloton (kT) (TNT equivalent)	4.184	$\times 10^{12}$	joule (J)
British thermal unit (Btu) (thermochemical)	1.054 350	$\times 10^{3}$	joule (J)
foot-pound-force (ft lbf)	1.355 818		joule (J)
calorie (cal) (thermochemical)	4.184		joule (J)
Pressure			
atmosphere (atm)	1.013 250	$\times 10^{5}$	pascal (Pa)
pound force per square inch (psi)	6.984 757	$\times 10^{3}$	pascal (Pa)
Temperature			
degree Fahrenheit (°F)	[T(°F) − 32]/1.8		degree Celsius (°C)
degree Fahrenheit (°F)	[T(°F) + 459.67]/1.8		kelvin (K)
Radiation			
activity of radionuclides [curie (Ci)]	3.7	$\times 10^{10}$	per second (s^{-1}‡)
air exposure [roentgen (R)]	2.579 760	$\times 10^{-4}$	coulomb per kilogram ($C\ kg^{-1}$)
absorbed dose (rad)	1	$\times 10^{-2}$	joule per kilogram ($J\ kg^{-1}$§)
equivalent and effective dose (rem)	1	$\times 10^{-2}$	joule per kilogram ($J\ kg^{-1}$**)

*Specific details regarding the implementation of SI units may be viewed at http://www.bipm.org/en/si/.

†Multiply the U.S. customary unit by the factor to get the international unit. Divide the international unit by the factor to get the U.S. customary unit.

‡The special name for the SI unit of the activity of a radionuclide is the becquerel (Bq). ($1\ Bq = 1\ s^{-1}$).

§The special name for the SI unit of absorbed dose is the gray (Gy). ($1\ Gy = 1\ J\ kg^{-1}$).

**The special name for the SI unit of equivalent and effective dose is the sievert (Sv). ($1\ Sv = 1\ J\ kg^{-1}$).

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Acknowledgements

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Executive Summary

Most current casualty estimates for nuclear detonation scenarios combine neutron and photon doses, and assume the same biological effect of neutrons and photons. However, research indicates a potentially higher biological effect from neutrons depending on the dose and energy of the neutrons. To improve current casualty estimations for nuclear detonation scenarios, an approach to account for the relative biological effectiveness (RBE) of neutrons from prompt radiation exposures and their impact on lethality and injury is required. This report details a series of efforts to address this need. The complexity of neutrons and their interactions are reviewed. Studies that aim to characterize the energy range and radiation doses of neutrons that might be encountered in surviving populations are presented. In particular, urban radiation transport studies were conducted and revealed that neutron exposures in surviving populations would likely be in the low energy and low dose range where neutron RBEs for deterministic effects (such as lethality and injury) are expected to be greater than 1. Radiobiology studies of neutrons are reviewed in an attempt to identify appropriate experimental data for estimating RBEs for lethality for these types of neutron exposures. Unfortunately, many of the studies conducted to date have not been conducted with neutron energies and doses relevant to scenarios currently under evaluation. Further, complexities exist in extrapolating animal data to humans, particularly with neutrons, due to the significant differences in organ sizes and depths, which results in significantly different target organ doses and effects from the same exposures. Nevertheless, a selection of animal experiments involving whole body exposures[1] that could provide important insight on the lethality dose response from mixed field exposures (neutron and photon) were identified. These studies were compared to photon exposures from ^{60}Co to identify the dose-dependent behavior of RBEs for neutrons. From this work, an approach for estimating dose-dependent neutron RBEs was developed. Although the approach does not account for all parameters of importance (i.e. the neutron to gamma ratio and neutron energy), the work does provide a starting point for estimating an appropriate RBE for use in casualty estimation tools. We review neutron RBEs currently used for deterministic effects and find that most of these are based on effects observed in rodents, which may overestimate the effects observed in larger animals. Based on the collective findings presented in this work, we suggest a single neutron RBE of 2, which we expect to be adequately conservative (i.e. a value that will not under estimate the effects of neutrons) while providing more precise estimates. A dose-dependent RBE relationship was also developed for non-human primates since the slope of the lethality curves differ. However, since the slopes mixed field and gamma lethality curves are not statistically different, it is unclear whether the dose-dependent function would provide a more precise estimate. It is also unclear how easily this function can be integrated into casualty estimation codes. More detailed computational models and studies can determine neutron doses to critical target organs in humans, and we highly recommend revisiting the current assessment of neutron RBEs and updating as these data become available.

[1] We note that inhomogeneous exposures, which are likely in NUDET scenarios, will result in different lethality response and injury profiles. This aspect should considered in future work.

Section 1. **Introduction**

Current Defense Threat Reduction Agency (DTRA) modeling efforts are focused on improving casualty estimation codes for nuclear weapons effects. Nuclear detonation (NUDET) scenarios involve both neutron and gamma exposures, but most casualty estimations assume the contribution of neutron exposures to health effects to be the same as gamma radiation. However, this simplification is not accurate, and depending on the scenario details, may result in a significant underestimation of casualties and resulting health effects.

For the purposes of NUDET casualty estimations, the focus is on acute (deterministic) effects, and casualties as defined as those persons that acquire acute injuries that result in overt clinical signs and symptoms, require medical care, and/or impair combat effectiveness. We note that for radiation casualties, as currently defined in our casualty estimation tools, do not include stochastic effects such as increased carcinogenic risk, that doses required for these increased risks are much lower than that for acute (deterministic) effects, and further note that neutron RBEs for stochastic effects appear to be much greater than for deterministic effects.

For both deterministic and stochastic effects, the neutron energy, total dose, and ratio of neutron/gamma radiation for a specific scenario will dictate resulting health effects. Further, these parameters will be affected by urban environments, therefore, many of the assumptions previously held for open field environments are not accurate for the urban setting. To shed light on what doses, neutron/gamma ratios, and neutron energies might be encountered in the survivable range of NUDET exposures, urban radiation transport studies have been performed on selected urban scenarios. The data obtained in these studies provide insight on the nature of radiation exposures that could be anticipated in survivors of NUDET scenarios. Further, this information can help determine the type of radiobiology information needed for the integration of neutron effects into modern casualty estimation codes.

Section 2. **Purpose**

The purpose of the work is twofold:

- To identify information on the types of neutron exposures that might be encountered in a NUDET scenario and
- To determine what relative biological effectiveness (RBE) value might be appropriate to account for the potential increased biological impact of neutrons in these scenarios on acute health effects and mortality

Since many factors impact the potential dose from neutrons to persons exposed in NUDET scenarios, urban radiation transport studies were needed to determine:

- Whether neutrons would contribute to exposures in potential survivors; i.e. whether neutrons would have any impact on injury or mortality casualty estimates
- What energies and doses of neutrons might be relevant in persons involved in NUDET scenarios when accounting for the urban environment

The first aim was to inform whether we should have any concern of neutron exposures in NUDET scenarios at all. Once establishing the existence of a role of neutrons on casualties in NUDET scenarios, the second aim sought to characterize potential neutron exposures. Since neutrons are high linear energy transfer (LET) radiation, they have an increased biological effectiveness under certain exposure scenarios. However, the RBE of neutrons are dependent upon a variety of factors, two of which are the dose and energy of the neutrons involved. Therefore, these were two important parameters to characterize in the urban radiation transport work.

After establishing the relevance of neutron exposures in NUDET scenarios and the nature of neutrons involved, the relevant RBEs for neutrons must be established to accurately account for the impact on health effects and casualty estimations. Therefore, the literature on neutron radiobiology was reviewed to identify information on RBEs of neutrons that would be relevant for use in casualty estimation tools. Although neutrons have RBE values for stochastic effects such as carcinogenesis, the near-term aim of our work is to update casualty estimation codes for acute health effects (i.e. deterministic effects). Therefore, the review of neutron radiobiology was focused on studies with relevance to deterministic effects. The RBEs reported for stochastic effects differ significantly from those for deterministic effects and hence are not useful for our current purposes. The amount of data on deterministic effects of neutrons is limited, particularly for the neutron energies and doses of relevance as identified in the radiation transport work. However, the current literature is interpreted to the limit possible for identifying a relevant RBE, and the use of RBE for neutrons by other communities is briefly summarized. Together this information provides guidance for establishing a near term solution for estimating the impact of neutrons in casualty estimation tools. Then, future work that could be used to more precisely account for the impact of neutrons is discussed.

Section 3. **Background**

3.1 Interaction of Neutrons with Matter

Neutrons are neutral particles that can have a range of energies which impact the amount of energy they transfer as they interact with biological matter. Neutrons are considered high linear energy transfer (LET) radiation since they are densely ionizing, or result in a high concentration of ionizations as they pass through material. However, the concentration of these ionizations and the degree to which neutrons are densely ionizing depends on their initial energy as well as the matter in which they interact. Figure 1 below illustrates the difference in ionizations between high and low LET radiations (Jones 2015). The dense number of ionizations from high LET radiations result in a higher number of non-repairable DNA lesions. Figure 1 illustrates the difference in the local spatial distribution in ionizations between low and high LET radiation.

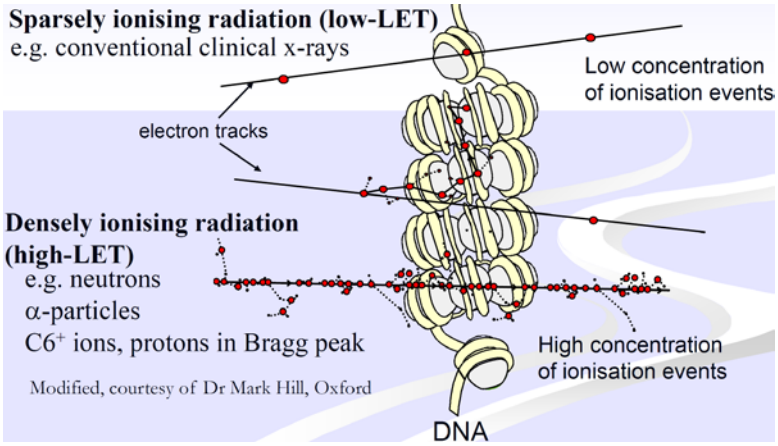

Figure 1. Comparison of ionization densities from low LET and high LET radiations (Jones 2015).

Neutron energies can range from less than one electron volt (eV) to the MeV range, and the energy of a neutron will impact its depth of penetration as well as the interactions that can occur within matter that it passes through. Although nuclear scenarios can lead to a wide range of neutron energies, the urban environment is expected to shield and thermalize neutrons. Higher energy neutrons (>1 MeV) may behave roughly the same as gamma radiation. However, if the majority of survivable exposures were to involve neutrons that are slowed and have energies well below 1 MeV, the effect of these neutron exposures would be expected to be significantly different from gamma exposures.

The degrees of ionization from neutrons vary among different energies and are dependent on the types of matter because of the physical mechanistic interactions that occur between neutrons and matter. The primary types of interactions include scattering (elastic and inelastic) and absorption (capture and fission). Significant ionization results from recoil protons, which can have a significant biological effect based on their energy and localized absorption. In biological tissue,

significant hydrogen capture leads to higher doses in hydrogen rich, or lipid rich, tissues (Jones 2015). Specific tissue composition can result in variabilities in dose since different elements (i.e. carbon, nitrogen, and oxygen) will each undergo neutron capture reactions. The fact that boron has high neutron capture has been utilized in radiation therapy by the incorporation of boron into biomolecules.

3.2 Relative Biological Effectiveness (RBE)

RBE is a way of expressing the ratio of dose in low to high LET radiation for the same biological effect. Note that different RBEs can exist for the same radiations when different biological endpoints are compared. For example, an RBE based on comparison of whole animal mortality may be different than the RBE for cell killing or the induction of double strand breaks *in vitro*. Since this is particularly true for neutrons, cross comparisons between reported RBEs can be very difficult to interpret, and particular attention must be paid to the details in which the RBE estimates were developed.

$$\mathrm{RBE} = \frac{D_R}{D_X} \tag{1}$$

where RBE is the ratio of the reference low LET radiation, D_R, and that of comparison or high LET radiation, D_X, for the same biological endpoint. Currently, the reference low LET radiation for developing an RBE is ^{60}Co or 6 MV x-rays, whereas formerly, 150-250 keV x-rays were used.

In general, for neutrons and other high LET radiations, the RBE is inversely related to the radiation energy (ICRP 1989). Low energy neutrons generally have higher LET and therefore, RBEs, as compared to high energy neutrons. The RBE of neutrons also vary (inversely) depending on the dose, dose per fraction, and dose rate of neutrons during an exposure. Other considerations for RBE are the volume of tissue in question and the specific tissue and location of the tissue of concern. The particular endpoint under consideration for RBE (e.g. 10% cell killing, chromosomal breaks, etc.) will dictate the RBE established for that endpoint (Barendsen 1992). The complexity of establishing RBEs arises from the many factors that impact biological effect and the difficulty in differentiating stochastic and deterministic effects has been recognized (Higley, Kocher et al. 2012) and is the topic of active research by a European consortium (Ottolenghi, Baiocco et al. 2015).

The emphasis of the current effort is to gain an understanding of the impact neutrons have on deterministic effects, in particular acute lethality and tissue damage leading to acute effects such as organ system dysfunction. However, since the RBEs of neutrons have significantly different values for biological endpoints relating to stochastic effects such as carcinogenesis, a different notation is used to delineate RBEs that relate to acute (deterministic) effects, RBE_m, and those that relate to stochastic effects, RBE_M (ICRP 1989, ICRP 2003). RBE_M values for neutrons tend to be significantly greater than RBE_m values (ranging from 2-4). For example, RBE_M values range from 4-12 for 1-5 MeV neutrons whereas RBE_m values range from 2-4 for the same energy neutrons (Barendsen 1992). For the discussion below, the focus is on the observed RBEs for the endpoints

discussed. Relevance of the collective data is then discussed in the context of acute effects and what information there is to support accounting for neutron RBE in estimating acute lethality and injury from mixed field exposures.

Section 4. **Urban Radiation Transport Studies**

Neutrons from the prompt environment of an urban NUDET will have a mean radiation length that depends on the neutron energy distribution of the source more than the yield of the weapon. Neutrons are non-interactive with each other, and the distance they travel depends on the environment around the detonation. In Hiroshima and Nagasaki, the detonations occurred at least 500 m above the ground and only a small fraction of prompt neutrons made it to the surface due to neutron capture by atmospheric nitrogen. In the case of a surface burst or an urban improvised nuclear device (IND), the weapon effects will be attenuated, and survivable casualties are likely to be much closer to the detonation. As a result, the survivors may be exposed to prompt neutrons as part of their total radiation dose.

In Monte-Carlo Modeling of the Prompt Radiation Emitted by a Nuclear Device in the National Capital Region, Revision 1 (Kramer, et al. 2016), the Human Survivability Research and Development (HSRD) Integrated Project Team (IPT) performed a study of radiation effects in a Washington, DC scenario. The HSRD IPT specifically examined the impact that urban terrain can have on the shielding and attenuation of prompt radiation as compared to a similar event in an open field. **The study showed that the percentage of absorbed dose from prompt neutrons in the moderate radiation injury zone[2] can increase from 13% of the total prompt absorbed dose in the open, to as much as 43% of the total dose in the urban scenario.** As a result, the surviving affected population would be closer to the detonation than would be expected in an open field. DTRA-TR-13-045 (R1) did not take into account other weapon effects that would change the location of survivable areas, delayed radiation from the rising fireball, exposure from ground activation, or relative biological effectiveness of the neutrons. However, the study provided insight on whether neutrons could play a role in the dose estimates and potential health effects to a larger degree than observed in Hiroshima and Nagasaki.

