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Source: Radiation Research, 195(5) : 480-496

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RADE-20-00213.1

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RADIATION RESEARCH **195**, 480–496 (2021)
0033-7587/21 $15.00
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DOI: 10.1667/RADE-20-00213.1

MEETING REPORT

Neutron Radiobiology and Dosimetry

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Stricklin, D. L., VanHorne-Sealy, J., Rios, C. I., Scott Carnell, L. A. and Taliaferro, L. P. Meeting Report: Neutron Radiobiology and Dosimetry. *Radiat. Res*. 195, 480–496 (2021).

As the U.S. prepares for the possibility of a radiological or nuclear incident, or anticipated lunar and Mars missions, the exposure of individuals to neutron radiation must be considered. More information is needed on how to determine the neutron dose to better estimate the true biological effects of neutrons and mixed-field (i.e., neutron and photon) radiation exposures. While exposure to gamma-ray radiation will cause significant health issues, the addition of neutrons will likely exacerbate the biological effects already anticipated after radiation exposure. To begin to understand the issues and knowledge gaps in these areas, the National Institute of Allergy and Infectious Diseases (NIAID), Radiation Nuclear Countermeasures Program (RNCP), Department of Defense (DoD), Defense Threat Reduction Agency (DTRA), and National Aeronautics and Space Administration (NASA) formed an inter-agency working group to host a Neutron Radiobiology and Dosimetry Workshop on March 7, 2019 in Rockville, MD. Stakeholder interests were clearly positioned, given the differences in the missions of each agency. An overview of neutron dosimetry and neutron radiobiology was included, as well as a historical overview of neutron exposure research. In addition, current research in the fields of biodosimetry and diagnostics, medical countermeasures (MCMs) and treatment, long-term health effects, and computational studies were presented and discussed. © 2021 by Radiation Research Society

INTRODUCTION

Developing a better understanding of radiation-induced health effects from neutron exposures supports the mission goals of the National Institute of Allergy and Infectious Diseases (NIAID), Radiation Nuclear Countermeasures Program (RNCP), the Department of Defense (DoD), Defense Threat Reduction Agency (DTRA) and the National Aeronautics and Space Administration (NASA). These agencies seek to characterize radiation risks from different exposure scenarios, develop risk assessment models and advance medical countermeasures (MCMs) for radiation injuries. Both DoD and NIAID are concerned with the effects of neutron exposure after a nuclear detonation scenario due to the health impacts on military personnel and the general public, respectively. NASA is interested in understanding the effects of neutron exposures on astronauts in deep space for long-duration spaceflight missions, such as those to the Moon and Mars. Each government agency has an independent and distinct mission that includes consideration of the effects of neutron exposures on humans. Due to the common interest in understanding the health effects of neutron exposures, a Neutron Radiobiology and Dosimetry Workshop was convened on March 7, 2019, to consider the state of the science in neutron radiobiology, discuss the complexity of neutron exposures, and review the current understanding of their biological effects. The workshop also examined the gaps in knowledge that limit the ability to estimate health effects and the relative biological effectiveness (RBE) of neutrons. The desired outcomes of the workshop included: 1. A greater understanding of existing knowledge gaps; 2. A discussion of facilities and resources needed and current limitations in conducting neutron or mixed-field studies; and 3. Harmonization of the biological experimental parameters necessary to achieve effective and informative studies. Presentation summaries are provided below for the invited speakers listed in Table 1.

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TABLE 1
Workshop Speakers and Presentation Titles[a]