Additional work has been performed to better characterize the neutron energies and doses to the potential surviving population exposed to prompt radiation in urban NUDET scenarios. Further, this work incorporates different estimates of the relative biological effectiveness of neutrons to study the impact on the moderate injury zone and uses NucFast[3] estimates of thermal fluence and peak ground pressure to eliminate the areas where there would be few survivors. It also expands the previous study by using an unclassified thermonuclear source term (Auxier, Burson et al. 1972) at the same 10 kT yield. These calculations were designed for a 42-energy bin neutron spectrum to be captured for every point on a 10 m x 10 m grid. This allowed the authors to apply energy and absorbed dose dependent RBE functions and to use different fluence to absorbed dose conversions without having to re-run the entire radiation transport calculation.

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[2] In this study, the moderate radiation injury zone was defined as the $LD_{50/60}$ bone marrow (BM) dose of 2.9 Gy to 0.5 Gy BM dose.

[3] NucFast is a 3D, fast-running, GIS-based engineering-level software application to determine blast, thermal and related effects from a nuclear detonation in urban/suburban/rural terrain.

4.1 Source Terms

Two neutron source terms were used to simulate the prompt neutrons emitted by the weapon in the first microseconds of the detonation. The prompt gamma spectrum has a negligible impact on these scenarios (as demonstrated in DTRA-TR-13-045 (R1)). The first spectrum is from the 'Little Boy' weapon used in Hiroshima and was developed for simulations by the Radiation Effects Research Foundation in Dosimetry Systems 2002 (DS02) (Young and Kerr 2005). This is a gun-style weapon and the spectrum has been made isotropic for the purposes of this study and normalized to 10 kT to match the DTRA-TR-13-045 (R1) study and the DHS planning guidelines. The second spectra is from an unclassified 1972 report, Nuclear Weapons Free-Field Environment Recommended for Initial Radiation Shielding Calculations (Auxier, et al. 1972). The "Low Yield" spectrum was used, and the neutron output was normalized to 10 kT.

The significant difference between the two spectra are the number of neutrons emitted above 6 MeV, and in particular, 14 MeV neutrons, which give the neutrons much more penetrating power. The two spectra are shown in Figure 2.

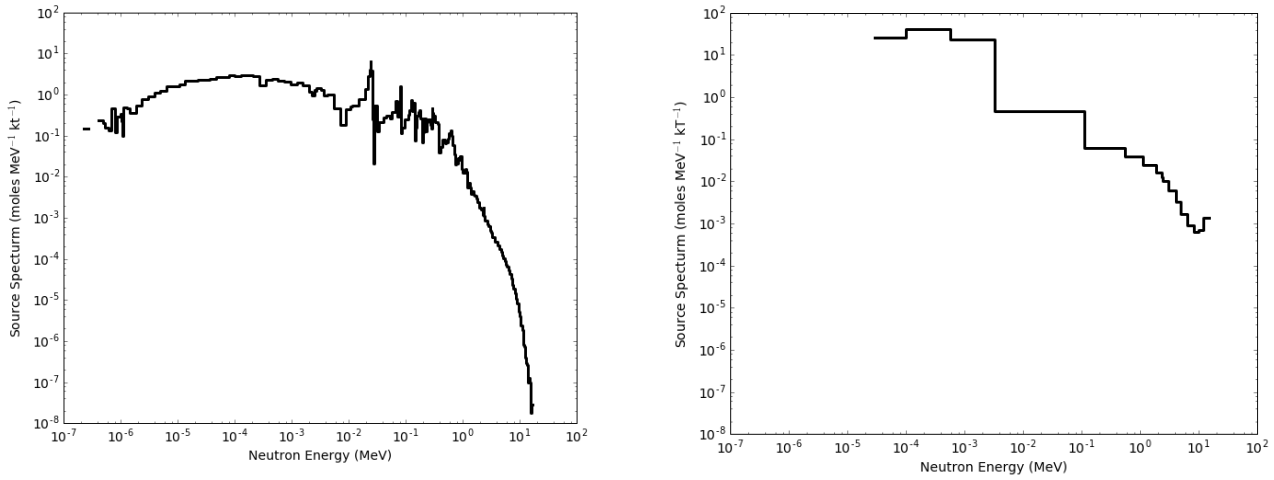

Figure 2. 'Little Boy' source from DS02 on the left and the Low Yield Thermonuclear spectra from Auxier, et al. 1972 on the right.

4.2 Urban Geometry Methodology

The general purpose Monte Carlo N-Particle (MCNP) code for neutron, photon, electron, or coupled neutron/photon/electron transport (X-5 Monte Carlo Team 2008) was used to calculate dose distributions in the environment. Our HSRD model translates an urban geometry to an input

file for the MCNP radiation transport code. The urban geometry is derived from LIDAR4 data, which contains georeferenced building footprints and orientations, building elevations, and a representation of each building's shape at approximately 1-meter resolution. The urban geometries were obtained from the National Geospatial-Intelligence Agency (NGA) in an ArcGIS Shapefile data format (.shp). We use a Shapefile to MCNP Input Conversion Algorithm (Shape2MCNP), an Applied Research Associates, Inc. (ARA, Inc.) copyrighted module created for use in Esri's ArcMap™[5], to convert a portion or an entire map layer into a three-dimensional matrix of voxels in MCNP's input format.

For these simulations, the building structures are defined by a 3-D lattice with 5-m x 5-m x 5-m voxels. For the Washington, D.C. model, an additional improvement was made by populating lattice elements of each building with different features depending on the particular building type from the Federal Emergency Management Agency (FEMA) Hazus[6] (Hazards-US) dataset (FEMA 2003). There are sixteen different Hazus building types, though not all were used in the section of the Washington, D.C. model. A representation of the urban geometry is shown in Figure 3. Additional details about model construction have been previously published (Kramer, Li et al. 2016).

Figure 3. A representation of the Washington, D.C. model in MCNP6.

[4] The term LIDAR comes from Light Detection and Ranging, similar to the term radar. LIDAR is a commercially available, remote-sensing technology that measures distance by illuminating a target with a pulsed laser and analyzing the reflected light.

[5] Esri is a commercial supplier of geographic information system software and geodatabase management applications.

[6] Hazus is a nationally applicable standardized methodology that contains models for estimating potential losses from earthquakes, floods, hurricanes, and tsunamis. It is FEMA's methodology for estimating potential losses from disasters.

4.3 Representative Neutron Spectrum from Radiation Transport Calculation

Three areas of the moderate injury zone (between 2.9 Gy and 0.5 Gy total bone marrow absorbed dose with RBE adjustment) were chosen to extract neutron spectra from both the 'Little Boy' and 'Low Yield Thermonuclear' scenarios. The spectra are shown in Figure 5 and Figure 6. These are compared to the neutron spectra calculated by MCNP6 within 20 m of the detonation location. The locations sampled for the spectra are shown in the black areas in the corresponding right plot. The grey areas are other parts of the moderate injury zone for orientation purposes. The 42-energy bins correspond to the energy binning in ICRP-116 for Male Bone Marrow dose in ISO configuration (ICRP 2010). Only bins below 20 MeV were used since that usual limit for neutron energies in these scenarios.

The major features of both of the spectra from both 'Little Boy' and 'Low Yield Thermonuclear' devices are an increase in the low-energy (~10^{-7} MeV), thermalized neutrons and a decrease in the fast and intermediate energy neutrons (> 0.1 MeV) compared to ground zero. The effect is larger in the shielded areas (NW section of the city) than in the roads to the south and north that are mostly unobstructed. Again, this change is observed in both the 'Little Boy' and the 'Low Yield Thermonuclear' scenarios.

Table 1 and Table 2 show reductions of the 42 energy bins into 3 different energy regions for the two different source terms. The three regions correspond to different qualitative mechanisms for biological interactions as described in Radiobiology for the Radiologist (Hall and Giaccia 2006). The fractions are presented in two different ways: first, the fraction of the total number of free-in-air neutrons at that location and second, the fraction of the absorbed bone marrow dose at that location as estimated by the ICRP-116 male bone marrow in ISO fluence to dose conversion (ICRP 2010). The absorbed doses in the tables are not multiplied by an RBE factor, and the fractions were calculated by averaging the distribution over all areas within the urban calculation where the absorbed dose was between 0.5 and 2.9 Gy. The photon total bone marrow absorbed dose fraction in Table 1 was 0.65, and the average distance from the detonation was 692 m. The photon total bone marrow absorbed dose fraction in Table 2 was 0.47, and the average distance from the detonation was 834 m.

Table 1. Fraction of neutrons in scenario with 'Little Boy' source for different energy regions both by fluence and weighted by ICRP-116 Neutron Male Bone Marrow ISO fluence to dose conversion

Fraction Type	Thermal Region (<0.1 MeV)	Intermediate Fast Neutrons ($0.1 < E_n < 6$ MeV)	Inelastic Collision Region (> 6 MeV)
FIA Neutron Fluence Fraction	0.89	0.11	0.00018

Fraction Type	Thermal Region (<0.1 MeV)	Intermediate Fast Neutrons ($0.1 < E_n < 6$ MeV)	Inelastic Collision Region (> 6 MeV)
ICRP-116 Neutron Male Bone Marrow ISO Fraction (no RBE)	0.54	0.45	0.0036

Table 2. Fraction of neutrons in scenario with ORNL Thermonuclear spectrum in different energy regions both by fluence and weighted by ICRP-116 Neutron Male Bone Marrow ISO fluence to dose conversion

Fraction Type	Thermal Region (<0.1 MeV)	Intermediate Fast Neutrons ($0.1 < E_n < 6$ MeV)	Inelastic Collision Region (> 6 MeV)
FIA Neutron Fluence Fraction	0.77	0.22	0.0048
ICRP-116 Neutron Male Bone Marrow ISO Fraction (no RBE)	0.49	0.40	0.11

4.4 Neutron Doses

Additional insight regarding the relative contribution of neutrons total dose was examined in potentially survivable regions. Table 3 provides bins of total absorbed doses, the relative contribution of neutrons to those doses (not accounting for RBE effects), the average distances for which those doses would be experienced, and the mean energy of neutrons that reach those locations.

Table 3. Contribution of neutrons to total dose in from two different NUDET spectra.

Source	Neutron Abs. Dose Bin (Gy)	Total Absorbed Dose (Gy)	Ave. % Neutron Abs. Dose (No RBE)	Average Distance (m)	Mean neutron energy (keV)
Little Boy	0.01-0.1	0.17	24	903	56.7
	0.1-0.3	0.62	29	758	51.7
	0.3-0.6	1.34	32	663	45.3
	0.6-0.9	2.00	37	621	44.6
	0.9-1.2	2.80	37	579	41.4
	1.2-1.5	3.66	37	555	40.4

Source	Neutron Abs. Dose Bin (Gy)	Total Absorbed Dose (Gy)	Ave. % Neutron Abs. Dose (No RBE)	Average Distance (m)	Mean neutron energy (keV)
	1.5-1.8	4.65	35	532	42.0
ORNL Thermonuclear spectrum	0.01-0.1	0.16	31	992	129
	0.1-0.3	0.44	42	953	157
	0.3-0.6	0.92	48	870	177
	0.6-0.9	1.47	50	825	187
	0.9-1.2	2.09	50	779	187
	1.2-1.5	2.64	51	756	192
	1.5-1.8	3.28	50	730	192

The data in Table 3 show that the contribution of neutrons can constitute from 24 to 51% of the total prompt radiation dose at a distance of 1 km and that the contribution is highly dependent on the specific weapon spectra. Neutrons have a higher average energy (100-200 keV) and contribute more to total dose at farther distance in the thermonuclear source. However, in both cases, the predominate energy of the neutrons is low (<200 keV) and the average neutron dose is relatively low (<2 Gy). As will be discussed in greater detail in the following sections, both of these factors have an inverse relationship to the neutron RBE. It is anticipated that a neutron RBE that is greater than 1 would be appropriately applied to the potentially survivable doses in NUDET scenarios. Application of a neutron RBE will impact the predicted number of casualties and fatalities in NUDET scenarios since accounting for the neutron RBE will increase the total absorbed dose and anticipated effects of the exposure in terms of lethality and injury.

4.5 Relevant Neutron Energies

The average energy-weighted neutron energy is shown in Figure 4 and Figure 5 as a function of ground distance from the detonation. The vertical dashed lines indicate where the total bone marrow dose is between 2.9 Gy and 0.5 Gy for that scenario. The red dots indicate the average energy-weighted neutron energy. An RBE was not used in calculating the average or in the determination of the injury zone used and shown in these plots.

The average energy-weighted neutron energy for the ‘Little Boy’ scenario in the moderate injury zone is about 55 keV. The average total-bone-marrow-dose-weighted neutron energy for the moderate injury zone in the ‘Low Yield Thermonuclear’ scenario is 250 keV.

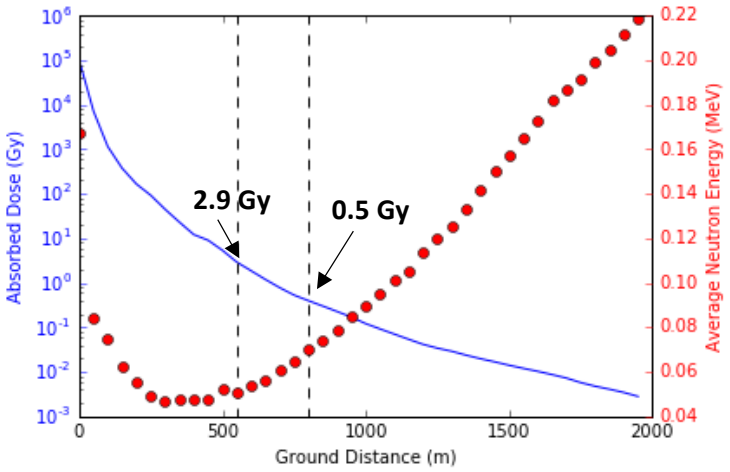

Figure 4. 'Little Boy' source in Washington, D.C.

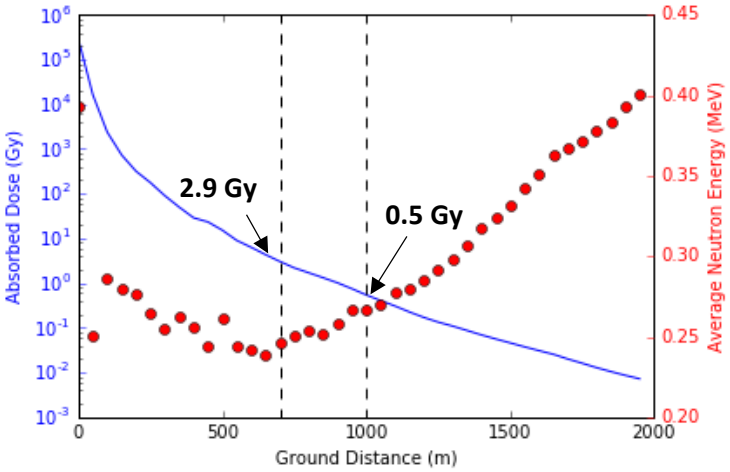

Figure 5. 'Low-Yield Thermonuclear' source in Washington, D.C.

Section 5. **Radiobiology Studies on Neutron RBEs**

Based on preliminary insight from urban scenario analyses in which mean survivable mixed field exposures were in the energy range below 1 MeV, the experimental literature was reviewed to obtain a high level overview of the base of knowledge available on the deterministic health effects from neutron exposures, in particular, acute injury leading to acute radiation syndrome (ARS) and/or lethality. However, the situation is complex since exposures will be variable and the effect of neutrons depend on the specific exposure parameters. Since neutron experiments have been conducted with many different aims in mind, considerable interpretation is needed to glean what is relevant and useful for our specific application.

5.1 *In Vivo* Dose Response Studies

A number of animal studies have been conducted with neutron exposures; however, interpretation of these studies and their applicability to human exposures is difficult. The dose, dose rate, neutron energy, uniformity of exposure, and specific tissue exposed can affect the biological impact of neutrons. Lethal dose (LD_{50}) studies in different animal species by definition are using variable doses as well as different tissue densities and depths depending on the species. Therefore, in the design of the studies, several parameters can impact the results observed. Additionally, studies vary in whether monoenergetic, fission neutrons of variable energy, or mixed field (combination of fission neutrons and gamma) radiation are used. Comparison of results from these types of studies show that the exposure details greatly impact observed results.

As noted previously, variability of RBE is observed across species, presumably due in part from known species differences in radiation response. However, in the case of neutrons, this variability is also due to differential organ doses among different species. Further noted by the experimental community is the high degree of intra-species variability observed in neutron radiobiology experiments due in part to uncertainty in target organ doses from the neutron component of irradiations (MacVittie, et al. 1991).

The emphasis of the current review of animal models here has been on large animal models. Useful insights have been gleaned from rodent models; however, due to the nature of organ dose distribution with neutrons, studies in larger animal models provide more useful information. However, one study in rodents worth noting provided a detailed characterization of the sensitivity of the hematopoietic system in two rodent models to 1 MeV fission neutrons. Although different endpoints were examined, RBEs ranged from 2.2 to 2.8 with an RBE for stem cell sensitivity of 2.3 (Meije 1996).

Neutron exposure studies have been performed in dogs, sheep, the minipig, and non-human primates and provided observational level data regarding the differences in mortality risks from neutron exposures. The studies provided in Table 4 do not represent an exhaustive review of the literature, but do serve to provide ample insight on the impact of neutron exposures on survival.

In the beagle study conducted by MacVittie, et al. 1991, the RBE observed for surviving GM-CFC cell survival fractions (based on D_o values) was 1.9, whereas the RBE based on $LD_{50/30}$ was 1.69 for mixed field irradiation as compared to ^{60}Co (MacVittie, et al. 1991). Other studies that examine

the shift in LD_{50} curves report variable RBEs as shown in Table 4. Direct comparisons across studies are difficult since the neutron energies and the proportion of neutrons in mixed field experiments vary across studies. As noted previously, neutron energy has a significant impact on the effect of neutrons. In mixed field studies, the neutron to gamma ratio can also significantly impact the effect of neutrons as illustrated by Wang, et al. (1991) and in the studies conducted in the former Soviet Union. Further, mixed field exposure scenarios, as opposed to neutron or gamma exposure alone, are thought to result in some synergistic impacts to tissues (MacVittie, et al. 1991). Although the precise mechanisms of this synergism have not been fully elucidated, observational level studies support this assertion.

Table 4. Large animal survival experiments with neutrons.

Species	Exposure	Dose Rate (Gy/min)	Endpoint	MLT Dose Gy (bilateral)	RBE	Reference
Beagle	0.85 MeV ave. (n/γ, 5.4/1) ^{60}Co (comparator)	0.4 0.1	$LD_{50/30}$	(1.5) (2.6)	1.7	(MacVittie, et al. 1991)
Mongrel	Mixed field (90% n) Mixed field (50% n) Mixed field (10% n) ^{60}Co	0.01 0.4 0.6 0.3-1.1	$LD_{50/5}$	2.8 5.0 7.0 7.7	2.9 1.6 1.1 -	(Wang, et al. 1991)
Mongrel	Mixed field (90% n) Mixed field (50% n) Mixed field (10% n) ^{60}Co	0.01 0.4 0.6 0.3-1.1	$LD_{50/30}$	1.7 2.3 2.8 3.0	1.7 1.3 1.1 -	(Wang, et al. 1991)
Beagle	1 MeV neutrons (n/γ, 6/1) ^{60}Co 1 MeV neutrons (n/γ, 6/1) 250 kVp x-rays	0.6 0.1 0.6 0.2	$LD_{50/30}$	1.2 2.6 1.2 2.3	2.3 2.0	(MacVittie, et al. 1984)
Beagle	14.6 MeV neutrons 1 MVp x-rays	0.02 0.09	$LD_{50/30}$	2.8 2.9	1.0	(Earle, et al. 1971)
Beagle	Mixed field, 1MeV, n/γ 0.67/1 250 kVp x-rays	0.2 0.2	$LD_{50/60}$	(2.2) 2.1	0.9	(George, et al. 1968)
Beagle	Pulse mixed field (1MeV)	up to 2000	$LD_{50/30}$	(2.1)	1.24[7]	(Pitchford and Thorp 1968)
Mongrel	Fission neutrons (n/γ, 2.3/1) 1 Mvp x-rays	up to 4000 0.1	$LD_{50/30}$	2.0 (2.3) 2.8 (3.4)	1.38 (1.46)	(Ainsworth, et al. 1965)
Mongrel	Fast neutrons (n/γ, 2.2/1) 250 kVp x-rays	Not provided	$LD_{50/30}$	2.4 2.1	0.9	(Alpen, et al. 1960)
Beagle	Fast neutrons	~0.2	$LD_{50/30}$	2.7	1.3	(Bond, et al. 1956)

[7] RBE relative to the $LD_{50/30}$ of 2.6 Gy for ^{60}Co in the MacVittie studies.

Species	Exposure	Dose Rate (Gy/min)	Endpoint	MLT Dose Gy (bilateral)	RBE	Reference
Sheep	Mixed field neutrons	0.1-10^6	$LD_{50/60}$	(1.7)	NR	(Mobley, et al. 1974)
Minipig	Pulsed mixed field	up to 2000	$LD_{50/30}$	2.2		(Wise and Turbyfill 1970)
Minipig	Mixed field (n/γ, 5) Gamma mixed (n/γ, 0.7)	1.3-2.5 1.3-2.5	$LD_{50/7.5}$	4.3 8.7	2	(Jones, et al. 1972)
Macaca mulatta	Mixed field 250 kVp x-rays	0.2 0.2	$LD_{50/60}$	3.8 5.0	1.3	(Stanley, et al. 1966)
Macaca mulatta	Pulse mixed field Fission neutrons (1 MeV) 300 kV x-rays	up to 2000 0.1 0.3	$LD_{50/60}$ $LD_{50/60}$ $LD_{50/60}$	(3.8) 2.7 5.3	1.34[8] 2	(Wise and Turbyfill 1968)
Macaca mulatta	Fission neutrons (1 MeV) 300 kV x-rays	0.1 0.3	$LD_{50/7}$ $LD_{50/7}$	4.7 -	2[9]	(Broerse, et al. 1978)

*MLT, midline tissue dose; NR, not reported; values in parentheses are unilateral exposures.

In the majority of the studies cited here, bone marrow failure is the source of lethality in the 30- and 60-day experiments. The studies note significant hemorrhage and infection found among the animals. A couple of studies note significant GI impacts, and one study cites pulmonary edema as the source of lethality. These findings are discussed below.

5.1.1. Impact on Medical Countermeasure Treatment

In non-human primates, the lethality of fission neutrons were compared to 300 keV x-rays with and without bone marrow transplantation (Broerse, et al. 1978). In this study, authors note that the mean survival time was significantly shorter after neutron exposures (11 days vs. 15 days). Further, the $LD_{50/7}$ for neutron exposures was determined to be 470 cGy which limited the effectiveness of bone marrow transplantation above 440 cGy whereas the same treatment was effective after x-rays with doses up to 860 cGy. These findings led the authors to consider whether neutron exposure results in more significant damage to the gastrointestinal (GI) tract than x-rays.

In the beagle dog, the efficacy of therapy consisting of fluids, antibiotics, and blood products was compared between mixed field and ^{60}Co irradiated animals (MacVittie, et al. 1991). In this study,

[8] RBE relative to the $LD_{50/60}$ observed in Macaca mulatta in the 1966 study of Stanley et al.

[9] RBE based on differences in rescue of animals by bone marrow transplantation with 440 cGy fission neutron exposure compared to 860 cGy for 300 kV x-rays,

the dose modifying factor (DMF) for treatment was reduced from 1.3 to 1.21 in the mixed field irradiated animals.

5.1.2. Differences in Pathology from Neutron Exposures

Most studies reviewed during this work attribute the mortality observed from neutron exposure to bone marrow failure. However, most of the reports do not provide details on the pathology of the animals. In many cases, septicemia is referenced but does not provide details on the impacts to the GI system in those animals. Other studies do provide some insight that the primary mechanism of lethality in neutron exposures may vary from gamma exposures and involve the GI system to a greater degree than gamma-only exposures.

In $LD_{50/60}$ mixed field neutron exposures studies in sheep, the majority of deaths were observed 4-8 days post-irradiation as compared to the majority of deaths occurring about 3 weeks after exposure in ^{60}Co irradiated sheep (Mobley, et al. 1974). Mortality at 4-8 days post-exposure is consistent with the acute phase of the GI syndrome.

Similarly, a study examining GI mortality in minipigs reported the $LD_{50/7.5}$ for fission neutrons and gamma exposures to be 430 and 870 cGy, respectively (Jones, et al. 1972). Although Wise and Turbyfill (1970) did not provide a reference value for the $LD_{50/30}$ response to gamma radiation for the minipigs in their study, interesting pathological findings were noted (Wise and Turbyfill 1970). The most common cause of mortality in the minipigs was attributed to pulmonary edema. Widespread hemorrhage was also noted. The impact of pulmonary effects on the 30-day lethality has not been widely discussed in other studies, and the observation in this study may be due to species differences of the minipig.

Another study in mongrels showed that the dose for inducing GI syndrome decreased as the neutron to gamma ratio increased (Wang, et al. 1991). In this study, the RBE for fission neutrons was reported to be greater than 3 although the endpoint for this estimate was not provided. Authors note that GI injury contributed to the severity of bone marrow syndrome more than gamma exposure alone.

With regard to the series of experiments that have been summarized from the Russian studies, the estimated RBE for intestinal effects in mice was 4 as compared to RBEs in the range of 1.8 to 2.4 for dogs (Grachev and Sverdlov 2006) although the level of GI injury at which the RBEs were determined was not provided. The authors hypothesized that as the size of the animal species increases, the importance of the GI syndrome decreases. These observations may be correlated to the relative mass of the species and target tissue affected. Regardless, studies in dogs and monkeys which specifically examine the RBE for the LD_{50} for the GI syndrome (lethality in 5-7 days, depending on species, see Table 4) confirm the range of RBEs observed in the Russian studies (Broerse, et al. 1978, Wang, et al. 1991). Although bone marrow effects were the primary source of mortality in Alpen's study in mongrels with fast neutrons, authors reported an RBE for neutrons in the GI tract of 2-2.5 presumably, although not explicitly stated, based on the threshold where gastrointestinal lesions were observed. This can be only considered a rough estimate since the photon exposures did not result in GI lesions in the study but a disproportionate amount of damage

to the intestinal mucosa was observed in animals exposed to neutrons (Alpen, et al. 1960). Enteritis and colitis were also more prominent in these animals.

Another study examined the pathological impact of fast neutrons on the pancreas, pylorus, and duodenum of dogs after thoracic exposure in which the abdomen was included in the field (Zook, et al. 1983). The RBE for tissue damage to the GI tract in this study ranged from 3 to 4.5 compared to photons. Although the authors note that the RBE estimates are based on clinical signs, gross and microscopic pathology, the level of injury at which the RBEs were determined was not provided. Based on the data presented in the paper, the threshold for GI injury as indicated by a tissue pathology score of 1 (severity was graded from 1 to 10) may have been used to determine the RBE estimates.

5.2 *In Vitro* Studies

Studies from the former Soviet Union on *in vitro* cell survival demonstrated variable RBEs depending on neutron energy as illustrated in Table 5. An increase in RBE was observed as neutron energy decreased in the energy range of 0.35 to 22 MeV.

Table 5. RBEs from *in vitro* studies conducted in the former Soviet Union (Grachev and Sverdlov 2006).

	RBE[10]			
Endpoint	0.35 MeV	0.84 MeV	1.2 MeV	22 MeV
CHC survival	4.5	4.3	2.8	1.3
Bone marrow cell survival (mice)	3.7	2.3		
Fragments (CHC) mono-energetic neutrons	5	4.4		
Fragments (CHC); fission neutrons	8	5.9		

*CHC, Chinese hamster cells

The Russian studies also found that effects on chromosomes followed a linear dose response rather than a linear quadratic dose response observed with gamma radiation. Over the dose range from 0.4 to 2.2 Gy, the RBE changes from 5.2 to 2.1 based on the yield of chromosomal aberrations (CAs). Intermediate neutrons resulted in a sharp increase in chromosome damage with RBEs ranging from approximately 10 for number of aberrant metaphases to 6 for the yield of dicentric chromosomes as compared to 6 MeV neutrons. Neutrons of 144 keV resulted in more moderate increases with RBEs on the order of 2 when compared to 6 MeV neutrons. Studies further showed that neutron chromosomal damage does not follow a Poisson distribution that is observed with

[10] The reference radiation is listed as 250 kVp x-rays or ^{60}Co.

gamma radiation. Neutrons result in more damage per cell but have a larger number of cells without aberrations. The maximum value of RBEs, ranging from 5-24, were also observed at low doses (2.5 – 0.5 cGy).

Considerable differences were observed in the effect of monoenergetic neutrons and fission neutrons with the same mean energy. As shown in Table 5, the yield of fragments are greater from fission neutrons (RBE of 8 and 5.9 for 0.35 and 0.85 MeV, respectively).

Studies on cell survival and proliferation in human bone marrow (BM) cells and hematopoietic spleen colonies from mice have been conducted to examine the RBE of neutrons of different energies. As shown in Table 6, two assays were used to examine the survival and repopulation of bone marrow cells exposed to variable doses of monoenergetic and fission neutrons (Boyum, Carsten et al. 1978). The highest RBEs were observed with lower energy neutrons (3.7-4.1) and fission neutrons[11] (2.4-2.6). The study which examined colony forming units (CFUs) from mouse spleens resulted in RBEs that ranged from 1 after exposure to 13.4 MeV neutrons to 3.26 after 0.43 MeV neutrons (Carsten, Bond et al. 1976).

Table 6. RBEs from *in vitro* studies on human bone marrow cells (Boyum, et al. 1978)[12].

	RBE[10]			
Endpoint	0.44 MeV	6 MeV	15 MeV	Fission
Human BM DC	3.7	1.8	1.6	2.6
Human BM CFU-C	4.1	2.0	1.6	2.4

*DC, diffusion chamber; CFU-C, colony forming unit – cell

Chromosomal aberration (CA) studies in human lymphocytes exposed *in vitro* to different gamma and neutron doses confirm the findings from the Russian studies discussed above. As illustrated in Figure 6, the dose response curve for fission neutrons based on dicentrics per cell follows a linear response (Lloyd and Dolphin 1977, Edwards 1997). Higher energy neutrons (14.9 MeV) and gamma radiation follow a linear-quadratic response. Studies on CA yields after 24 keV neutron irradiations demonstrated a linear slope coefficient (0.821 dicentrics/cell-Gy) similar to that found with 0.9 MeV mean energy fission neutrons (Edwards, et al. 1990).