Speakers	Representing/affiliation	Title
Paul Blake, PhD	DoD	Concluding remarks
Marjan Boerma, PhD	University of Arkansas for Medical Sciences	Effects of low-dose chronic neutron exposures on cardiac function
David Brenner, PhD	Columbia University	Radiation biodosimetry in a mixed neutron-photon field
Lisa Scott Carnell, PhD	NASA	NASA inter-agency stakeholder
Lynnette Cary, PhD	AFRRI[3]	Identification of effective countermeasures against neutron radiation
Polly Chang, PhD	SRI Biosciences	Overview of neutron effects *in vitro* and *in vivo* small animal models
Mark Christl, PhD	NASA	Neutron relevant scenarios for space
Marco Durante, PhD	GSI Helmholtz Centre for Heavy Ion Research	Neutron radiobiology
Stephen Egbert, PhD	Leidos	Neutron dose in epidemiological cohorts
Lawrence Heilbronn, PhD	University of Tennessee	Principles of neutron interactions and dosimetry
Juliann Kiang, PhD	AFRRI[c]	Neutron effects on acute radiation syndrome: radiation dose rates and genders
Evagelia Laiakis, PhD	Georgetown University	Metabolomics of neutron responses and mixed fields
Thomas MacVittie, MS, PhD	University of Maryland	A systematic review of the hematopoietic acute radiation syndrome in canines and NHPs
Robert Prins, PhD	Applied Research Associates, Inc.	Neutron dose to personnel using a computational human phantom
Carmen Rios, PhD	NIAID	NIAID inter-agency stakeholder
David Schauer, DSc	AFRRI[c] and NCRP[d]	Panel discussion moderator
Edward Semones, MS	NASA	Panel participant on astronaut exposure to radiation on ISS missions
Daniela Stricklin, PhD, MPH	DTRA[b]	The significance of neutrons in nuclear detonation scenarios and reactor accidents
Lanyn Taliaferro, PhD	NIAID	Introduction and goals of meeting
LTC Jama VanHorne-Sealy, MS	DoD	DoD inter-agency stakeholder

[a] Workshop speakers had an opportunity to review this meeting report prior to journal submission.
[b] Presented on behalf of DTRA; work previously conducted at ARA.
[c] Armed Forces Radiobiology Research Institute.
[d] National Council on Radiation Protection and Measurements.

BACKGROUND

Stakeholder Interests and Needs

DTRA/DoD requirements. The DTRA/DoD is interested in understanding the radiological environment to which service members may be exposed while on duty. Research in this area focuses on maintaining service member safety. The President's 2018 Nuclear Posture Review (*1*) states:

> ''. . .the United States will sustain and replace its nuclear capabilities . . .and strengthen the integration of nuclear and non-nuclear military planning. Combatant Commands and Service components will be organized and resourced for this mission, and will plan, train, and exercise to integrate UNITES STATES nuclear and non-nuclear forces to operate in the face of adversary nuclear threats and employment.''

LTC Jama Van-Horne Sealy emphasized the expectation that military personnel must be prepared to operate in an integrated battlefield composed of conventional and nuclear weapons. Furthermore, the expectation is that service members will continue missions regardless of a nuclear detonation; and battlefield operations will not cease, as previously thought. Since the type of nuclear detonation can dictate the health effects expected, understanding the complexity of nuclear exposures is crucial. For example, large-yield detonations (>10 kilotons, kT) will have greater radiological output, but the greatest source of injuries will be due to blast and thermal burns. On the other hand, small-yield detonations (<10 kT) may yield less physical damage but may result in greater radiation injury, due to increased neutron exposures. Similarly, enhanced radiation weapons will result in a decreased destructive force, but an increased radiation release (*2*).

Given the possible mass destruction scenarios, it is important to understand the effects of nuclear weapons. Prompt effects include initial radiation (emitted within 1 min of exposure), thermal radiation, blast and shock, and electromagnetic pulse. In addition, delayed radiation exposures can also occur from fallout. The health effects of initial radiation exposure can vary due to the percentage composition of gamma rays, neutron, beta and alpha particles, as well as the type of burst (e.g., air, ground, high-altitude, underwater, underground, etc.). In all cases, service members will likely experience a combination of exposures. Some individuals may be out in the open and receive severe blast and thermal burns, while others may be partially protected from blast effects. Neutron detonation

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transport models have shown that in urban environments, the neutron spectrum is both hardened and thermalized, potentially changing its biologically damaging effects.