[11] Mean energy of the fission neutrons were not provided in this study.

[12] Boyum, et al. 1978 notes, “Macrophage survival curves yielded similar [RBE] values, whereas those obtained from lymphocytes were more variable, and mostly larger."

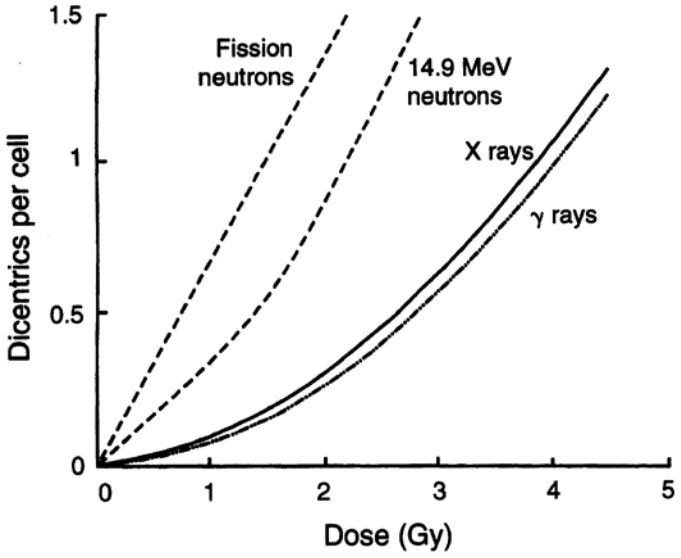

Figure 6. Yield of dicentrics in human lymphocytes as a function of dose for selected neutron and photon radiations (Edwards 1997).

A number of other studies have examined the radiobiological effectiveness of fast neutrons. Although many of these studies are at neutron energies beyond the range of relevance to our current focus, a number of observations may also be relevant for lower energy neutrons. For example, 43 MeV neutrons were found to be more effective in inducing double strand breaks, fragments, and cell killing in CHCs, with an RBE of 2.1 for the latter. In the case of neutron irradiation, more irreparable fragments were observed as well as longer delays in cell division, which delayed effects on cell proliferation (Ngo, et al. 1991).

Many other studies on *in vitro* induction of chromosomal aberrations have been performed for various neutron exposure conditions and are provided in Table 11 of Appendix B. In these studies, neutrons demonstrate a much higher yield of chromosomal aberrations as compared to low LET radiation, with RBEs ranging from 4 to 94. However, chromosomal aberrations have been used mainly to estimate stochastic RBEs of neutrons effects (RBE_M) since they may not be directly related to acute effects at the whole organism level (ICRP 2003). The distribution of aberrations as noted previously vary from that of low LET radiation, demonstrating a non-homogenous induction of DNA damage, but also a non-homogenous distribution of aberrations among the pool of cells exposed (Edwards 1997). Therefore, direct correlation of chromosomal aberrations from neutrons to acute effects is more complex than with gamma radiation. As an example, a recent study examined the *in vitro* yield of chromosomal aberrations in human lymphocytes exposed to thermal neutrons (Schmid, et al. 2013) and examined the intracellular distribution of dicentric chromosomes as shown in Table 7. The frequency of aberrations among the cells do not follow a Poisson distribution and is over-dispersed as indicated by a *u* value greater than 1.96.

Table 7. Intracellular distribution of dicentrics by thermal neutrons in human lymphocytes (Schmid, et al. 2013)[13].

Neutron fluence (10^{12} cm^{-2})	Dose (Gy)	Cells scored	Distribution of dicentrics								
			0	1	2	3	4	5	6	σ^2/y	u value
0*	0*	28,000	27991	9						1.0	−0.04
0	0	3,200	3199	1						1.0	0
1.11	0.375	800	720	70	9	1				1.15	3.04
2.21	0.750	700	537	133	25	4	1			1.15	2.79
3.31	1.125	600	384	154	49	12	1			1.16	2.67
4.42	1.500	600	349	155	76	11	8	1		1.26	4.50
5.52	1.875	500	256	148	72	14	8	0	2	1.26	4.14

In Table 7, the distribution of cells not affected by radiation do not increase in the manner expected. Knowing the proportion of cells remaining with zero or single aberrations is probably as important in understanding the risk of acute effects as knowing the total yield of aberrations. Neutrons are effective at creating multiple lesions in a single cell and increasing the overall observed yield of aberrations. However, due to the over dispersion of damage in individual cells (i.e. many cells with > 1 aberration), the increase in aberration yield does not follow the same proportional increase in the number of cells affected.

Although a significant volume of literature exits and has been reviewed on the induction of mutations, micronuclei, chromosomal aberrations, and transformation of cells (Hill 2004), the RBE of these effects, which tend to be larger than that for cell killing or LD_{50} effects and their relevance to deterministic effects associated with acute injury, is not easily extrapolated (Higley, et al. 2012).

5.2.1. Neutron and Gamma Interactions

In vitro studies in Chinese hamster cells show that exposure to x rays followed directly with fast neutron exposure result in effects that are nonlinear (McNally, et al. 1984). Cell survival is less than would be expected from the exposures if the doses were added independently, which implies there is interaction between the damage caused by x rays and neutrons. More recent studies examined the cell survival of CHC after exposure to epithermal neutrons (Mason, et al. 2011). The investigators examined the overall biological effectiveness of mixed field irradiation from epithermal neutrons based on low LET and high LET components. Observed effects were dependent on the composition and quality of the different dose components. Experimentally derived RBEs for the high-LET dose components of the mixed fields were significantly greater than historical data on fast neutrons. This observation was attributed to the interactions between the biological damage produced by high- and low-LET radiation in a mixed field environment.

[13] 0*, background frequency in lymphocytes from the standard donor determined in previous neutron experiments (Schmid et al. 2000, 2002, 2003).

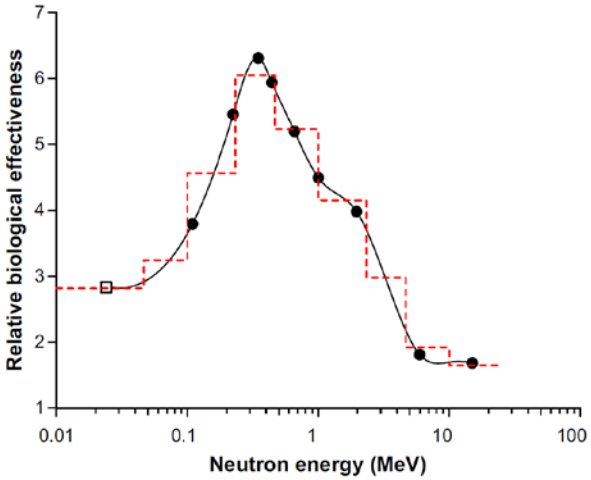

Figure 7. RBEs for variable energy neutrons based on 37% CHC survival (Mason, et al. 2011).

Based on improved understanding of the tracks induced by secondary protons, detailed studies are underway to better understand and account for all secondary species from neutron interactions (Baiocco, et al. 2015). These researchers further propose to describe the RBE of neutrons by fully describing field characteristics through modeling efforts involving transport calculations and biophysical track structure calculations that predict DNA damage (Baiocco, et al. 2016). These efforts seek to inform the biological effectiveness in a mixed field environment and provide insight on the reaction mechanism interplay from secondary particle contributions to neutron dose. Similarly, other groups have used MCNP simulations of DSBs to account for all particle interactions, estimate the effects of neutrons, and help extrapolate across different physical and biological scales (Stewart, et al. 2015); however, further work is needed to validate the computational approaches.

5.3 Discussion

5.3.1. *In Vivo* Animal Studies

Although another body of literature exists on rodent models, the neutron dose response data from whole animal studies discussed in this technical report focused on larger animal species because the tissue doses distribution for neutrons in rodents vary greatly from that in large animals. Further, known species differences between rodents and humans further complicate relevant dose response extrapolation.

From the large animal dose response studies, RBE values for the $LD_{50/30-60}$ (or the RBE relevant for mortality due to hematopoietic syndrome) ranges from 0.9 to 2.3 (Table 4). RBE values $LD_{50/5-7.5}$ relevant to GI syndrome range from 1.1 up to 2.9, depending on neutron energy and neutron to gamma ratio (Table 4). An RBE of about 2 for GI lethality was consistently observed in $LD_{50/5-7}$ studies in several species (dogs, minipig, and monkey). Although the RBEs reviewed here are based on a wide range of studies and may not precisely reflect the RBE of the potentially survivable

neutrons exposures resulting from a nuclear detonation, the range of RBEs do provide perspective on the reasonable range for neutrons in such scenarios.

Since these studies vary in experimental approaches that impact the effect of neutrons, only general interpretations can be made. For example, mixed field exposures are different from monoenergetic neutron exposures, and the effect of mixed field exposures are affected by the neutron to gamma ratio and the mean neutron energy. Although large animal studies provide more reliable insight to potential human effects, biologically-based species differences still exist as well as different tissue dose distributions for each species.

Another limitation with utilizing the whole animal RBEs based on LD_{50} studies is that a single RBE is interpreted for the endpoint. However, we know that RBE can vary based on total dose. Therefore, the RBE may vary for LD_{10} and LD_{90} endpoints. To accurately evaluate neutron RBE as it changes with dose and energy, a more detailed modeling approach would be needed.

Some whole animal studies have examined the surviving population of selected cells after *in vivo* irradiation. These studies provide insight on the acute effects observed at the tissue level based on the amount of radiation received at the tissue level, and account for tissue dose distribution at the target. Further, these studies provide insight on the RBE effects on specific tissues or organs. For example, hematopoietic bone marrow sensitivity in rodents to 1 MeV neutrons was estimated to be 2.3 (Meije 1996) based on D_o values. However, the RBE for bone marrow cell survival in mice to lower energy neutrons, 0.35 and 0.85 MeV, were considerably higher, 4.5 and 4.3, respectively (Grachev and Sverdlov 2006). In canines, clonogenic marrow progenitor cells (GM-CFC) were assayed after *in vivo* irradiation to neutrons with average energy of 0.85 MeV. The calculated RBE based on the D_o value reflecting a 37% reduction in cell survival was 1.8, similar to the RBE based on animal survival in the same study which was 1.7 (MacVittie, Monroy et al. 1991). The difference in tissue depth is likely the source of the different RBEs observed in mice and dogs.

5.3.2. *In Vitro* Cell Culture Studies

Research based on *in vitro* exposure of cells provides an efficient means to study a wide variety of neutron energies and doses. Although assays such as the dicentric assay have reliably been used to estimate the acute effects, such as hematopoietic syndrome, after gamma exposures, significant difficulty remains in estimating the appropriate dose and effects relevant to an *in vivo* exposure when neutrons are involved due to their over-dispersion of damage as compared to photons and differential tissue absorption that is significantly impacted by neutron energy. Nevertheless, such *in vitro* data have provided insight on the cell sensitivity to different types of neutron radiation and tissue specific neutron RBEs.

Cell survival studies in CHCs show the decrease in RBE (4.5 to 1.3) with increasing neutron energy ranging from 0.35 MeV to 22 MeV. Human progenitor cells irradiated *in vitro* had similar RBEs ranging from 4.1 to 1.6 for 0.44 and 15 MeV neutrons, respectively. Fission neutrons were noted to result in RBEs of 2.4-2.6 in the same cell systems (Grachev and Sverdlov 2006). Note that the original references for these studies are in Russian, and the summary provided by Grechev and Sverdlov only reference lethality as the endpoint.

Other studies on CHC cell survival, assessed at a surviving fraction of 37%, estimate much higher RBEs (3.5-6.2) for mixed field environments with neutron energies in the epithermal range (Mason, et al. 2011). These types of data can help us understand cellular level response and potential increased morbidity of different acute radiation syndromes resulting from exposures. However, care must be taken in extrapolating such observations to the anticipated responses in humans. For example, *in vitro* RBEs for cell survival endpoints generally demonstrate higher RBE values than are observed in *in vivo* studies, which are probably due to differences in actual tissue dose distributions that are difficult to account for without more detailed computational studies.

The yield of chromosomal aberrations after *in vitro* irradiations are another endpoint that is often examined for RBE comparisons. Neutrons generally demonstrate a much higher yield of chromosomal aberrations as compared to low LET radiation, with RBEs ranging from 4 to 94. However, as previously discussed, these studies cannot easily be used to directly relate to the risk of acute health effects from neutrons due to the complex nature of whole body neutron exposures (over-dispersion and energy dependent, differential tissue doses). While the yield of chromosomal aberrations provide some insight on the greater effectiveness of neutrons in creating such damage due to the over-dispersion of damage among individual cells, the yield of aberrations are not directly proportional to cell killing. For example, a cell can only be killed once, regardless of whether it has 2 or 6 aberrations. The proportion of cells with no aberrations must be considered in extrapolating these effects to potential acute health effects, otherwise, an overestimation of RBE and effect will result. Data on the intercellular dispersion of aberrations could provide a way to correct for over dispersion and enable these endpoints to be used to estimate acute health effects.

An additional consideration may be needed to use chromosomal aberrations found in lymphocytes as a metric for examining the acute effects of neutrons. When CAs are used to estimate radiation dose after accidental exposures, the damage assayed is based on the pool of circulating lymphocytes in the body. These frequencies are related to dose, known human response to dose, and the radiosensitivity of hematopoietic stem cells to that dose. For low LET gamma radiation, the amount of radiation received may be easily correlated with the dose to the bone marrow where hematopoietic stem cells reside. However, in the case of neutrons in which the tissue dose distribution can vary significantly from that of gamma radiation, the relationship of chromosomal damage to lymphocytes may not directly relate to hematopoietic stem cell damage as closely as it does with gamma radiation due to the differential deposition of energy in the two different target tissues.

5.3.3. Whole Body versus *In Vitro* Data

ICRP Publication 92 states that the difference between the external and internal neutron field is substantial in a large receptor like a human (ICRP 2003). This is due to the neutron energy degradation resulting from interactions where finally a thermal neutron undergoing capture, generates the release of a substantial amount of gamma radiation. In this manner, a fast neutron field will only generate a few photons in *in vitro* studies as the neutron moderation is minor, resulting in less thermal neutron capture. Therefore, the dose from an external neutron field in an *in vitro* sample will be primarily from the charged neutron recoil particles. Animal studies will be more complex as the neutron moderation of the external field in the body will result in both charged

particle dose from the primary and scattered neutrons and secondary photons from the thermal neutron capture. Therefore, whole animal studies are more likely to provide a more reliable estimate of whole body effects. Nevertheless, tissue depths and volumes vary among species and careful attention must be paid in extrapolation from animals to humans, understanding the uncertainties involved.

In vitro studies do provide valuable insight on the energy and dose dependent nature of neutrons. Such studies could be leveraged within computational models to more fully develop parameters that could estimate the impact of neutron energy and dose on RBE for specific endpoints.

Section 6. **Analysis of Dose-Dependent Differences in Neutron and Photon Lethality**

To further evaluate the relative biological effectiveness (RBE) of neutrons as compared to photons in animal lethality studies, a more detailed examination of the neutron RBE estimates at the LD_{10}, LD_{50}, and LD_{90} values in select species was conducted. The aim was to determine whether RBE estimates vary at lower and higher lethality probabilities as would be expected since neutron RBE is dose dependent, as is lethality. We further examined an approach to estimate RBEs as a function of dose for the lethality endpoint.

In the previous section, a number of different endpoints, including the RBE estimates based on LD_{50} (Stricklin and Prins 2018) in a variety of experimental animal studies were identified. All of the neutron RBEs examined for the LD_{50} endpoint were less than 2. To examine whether dose has a significant impact on the RBE for lethality, we identified neutron mixed field/reactor and gamma (^{60}Co) dose response studies, which provided adequate data that could assess and compare the lethality responses at 10% and 90% mortality (LD_{10} and LD_{90}) in addition to the traditional LD_{50} endpoint. In this way, we could examine whether lower versus higher radiation doses in the lethality range would impact RBE estimates significantly.

We were able to identify studies for comparison in non-human primates (NHPs), miniature pigs (minipigs), and mongrel dogs (dogs). The LD_{10}, LD_{50}, and LD_{90} estimates for mixed neutron-gamma (reactor exposures) were extracted from the studies in NHPs, minipigs, and dogs. The experimental data were compared to the LD_{10}, LD_{50}, and LD_{90} from mortality studies of NHPs, minipigs, and dogs exposed to ^{60}Co gamma ray sources, and subsequently RBE estimates for each endpoint were developed and compared. To better describe the differences in RBE estimates that were observed for the different lethality values, a mathematical function was derived to estimate RBEs as a function of neutron dose for the three species.

6.1 Data Sources

Data for NHPs, minipigs, and dogs were identified for this analysis, and the data sources used are shown in Table 8. Out of a range of studies available, data sources were selected for which the irradiation parameters and other experimental conditions were as similar as possible and for which sufficient experimental data was provided to allow for the full dose response to be examined (i.e. from LD_{10} to LD_{90}). All doses reported in the selected studies are given as mid-line tissue dose. The lethality time window was 60 days for NHP studies and 30 days for dog and minipig studies.

Table 8. Data sources for neutron and photon dose response comparisons.

Reference	**No. Animals**	**Species**	**Radiation Source**	**n:γ ratio n-energy**	**Dose Rate**	**Geometry**
(Wise and Turbyfill 1968)	66	NHP	Reactor	0.67:1 0.01-3 MeV	Pulsed	Unilateral
(MacVittie, et al. 2015)[14]	90	NHP	^{60}Co		54.6 rad/min	Uniform (Rotational)

[14] Original data from Eltringham 1967 was obtained and reproduced in MacVittie, et al. 2015.

Reference	No. Animals	Species	Radiation Source	n:γ ratio n-energy	Dose Rate	Geometry
(Ainsworth, et al. 1965)	105	Dog	Reactor	5.25:1 < 1MeV	40 rad/min	Bilateral
(Shively, et al. 1958)	40	Dog	^{60}Co		6 rad/min	Bilateral
(Wise and Turbyfill 1970)	71	Minipig	Reactor	0.67:1 0.01-3 MeV	Pulsed	Unilateral
(Moroni 2018)[15]	32	Minipig	^{60}Co		60 rad/min	Bilateral
(George, et al. 1968)	83	Beagle Dog	Reactor	0.67:1 0.01-3 MeV	17 rad/min	Bilateral
(Norris, et al. 1968)	61	Beagle Dog	^{60}Co		15 rad/min	Bilateral

As shown in Table 8, the dose rates among the experiments varied significantly. In addition, there were differences in the irradiation geometry for the NHP and minipig studies. For the ^{60}Co study in NHPs (MacVittie, et al. 2015), each animal was uniformly irradiated by using a rotating platform, while the NHP reactor study (Wise and Turbyfill 1968) was done with a single pulse on one side of the animal (unilateral exposure). Similarly, for the minipig, the ^{60}Co study (Moroni 2018) used bilateral exposure, while the reactor studies (Wise and Turbyfill 1970) were pulsed and unilateral. However, studies on dogs using combinations of pulsed and continuous neutron irradiation as well as unilateral and bilateral exposure have shown little difference in LD_{50} values, other parameters being equal, for various combinations of dose rate and geometry (Ainsworth, et al. 1965). Although the difference in exposure geometries and dose rates can impact the precise dose response, these studies provide enough consistencies to examine the relative changes in RBE between the LD_{10}, LD_{50}, and LD_{90} estimates.

In the minipig exposures, the data for comparison between mixed field and gamma exposures were only available in different strains, which further complicates comparisons since different breeds are known to have differences in radiosensitivity (Moroni 2018). Only one mixed field study was available for evaluating the 30- to 60-day lethality dose response, and this study (Wise and Turbyfill 1970) used the Hormel-Hanford breed, while ^{60}Co exposure study (Moroni 2018) used the Sinclair minipig. The Sinclair minipig is derived from Hormel stock (from University of Minnesota) and appears to be related to the crossed Hormel-Hanford breed. Therefore, we will assume that these two breeds have similar radiosensitivity. Although some differences in radiosensitivity may exist between the breeds, the relative magnitude of the change in RBE estimates from the lower dose to higher dose region is valuable information. Additional ^{60}Co studies in Gottingen minipigs (Moroni, et al. 2011, Moroni 2018) are available; however, this breed has a distinctly different response compared to the Sinclair breed (Moroni 2018). Since no corresponding reactor studies are available for the Gottingen breed, these data were not used.

The data available in sheep from ^{60}Co (Hanks, et al. 1966) and mixed field exposures (Mobley, et al. 1974) were inconsistent with other findings. Although both experiments were conducted with the Columbia-Ramboullet breed, the ^{60}Co study reports a lower LD_{50} value than the mixed field study, resulting in RBEs less than 1 when compared. Interestingly, Hanks et al. (1966) also reports

[15] Personal communication, unpublished data.

significantly lower LD_{50} values than those obtained in x-ray studies, and inter-laboratory variations may contribute to the observations. Mobley and co-workers also have a study in sheep using ^{60}Co that would be the preferred comparison study; however, we are only able to access the abstract at this time which does provide an LD_{50} value (Mobley and De Feo 1968). Comparison of LD_{50} values between the two Mobley studies also supports an RBE less than 1. The $LD_{50/60}$ for ^{60}Co was 367 R or 352 rad whereas the value in the mixed field study was 377 rad (RBE = 0.93). Two noteworthy observations were found in the sheep studies; the mid-line tissue doses were 45% of free in air (FIA) exposures and the predominate cause of mortality in the mixed field sheep exposures were from gastrointestinal effects as compared to hematopoietic effects in other animals. The implications of these findings are discussed below.

Data are also available in the beagle dog for comparison of ^{60}Co exposures (Norris, et al. 1968) and neutron exposures (George, et al. 1968). However, the dose response curves in both types of exposures are very steep, and no dose dependent RBE was observed in these data.

6.2 Analyses

The re-evaluation of the dose response data and probit analyses were performed using the R programming language (**R** Core Team 2013). The data from the papers listed in Table 8 were transcribed into comma separated variable computer files with 3 columns, corresponding to doses in rad, total number of animals exposed at that dose, and the number that died within the time of the study at that dose. Unlike the published human LD_{50} probit function (Anno, et al. 2003), probit values for the animal studies in our comparisons were fit without log transformation of the dose data. The studies referenced in Table 8 do not log transform the data, and the dose values used do not span more than one decade. The R subroutine "glm" (Generalized Linear Model) was used to fit the data to calculate the maximum-likelihood fit of the slope, *b*, and the y-intercept, *a*, of the probit line. From these quantities, the LD_{50} value can be calculated as:

$$\mathrm{LD}_{50} = -\mathrm{b}/\mathrm{a} \qquad (1)$$

More details on using R for calculating probits are given in Crary and Stricklin, 2018.

To estimate the error in the LD_{50} determination, the following formula was used to calculate the variance, $\mathrm{Var}(\mathrm{LD}_{50})$:

$$\mathrm{Var}(\mathrm{LD}_{50}) = \left(\frac{1}{\mathrm{b}^2}\right)\left(\frac{1}{\sum_{\mathrm{i}=1}^{\mathrm{N}} \mathrm{n_i w_i}} + \frac{\left(\mathrm{LD}_{50} - \bar{\mathrm{d}}\right)^2}{\sum_{\mathrm{i}=1}^{\mathrm{N}} \mathrm{n_i w_i (d_i - \bar{d})}}\right). \qquad (2)$$

In this formula, LD_{50} and b are the maximum likelihood estimates of the probit parameters (median lethal dose and slope). The summations are over all dose values, where n_i is number of animals exposed at dose d_i, w_i is the weighting function appropriate for probit values, given by:

$$\mathrm{w_i} = \frac{\mathrm{Z_i^2}}{\mathrm{P_i}(1 - \mathrm{P_i})}. \qquad (3)$$

In this expression,

$$P_i = \Phi(Y_i) \tag{4}$$

and

$$Z_i = \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{1}{2} Y_i^2\right). \tag{5}$$

where Φ is the value of the cumulative standard normal distribution at quantile x and Y_i is the probit value at dose d_i given by:

$$Y_i = a + bd_i. \tag{6}$$

Also, in (2), $\bar{d}$ is the weighted average of the dose values used:

$$\bar{d} = \frac{\sum_{i=1}^{N} n_i w_i d_i}{\sum_{i=1}^{N} n_i w_i}. \tag{7}$$

The equations above are valid for other lethality dose points besides the LD_{50} by replacing the LD_{50} value with the new value. These equations were derived by using the analytical form of the likelihood as a function of LD_{50} and the probit slope, as well as the large sample properties of the maximum-likelihood estimators. Details can be found in Finney, 1971.

6.3 Comparison of Dose Response Curves

The results of the fits to the data are given in Figure 8 through Figure 11. The data show similar trends, although the LD_{50} values for the dogs and minipigs are significantly lower than the values for NHPs. The values for LD_{10}, LD_{50}, and LD_{90} and probit slopes for these data are given in Table 9 with the standard errors in the mean LD values calculated using the methods described above.

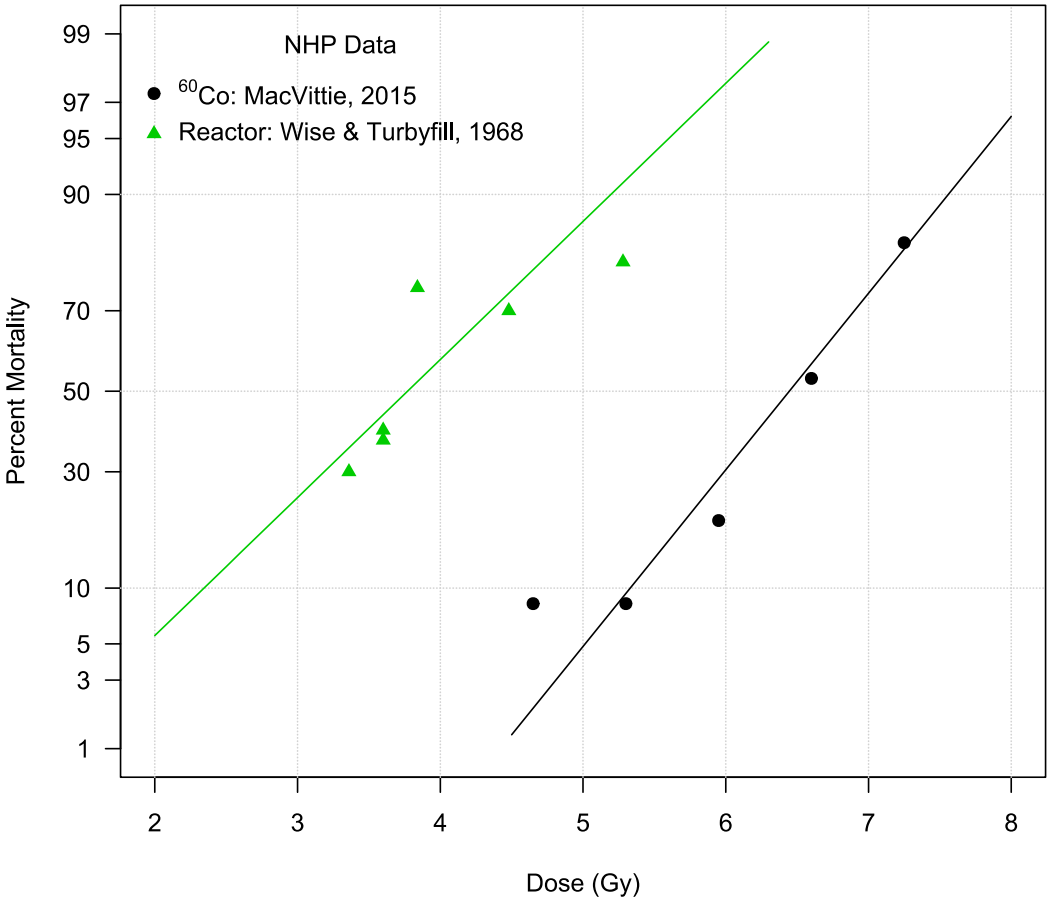

Figure 8. Probit fits to NHP data for ^{60}Co and mixed field studies.

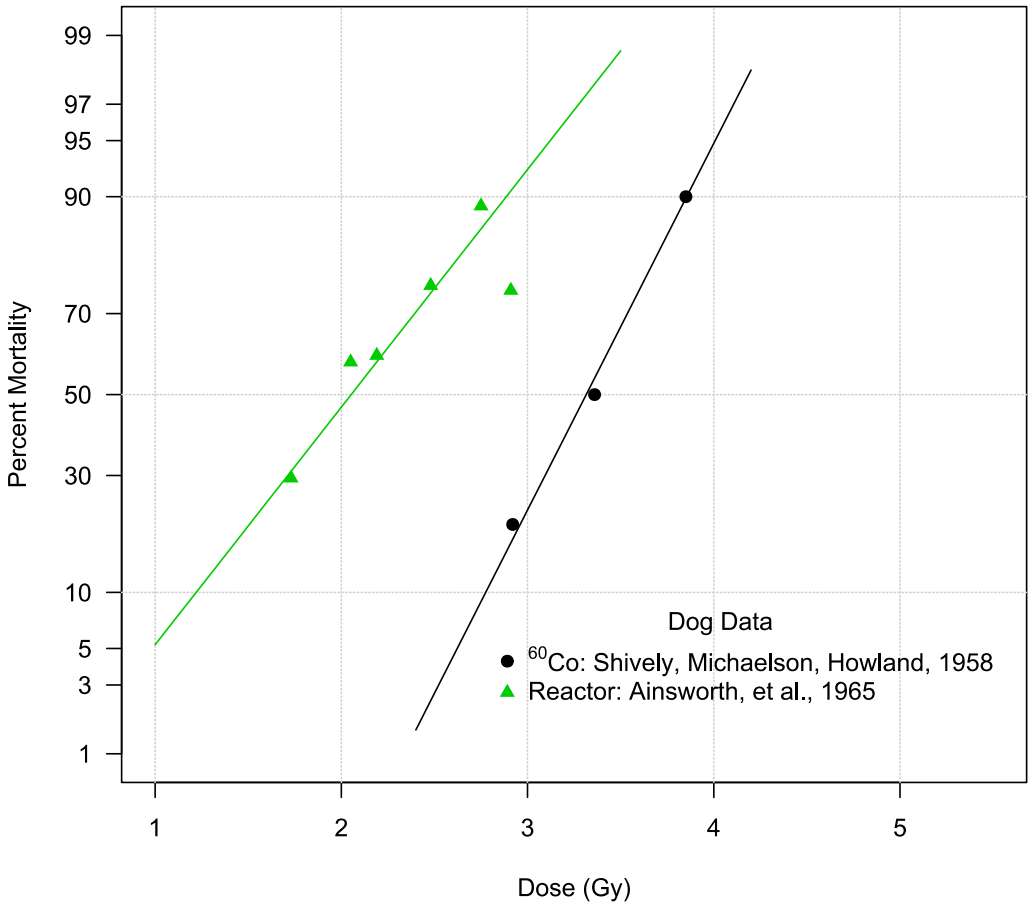

Figure 9. Probit fits to dog data for ^{60}Co and mixed field studies.

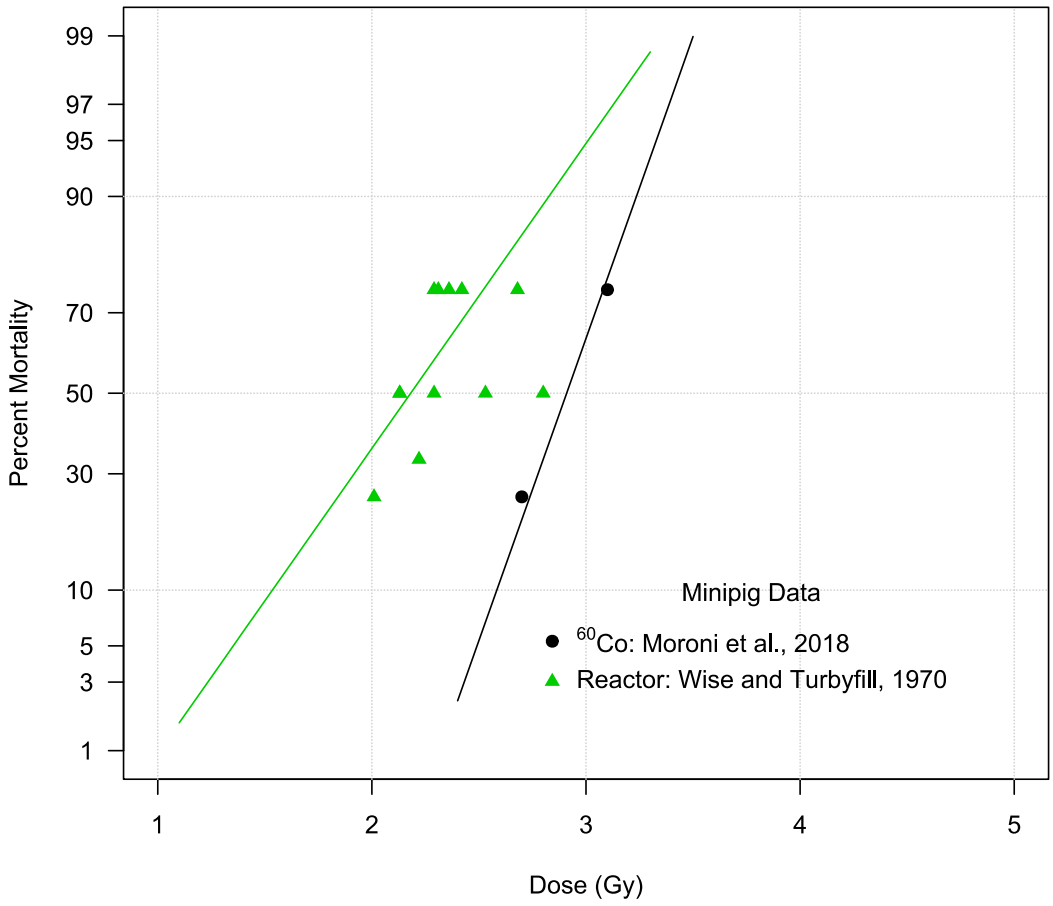

Figure 10. Probit fits to minipig data for ^{60}Co and mixed field studies.

The data derived from the publications shown in Table 8 were used to calculate the neutron RBE as the ratio of ^{60}Co LD values to mixed field LD values. The RBE estimates are also shown in Table 9 and Figure 12, in which the errors represent one standard deviation. The data for NHPs, mongrel dogs, and minipigs show a consistent trend of a lower RBE value at higher doses and the highest RBE at the lower end of the lethality dose response. This observation is not surprising since it is well established that the RBE for neutrons is dose dependent in an inverse manner (ICRP 1989). However, to determine whether the dose dependence will make a significant impact on the use of a single RBE for the dose response curve, we examined the statistical significance of the observed differences. Based on the evaluations, it is not possible to confirm this trend statistically. For the given errors, the results are consistent with a constant RBE for all the lethal dose values for a given species; taking the pairwise differences in RBE values for the minipig, dog or NHP RBEs, and assuming a Gaussian distribution for the errors, the hypothesis of a non-zero difference

in the RBE values cannot be rejected at the 10% level for any pair of RBEs derived for a given species.

The beagle data provided in Norris et al. (1968) describe their exposures in terms of mid-line air dose instead of mid-line tissue dose. The George et al. (1968) clinical observations continued for 60 days, but all fatalities in these data occurred before day 30. Results of a probit fit to the beagle data are shown in Table 9 and Figure 11.

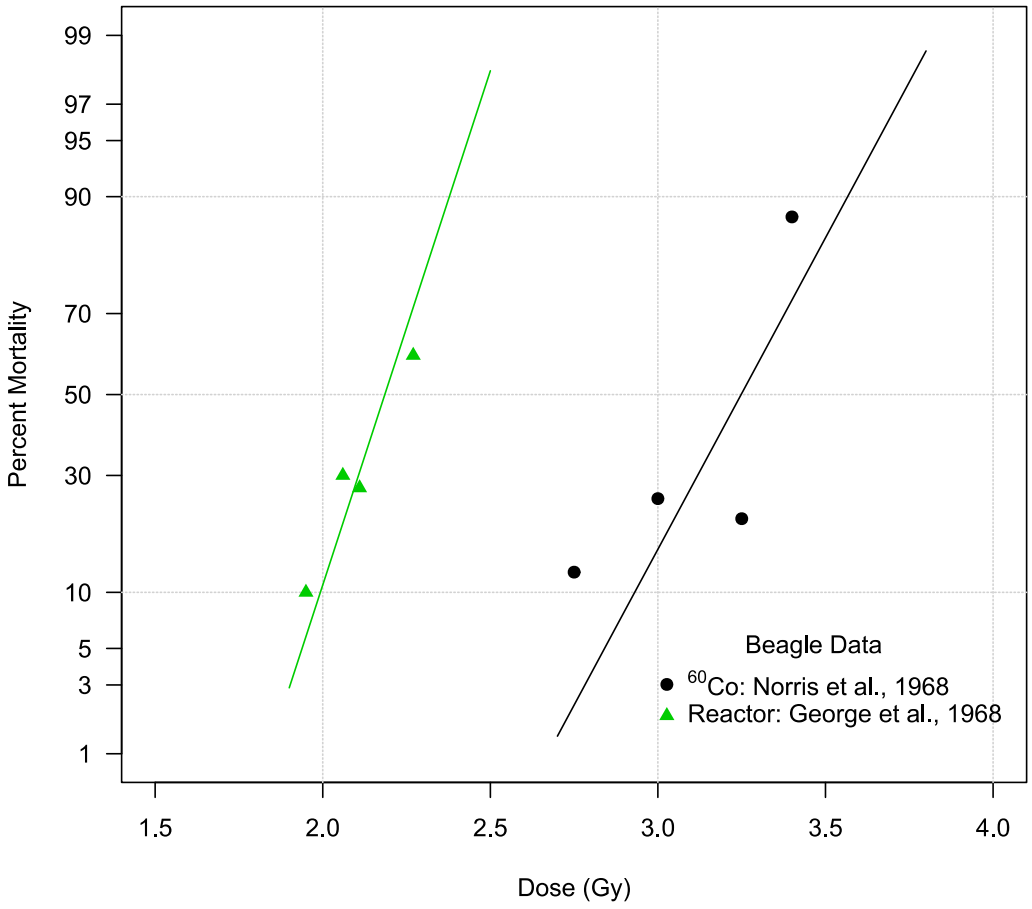

Figure 11. Probit fits to beagle data for ^{60}Co and mixed field studies.

The beagle data do not demonstrate a dose dependent RBE. The RBE remains fairly constant at approximately 1.5 for the entire dose response range. Therefore, no further dose dependence is explored with the beagle data.

Table 9. LD_{10}, LD_{50}, and LD_{90} values (in Gy) for NHP, dogs, and minipigs exposed to reactor mixed gamma-neutron field and ^{60}Co gamma rays.

Animal	**Radiation Source**	**LD_{10}**	**LD_{50}**	**LD_{90}**	**Slope**
NHP	Reactor	2.3 ± 0.9	3.8 ± 0.2	5.2 ± 0.3	0.9 ± 0.3
NHP	^{60}Co	5.3 ± 0.2	6.4 ± 0.15	7.6 ± 0.2	1.2 ± 0.2
NHP Est. RBE		**2.3 ± 0.8**	**1.7 ± 0.1**	**1.5 ± 0.1**	
Dog	Reactor	1.2 ± 0.3	2.0 ± 0.1	2.9 ± 0.2	1.5 ± 0.4
Dog	^{60}Co	2.8 ± 0.2	3.3 ± 0.1	3.9 ± 0.1	2.4 ± 0.7
Dog Est. RBE		**2.3 ± 0.5**	**1.6 ± 0.1**	**1.3 ± 0.1**	
Minipig	Reactor	1.5 ± 0.4	2.2 ± 0.1	2.8 ± 0.1	2.0 ± 0.6
Minipig	^{60}Co	2.6 ± 0.1	2.9 ± 0.1	3.2 ± 0.2	3.9 ± 1.8
Minipig Est. RBE		**1.7 ± 0.4**	**1.3 ± 0.1**	**1.1 ± 0.1**	
Beagle	Reactor	2.0 ± 0.0	2.2 ± 0.0	2.4 ± 0.0	6.7 ± 1.5
Beagle	^{60}Co	2.9 ± 0.1	3.2 ± 0.0	3.6 ± 0.1	4.0 ± 0.9
Beagle Est. RBE		**1.5 ± 0.0**	**1.5 ± 0.0**	**1.5 ± 0.0**	

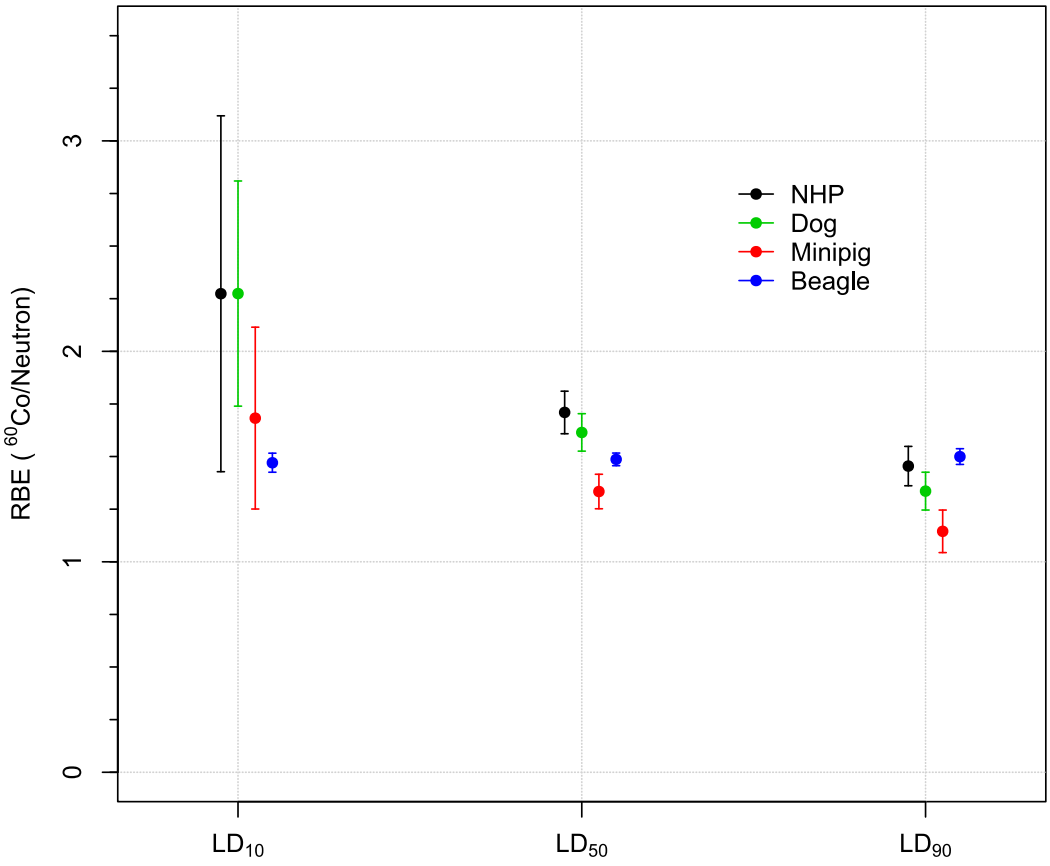

Figure 12. RBEs for NHP, mongrel dog, minipig, and beagle as a function of dose, with calculated standard errors.

6.4 Dose-Dependent RBE Function

To evaluate the dose dependent nature of the RBE estimates in those species where the dose dependence is observed, the mixed field and neutron doses for the entire range of LD values can be compared and the shape of the resulting curve can be examined. The following mathematical approach has been used to explore whether it is possible to use the model fits described above to derive a RBE as a function of the neutron (or gamma-ray dose) instead of endpoint dose for a given species. First, note that the percentage lethality p_l for an arbitrary neutron dose D is given by:

$$p_l = \Phi\big(b(D - LD_{50})\big). \qquad (8)$$

In this equation, b and LD_{50} are the probit slope and LD_{50} value for neutrons, respectively, and $\Phi(x)$ is the cumulative standard normal distribution at x, as described above. This is the basic equation for the probit (without logarithmic transformation of the dose). Equation (8) can be rearranged to give the dose at a specific percentage lethality level by acting on both sides of this equation with the inverse cumulative standard normal distribution, $\Phi^{-1}(p)$. This function takes a percentage, *p*, along the cumulative normal and gives the corresponding number of standard deviations from the mean for this *p* value:

$$\Phi^{-1}(p_l) = \Phi^{-1}(\Phi\big(b(D - LD_{50})\big) = b(D - LD_{50}) \tag{9}$$

where $\Phi^{-1}\big(\Phi(x)\big) = x$. Rearranging equation (9), one can express the dose as a function of p_l and the probit parameters:

$$D = \left(\frac{1}{b}\right)\Phi^{-1}(p_l) + LD_{50} \tag{10}$$

Equation (10) is also valid for gamma-radiation, if we replace the probit slope b and LD_{50} by the corresponding values for gamma-radiation.

For the purposes of this technical report, RBE is given by the ratio of the dose from ^{60}Co gamma rays to the neutron dose for a specific value of p_l. Equations (8) and (10) can be used to rewrite the RBE in terms of the neutron dose, as proposed above. At a specific neutron dose, *D*, probability of lethality, p_1, is given by equation (8), and the ^{60}Co dose, *D'*, which corresponds to the same, p_1, is given by:

$$D' = \left(\frac{1}{b'}\right)\Phi^{-1}(p_l) + LD_{50}{}' \tag{11}$$

which is equation (10) with the probit parameters for ^{60}Co (indicated by primes). Replacing p_l in equation (10) by the equation (8) (which is in terms of neutron probit values and dose) gives:

$$D' = \left(\frac{1}{b'}\right)\Phi^{-1}(\Phi(b(D - LD_{50})) + LD_{50}{}' \tag{12}$$

and again using the property that $\Phi^{-1}\big(\Phi(x)\big) = x$, gives:

$$D' = \frac{b(D - LD_{50})}{b'} + LD_{50}{}' \tag{13}$$

which is the ^{60}Co dose D' that gives the same endpoint as the neutron dose, D. The RBE as a function of neutron dose is given by equation (13) divided by D:

$$RBE(D) = \frac{D'}{D} = \frac{b(D - LD_{50})}{b'D} + \frac{LD'_{50}}{D} \tag{14}$$

or, rearranging slightly:

$$RBE(D) = \left(LD'_{50} - \frac{b}{b'}LD_{50}\right)D^{-1} + \left(\frac{b}{b'}\right) \tag{15}$$

This equation has a simple functional form:

$$\mathrm{RBE}(\mathrm{D}) = \mathrm{c}_1\mathrm{D}^{-1} + \mathrm{c}_2 \qquad (16)$$

The computed values for c_1 and c_2 for radiation doses in Gy are listed in Table 10. Therefore, for low doses where $\mathrm{c}_1\mathrm{D}^{-1} \gg \mathrm{c}_2$, or equivalently, $\mathrm{D} \ll \mathrm{c}_1/\mathrm{c}_2$, the RBE dose relationship is described by a power law with exponent equal to -1. Any RBE calculated using endpoints described by a probit will have this functional form. Note that when considering the error associated with the coefficients, the NHP c_1 coefficients are statistically significant.

Table 10. Coefficients for the dose-dependent RBE equation (16).

Species	$\mathbf{c_1}$	$\mathbf{c_2}$
NHP	3.5±0.0	0.8±0.1
Mongrel dog	2.0±0.1	0.7±0.1
Minipig	1.8±0.1	0.5±0.1

The beagle and sheep data have not demonstrated a dose dependent RBE for neutron exposures. However, in species where this behavior holds, the relationship outlined here may provide a more precise estimate of RBE effect than using a single RBE value.

As illustrated in Figure 13, the observed trends in RBEs appeared to be relatively consistent between the NHPs, mongrel dogs, and minipigs. The estimated RBEs increased going from the minipigs to dogs to NHPs, which may be associated with critical tissue volumes between the species. However, the differences in RBE among the species may also be dependent on differences in tissue depth among critical organs. More neutron energy is absorbed proportionally as compared to photons with greater volumes of tissue that the radiation must travel through to reach critical target organs. Therefore, relative to photons, a lower dose may be absorbed by some of the target organs that are surrounded by a greater volume of tissue. The precise location and mass of target organs and tissue depth vary among species. The two main target organs of interest in mixed field radiation are the gastrointestinal tract and the hematopoietic system. Although the hematopoietic system, and the bone marrow in particular, is the well-established target for 60-day lethality in humans exposed to gamma radiation, some evidence has demonstrated significant impacts to the gastrointestinal (GI) tract in mixed field studies. For example, the study in sheep noted that all of the mortalities were observed in the 4-8 day timeframe which is consistent with radiation injury to the GI tract (Mobley, et al. 1974). To better elucidate the differential doses to each of the target organs among the different animal species, radiation transport studies using computational phantoms are under consideration. The knowledge gained from such studies will help to better interpret the target organ doses in the animal models with respect to observed lethality and support extrapolation of these findings to humans.

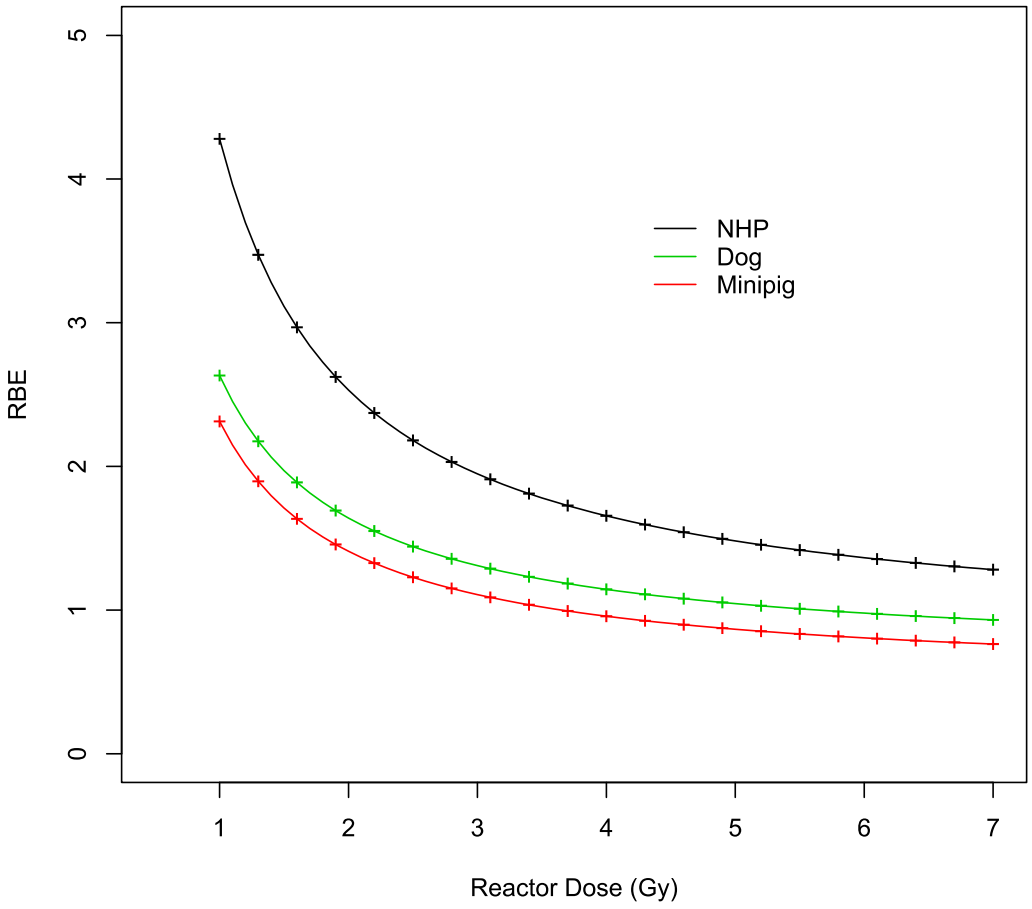

Figure 13. RBE as a function of reactor dose for NHP, mongrel dog, and minipig.

For the present, the NHP RBE estimates may be the most reliable values for implementation in casualty estimation codes in the near-term. Although the trends observed in Figure 13 might suggest an increasing RBE with species size, two other large animal species (beagle dog and sheep) provide conflicting evidence regarding the RBE of mixed field exposures compared to gamma-only exposures. Without more advanced computational models, NHP data are the most reliable information we have presently for extrapolating a neutron RBE to humans for the specific application of improving NUDET casualty estimation tools.

Section 7. **Relevant RBEs for NUDET Exposure Scenarios**

7.1 Insight from Radiobiology

General observations from neutron radiobiology studies provide insight on how, at the organism level, neutrons might impact the acute radiation syndrome. An increase in mortality and morbidity in exposures that include neutron doses would be expected based on the observation that lower energy neutrons have an RBE greater than unity. Neutrons can impact the organ systems of the body differently than gamma radiation and may, therefore, impact the course of radiation syndrome. According to ICRP 58, within the first 60 days following a nuclear detonation and neutron dose, the hematopoietic, respiratory, and gastrointestinal systems may see deterministic effects in a dose dependent manner (ICRP 1989). Even the skin and mucosa may experience transient erythema and edema leading to dry and moist desquamation, and epilation. The hematopoietic system is of particular interest since bone marrow stem cells are relatively radiosensitive. Significant damage to this organ system can lead to the inability to regenerate hematopoietic cell populations resulting in an increased risk of hemorrhage and infection. Neutrons dose may increase the risk of denudation and ulceration of the villi due to the loss of crypt stem cells in the GI tract leading to fluid loss, hemorrhage, risk of bacterial translocation, and the inability to effectively absorb nutrients (ICRP 1989). Neutron doses may impact the respiratory system through pulmonary edema and pneumonitis within the lungs. Based on observations in animals, neutron exposures are likely to speed the onset of ARS, increase the severity of symptoms, and delay recovery. Based on their differential tissue dose distribution as compared to gamma doses, neutrons may result in different organ systems impacting the course of ARS than is observed with gamma radiation exposures alone.

The re-analysis of animal dose responses in Section 6 provides additional insight into the change within neutron RBE as compared to gamma radiation for the lethality endpoint. The RBEs examined in the NHPs, mongrel dogs, and minipigs demonstrate a dose dependence, which is expected based on known radiobiological effects of neutrons. However, the RBE differences observed between the LD_{10} and LD_{90} values are not statistically different. Therefore, choosing a single RBE estimate for application in casualty estimation tools may be adequate. Nevertheless, the greatest RBE values are observed at the lower doses in the LD_{10} range. Since urban radiation transport studies show that most of the neutron doses outside of the severe damage zone (i.e. where persons are likely to survive the immediate impacts from blast and thermal environments) will be in the lower dose range, a conservative estimate of RBE (i.e. the RBE at the LD_{10}) may be prudent if a single RBE value is preferred. This will prevent underestimation of effects in populations surviving blast effects. If preferred, a dose-dependent RBE function has been established and is consistent with established radiobiological principles. This function can easily be adapted for use in casualty estimation tools. The next major step is to justify a species response that can be extrapolated to humans.

7.2 RBEs used Today

DOD casualty estimation codes currently assume an RBE of 1 for neutrons in nuclear detonation environments, the use of which may artificially reduce the calculated dose. This assumption has evolved from the thinking in the 1970's, which Glasstone documents: "For the neutron energy spectrum of nuclear weapons, the RBE for immediate (acute) radiation injury is close to 1.0" (Glasstone and Dolan 1977). This thinking was based on DOD research on incapacitation that involved supralethal doses of radiation. In fact, high doses of neutron radiation may result in an RBE closer to 1, but lower doses of neutrons are expected to have higher RBEs. Nevertheless, the reliance on an assumed RBE of 1 is documented in NATO planning guides (AMedP-7.5 and its associated technical reference manual, NATO 2016) which further indicate the assumption is made to avoid the controversy of varying values between gamma and neutron radiation and associated relative biological effects among different tissue types (Oxford 2016, Oxford, et al. 2016).

Currently, the Health Effects from Nuclear and Radiological Environments (HENRE) code that is being integrated into DTRA's casualty estimation platforms uses organ specific neutron RBEs when leveraging the legacy code from its Radiation Induced Performance Decrement (RIPD) module (Oldson, et al. 2015). There are different RBEs for hematopoietic endpoints as compared to GI effects. The MarCell[16] code which estimates lethality based on bone marrow stem cells uses an RBE of 4.25 for neutrons for the rate of irreparable damage within the cell kinetic model. The corresponding macroscopic RBE for lethality for neutrons would be approximately 2.7. However, one should note that this approach does not account for the inverse relationship between neutron RBE and dose. Another cell kinetic model based on the legacy code which estimates lymphopoiesis after radiation uses an RBE of 1 for neutrons. For the gut injury model, an RBE of 7 is used for the rate at which neutrons produce irreparable damage in the gut (as compared to gamma), which correlates with an RBE of approximately 3 for the prediction of tissue level effects. The scientific basis and technical references for which these values were originally based upon are not well-documented. Nevertheless, the values are relatively consistent with the review of neutron radiobiology described in Section 5. These have not been carried over to HENRE's new mechanistic models primarily due to limited details and data for accurately validating the models for neutron exposures and effects. We do observe that accounting for the cellular or molecular level impact of neutrons within the mechanistic models require different RBE values than those that would be applied to lethality on a whole organism level. For example, this has been seen in the data reviewed here where the RBE for an LD_{50} has a different magnitude than RBEs for chromosomal aberrations. Future studies should carefully examine the difference in lethality predictions of models accounting for RBE at a mechanistic level as compare to those based on whole organism response. Together with additional computational studies of dose distribution, such studies will provide a better understanding and more detailed picture of the biological effects of neutrons.

[16] MarCell is a bone marrow cell kinetic model originally developed by Jones, et al. 1993 and 1997 and that has been integrated into HENRE.

Outside of DOD, the National Atmospheric Release Advisory Center (NARAC) has developed and maintains a health physics code, HotSpot (HotSpot 3.0, https://narac.llnl.gov), for the Department of Energy (DOE). The tool has a nuclear explosion module that includes prompt effect, which accounts for both neutron and gamma exposures. This module uses a default RBE of 3 for neutrons that can be adjusted by the user. The basis referenced for the RBE value of 3 traces back to documents published by the International Atomic Energy Agency (IAEA) and the U.S. Nuclear Regulatory Commission (NRC) (Evans, et al. 1993, IAEA 2005). IAEA-TECDOC-1432 uses an absorbed dose to tissue to derive the generic reference levels of RBE-weighted absorbed doses for severe deterministic health effects for an external exposure. A neutron RBE value of 3 (referenced from ICRP 58) is used for deriving the RBE-weighted absorbed dose that theoretically results in the deterministic effect in 5% of the exposed population (ICRP 1989). However, these data are referenced back to hematopoietic system effects in mice. As identified previously, significant differences in absorption of neutron energy in critical tissues among different species make such extrapolations highly uncertain.

7.3 Practical Integration of Neutron RBEs into Casualty Estimations

The impact of weapons design influencing neutron RBEs was discussed in Section 4 and Appendix A when comparing fission versus thermonuclear weapon design. The clinical appearance and management of ARS induced by radiation from enhanced radiation weapons (ERWs) also differs from fission weapons. For further discussion of medical implications of ERWs, see Reeves 2012.

Other considerations that have also not been addressed in our work are the additional dependence of neutron energy on resulting RBE. Similar to the radiation dose dependence, the RBE of neutrons are inversely related to the energy of neutrons in the range of interest in our work. Therefore, higher neutron RBEs are expected for sub-MeV neutrons. Although many of the studies examined in this work did not address the energy of the neutron exposures, fission neutrons from reactor studies represent to some extent the neutron energies that may be encountered in NUDET scenarios. The exposure scenario (urban detonation versus open terrain/ battlefield) will dictate the precise neutron energies encountered by potential survivors, and the neutron energy spectrum in an exposure will impact the resulting effective RBE. Nevertheless, the current work and recommended RBE based on mixed field reactor studies should provide an adequate starting point for integrating neutron RBEs into military scenarios and casualty estimation tools. To more precisely account for the impact of neutrons in NUDET scenarios, the energy dependence of neutrons should be explored further in the near future. Computational experiments paired with *in vitro* experimental data may provide an efficient means for developing a dose and energy dependent RBE function for neutrons.

Section 8. **Conclusions**

A neutron RBE greater than one in most NUDET scenarios is expected. If a particular casualty estimation code can easily obtain total neutron dose, the dose dependent neutron RBE function based on NHP response as described in Section 6 is recommended for use in calculating casualties and fatalities. However, if a single RBE is required for implementation in a casualty estimation code, the value of 2 should be sufficient to account for the impact of neutrons. In fact, our statistical analysis showed no significant differences in response among the LD_{10}, LD_{50}, and LD_{90} estimates due to the large amount of variability in the data. Since the RBE value of 2 is between the LD_{10} and LD_{50} values in NHPs (2.27 and 1.71, respectively), this value should be sufficient to account for the added impact of neutrons on the acute phase lethality dose response.

Although the current work does not account for neutron energy explicitly, we believe the neutron RBE estimates presented here would improve casualty estimates for most mixed field exposures. The whole animal data on which our studies rely were acquired using reactor mixed field exposures that encompass a wide range of neutron energies. Although urban radiation transport analyses provide significant detail regarding the neutron energy, dose, and the neutron to gamma ratio of the radiation exposure in surviving populations in example NUDET scenarios, very limited empirical human data are available to support a neutron RBE under these precise conditions. Therefore, as an interim approach, adopting a neutron RBE based on NHP response until a more detailed NHP to human extrapolation can be made would allow improvements to be made in casualty estimation codes so that the impacts of NUDET scenarios are not underestimated or unnecessarily overestimated.

Future efforts should seek to better characterize the tissue dose distribution to allow for more reliable NHP to human extrapolations. Computational studies together with *in vitro* data may support this effort. Also, as discussed previously, the differential impact of neutrons among tissues should be evaluated more critically. Some evidence suggests that neutrons have different RBEs for the hematopoietic and GI systems compared to gamma radiation which may affect the course of acute radiation syndrome. Therefore, estimation of RBEs on cellular and tissue level events for different tissues would be valuable in better estimating the time-dependent clinical effects when considering mixed field exposures.

Future efforts could utilize industry-accepted computational phantoms to better study the atomic interactions among human reference tissues and neutron spectra at survivable distances. Computational phantoms can be used to study effects in the human body as each major portion of the body is segmented and given a material composition similar to that found in humans. These studies can better inform researchers of how and where energy is deposited based on directional dependencies that may be associated with an incident radiation spectrum. The computational phantoms distributed by the Radiation Safety Information Computational Center (RSICC) at Oak Ridge National Laboratory are recommended. Specifically, MCNP phantoms are the Korean Typical Man -2 (KTMan-2) which was funded by the Korean Ministry of Science and Technology and the pediatric phantoms developed by University of Florida from computed tomography

images. These phantoms are commonly used in the medical and radiation protection dosimetry industries.

As a final note, current NUDET casualty estimations are focused on acute (deterministic) effects, and casualties are defined as those persons that acquire acute injuries that result in overt clinical signs and symptoms, require medical care, and/or impair combat effectiveness. We note that radiation casualties, as currently defined in our casualty estimation tools, do not include stochastic effects such as increased carcinogenic risk, that doses required for these increased risks are much lower than that for acute (deterministic) effects, and that neutron RBEs for stochastic effects appear to be much greater than for deterministic effects. Therefore, the RBE estimates discussed here will not be applicable for estimating the long-term health effects in a potentially larger population size than is currently tracked in casualty estimation tools.

Section 9. **References**

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Section 10. **Abbreviations, Acronyms and Symbols**

ARA	Applied Research Associates, Inc.
ARS	acute radiation syndrome
CA	chromosomal aberration
CHC	Chinese hamster cells
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DTRA	Defense Threat Reduction Agency
ERWs	enhanced radiation weapons
eV	electron volt
FEMA	Federal Emergency Management Agency
FIA	Free in air
GI	gastrointestinal
GM-CFC	granulocyte-macrophage colony-forming cells
HENRE	Health Effects from Nuclear and Radiological Environments
HSRD	Human Survivability Research and Development
IAEA	International Atomic Energy Agency
IND	improvised nuclear device
IPT	integrated project team
LET	linear energy transfer
MarCell	bone marrow cell kinetic model
MCNP	Monte Carlo N-Particle
MLT	mid-line tissue dose
NARAC	National Atmospheric Release Advisory Center
NRC	Nuclear Regulatory Commission
NHP	non-human primate
NGA	National Geospatial-Intelligence Agency
NUDET	nuclear detonation
RBE	relative biological effectiveness
RBE_m	relative biological effectiveness – deterministic effects
RBE_M	relative biological effectiveness – stochastic effects
RIPD	Radiation Induced Performance Decrement
RSICC	Radiation Safety Information Computational Center
Shape2MCNP	shapefile to MCNP input conversion algorithm

Appendix A. **Urban NUDET Neutron Energy Spectra**

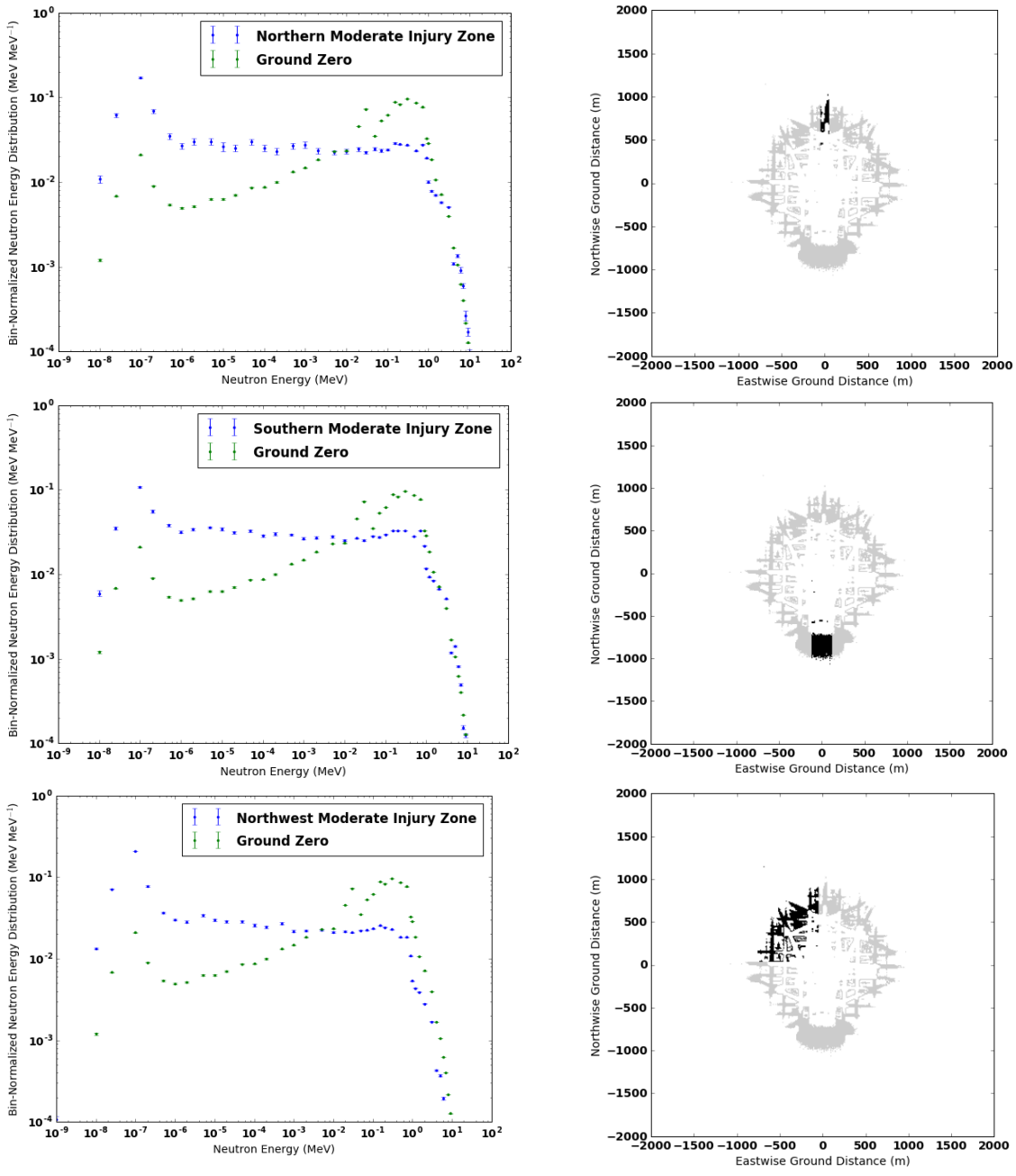

Figure 14. Neutron energy spectra (left) and corresponding urban zones sampled (right) for the 'Little Boy' source.

Spectra shown in Figure 14 are in 42-bins weighted by neutron energy and normalized by the width of the bin. Black parts of the right plots are where the Radiation Moderate Injury Zone was sampled. Grey parts are the rest of the Radiation Moderate Injury Zone for orientation. The left plots also contain spectra for the 20 m around the detonation location for comparison.

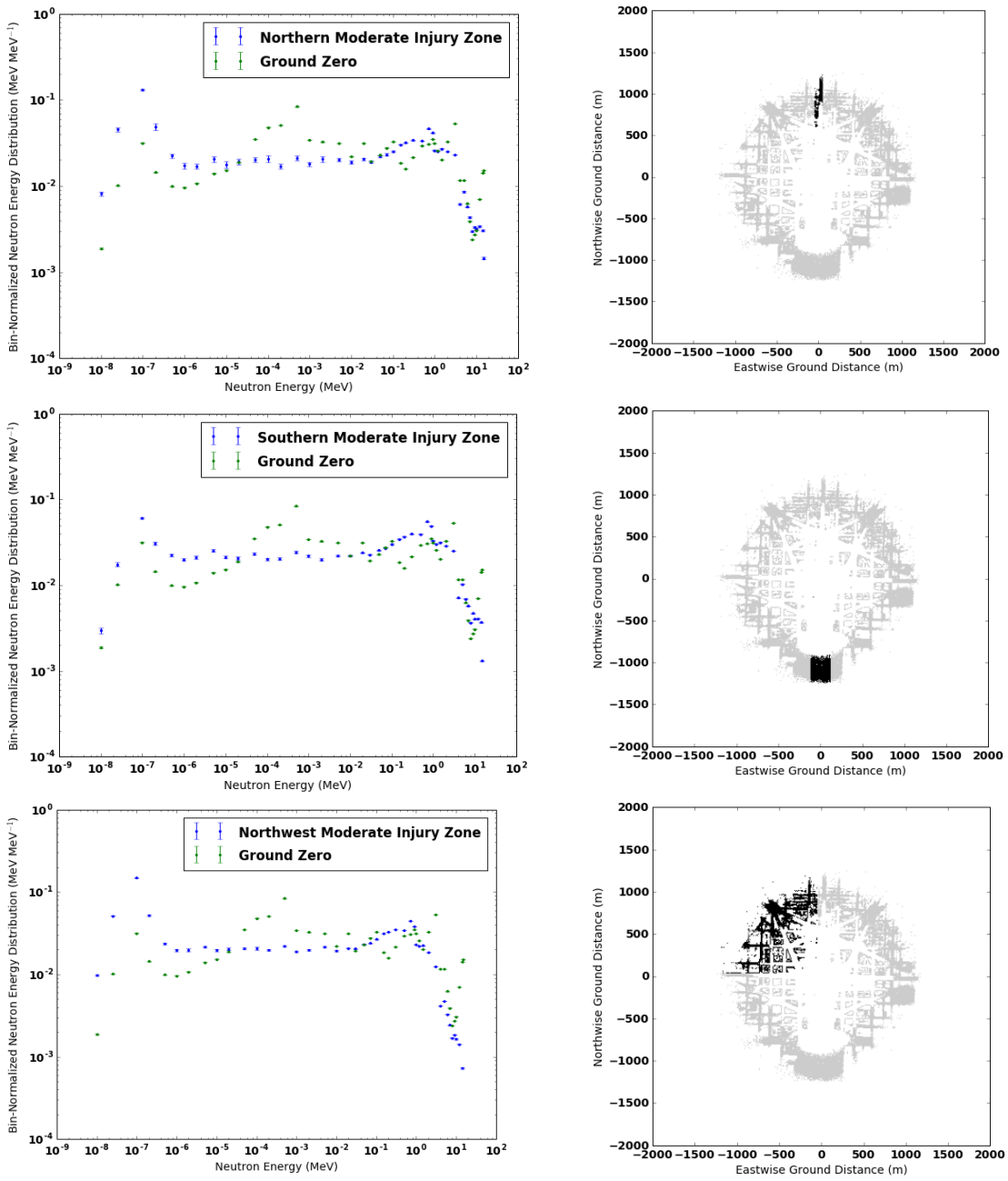

Figure 15. Neutron energy spectra (left) and corresponding urban zones sampled (right) for the 'Low Yield Thermonuclear' source.

Spectra shown in Figure 15 are in 42-bins weighted by neutron energy and normalized by the width of the bin. The black parts of the right plots are where the Radiation Moderate Injury Zone was sampled. The grey parts are the rest of the moderate injury zone for orientation. The left plots also contain spectra for the 20 m around the detonation location for comparison.

Appendix B. *In Vitro* Neutron Exposure Studies

Table 11. Neutron RBEs from *in vitro* chromosomal aberration studies.

Neutron Energy	Endpoint	Cell Type	RBE (reference radiation)	Reference
0.025 MeV	Dicentrics	Human Lymphocytes	36.4 ± 13.3 (Co-60)	(Schmid 2013)
0.036 MeV	Dicentrics	Human Lymphocytes	67.1 ± 28.9 (Co-60)	(Schmid 2003)
0.036 MeV	Dicentrics	Human Lymphocytes	16.6 ± 2.7 (220 kVp x-rays)	(Schmid 2003)
0.065 MeV	Fragments	Human Lymphocytes	2.4 ± 0.4 (250 kVp x-rays)	(Prasanna 1997)
0.144 MeV	Dicentrics	Human Lymphocytes	19.7 ± 2.2 (220 kVp x rays)	(Schmid 2003)
0.144 MeV	Dicentrics	Human Lymphocytes	79.4 ± 36.8 (Co-60)	(Schmid 2003)
0.186 MeV	Dicentric	Human Lymphocytes	11.2 (Co-60)	(Tanaka 1999)
0.370 MeV	Dicentric	Human Lymphocytes	16.4 (Co-60)	(Tanaka 1999)
0.385 MeV	Dicentrics	Human Lymphocytes	23.4 ± 2.5 (220 kVp x rays)	(Schmid 2003)
0.385 MeV	Dicentrics	Human Lymphocytes	94.4 ± 38.9 (Co-60)	(Schmid 2003)
0.565 MeV	Dicentrics	Human Lymphocytes	20.3 ± 2.0 (220 kVp x rays)	(Schmid 2003)
0.565 MeV	Dicentrics	Human Lymphocytes	82.1 ± 33.6 (Co-60)	(Schmid 2003)
0.570 MeV	Dicentric	Human Lymphocytes	10.7 (Co-60)	(Tanaka 1999)
0.790 MeV	Dicentric	Human Lymphocytes	7.1 (Co-60)	(Tanaka 1999)
1.00 MeV	Dicentric	Human Lymphocytes	7.0 (Co-60)	(Tanaka 1999)
1.151 MeV	Dicentrics	Human Lymphocytes	11.5 ± 1.3 (220 kVp x rays)	(Schmid 2003)
1.151 MeV	Dicentrics	Human Lymphocytes	46.3 ± 19.1 (Co-60)	(Schmid 2003)
~1.60 MeV Fission	Dicentrics	Human Lymphocytes	10.0 ± 0.9 (220 kVp x rays)	(Schmid 2003)
~1.60 MeV Fission	Dicentrics	Human Lymphocytes	40.4 ± 16.4 (Co-60)	(Schmid 2003)

Neutron Energy	Endpoint	Cell Type	RBE (reference radiation)	Reference
2.30 MeV	Dicentric	Human Lymphocytes	3.9 (Co-60)	(Tanaka 1999)
4.85 MeV	Dicentrics	Human Lymphocytes	8.0 ± 0.7 (220 kVp x rays)	(Schmid 2003)
4.85 MeV	Dicentrics	Human Lymphocytes	32.3 ± 13.3 (Co-60)	(Schmid 2003)
14.6 MeV	Dicentrics	Human Lymphocytes	4.1 ± 0.5 (220 kVp x rays)	(Schmid 2003)
14.6 MeV	Dicentrics	Human Lymphocytes	16.4 ± 6.8 (Co-60)	(Schmid 2003)