Deterministic effects that are now commonly referred to as ''tissue reactions'' (e.g., radiation-induced tissue damage) and stochastic effects (e.g., cancer and genetic risks), which occur due to exposure to different types of radiation, are quantified into an empirical value known as the RBE. The relative effects of different neutron energies are often characterized by their RBE versus photon exposures, a ratio that changes based on different biological end points, neutron energy and neutron dose (*3*). The neutron energy spectrum and neutron dose will depend on the type of nuclear detonation and the shielding experienced by those exposed; therefore, RBE factors for neutrons need to be quantified. To date, DTRA/DoD nuclear doctrine has assumed that the deterministic RBE for acute lethality neutrons is 1, where both high-energy (14 MeV) neutrons and photons have equal biological effects, as stated by Glasstone *et al*. (*4*), ''For the neutron energy spectrum of nuclear weapons, the RBE for immediate (acute) radiation injury is close to 1.0...''. If incorrect, this assumption would potentially underestimate the effects on personnel exposed to neutrons. It is important to note that these earlier studies focused on higher-energy neutrons in the 14-MeV energy range, whereas modern research indicates that initial neutron energy is slowed down to the range of 0.01–1 MeV in urban environments (*5*). As noted in the International Commission on Radiological Protection (ICRP) Publication 58, the deterministic RBE is predominantly inversely related to the neutron energy, hence at this lower energy range, neutrons can have a greater deterministic effect (*6*).

A thorough review of historic neutron studies was conducted by DTRA/DoD (*5*), with the goal of identifying methods to improve survivability and positive recovery outcomes. The data reviewed revealed many inconsistencies; studies often did not specify the neutron-to-gamma ratios, and in other cases, the neutron energy ranges were not reported. The DTRA/DoD requires research that can help improve the understanding of mixed-field biological effects and neutron mechanisms of fatality. Part of this research must include a mechanistic model for neutron damage and/or mixed-field exposures resulting in detrimental effects or lethality. In addition, it is critical that the DoD understands how the neutron-to-gamma ratio impacts the observed human effects.

The DTRA/DoD intends to focus on a neutron energy range of 0.01–1 MeV, since these energies may play an important role in human effects. Recent findings suggest that neutron exposure may, in fact, lead to greater gastrointestinal (GI) damage compared to X rays alone (*5*). If true, this finding would require changes in policies, procedures and plans to address battlefield casualties and the potential benefit of MCMs administered after exposure. Ultimately, the DTRA/DoD wants MCMs that would aid in minimizing acute, delayed and/or stochastic effects. The effects on humans and the magnitude of exposure must be well understood to successfully develop these MCMs.

NIAID/RNCP requirements. The NIAID/RNCP was created after the 9/11 attacks as part of a national effort to ensure U.S. emergency preparedness. In 2004, the NIH strategic plan and research agenda for medical responses to counter radiological and nuclear threats was established to define a flexible, collaborative and comprehensive program to address injuries sustained during a radiation public health emergency. The strategic plan was later refined to include: 1. research and product development; 2. animal model development; and 3. medical therapies and diagnostics. All these efforts are possible through the various inter- and intra-agency collaborations and the directed funding provided to the research community.

Dr. Carmen Rios presented on behalf of the NIAID/RNCP and focused on our shared interest in understanding the effects of radiation-induced tissue damage. In particular, these injuries include the acute radiation syndrome (ARS) and subsyndromes (e.g., hematopoietic, GI, skin, vascular), as well as late onset of lung, kidney, cardiovascular and cognitive disease. Due to the expected casualties after a nuclear detonation, the NIAID/RNCP is also interested in developing biodosimetry tools that can rapidly and accurately triage a large population of potentially-exposed individuals. The NIAID/RNCP has had continued interest in understanding the biological effects of neutrons, and has funded a neutron facility at Columbia University (New York, NY), which simulates the neutron spectrum at approximately 1 km from an improvised nuclear device (IND) event (*7*).

The NIAID/RNCP is aware of the ever-increasing threat of nuclear terrorism across the globe, including the possible use of an IND. While photons will always be the primary contributors to the exposure from INDs in terms of dose, when the increased RBE of neutrons are taken into account, neutrons will undoubtedly contribute significantly to the biological effects. For example, recent estimates for a 10 kT ground burst IND detonated in the center of Washington, DC suggest that neutrons will contribute 10–20% to the overall organ doses of the affected survivors (*7, 8*). These are much larger dose ratios compared to the air burst estimates at Hiroshima, due to buildings more effectively shielding photons compared to neutrons. Since, dose-for-dose, neutrons are generally more biologically hazardous than photons, if neutrons contribute 10–20% of the physical dose to IND survivors, they will undoubtedly play a major role in the resulting biological effects.

Criticality accidents provide a glimpse into the complex nature of dose estimation given the unknown contribution of neutrons. In 2000, Los Alamos National Laboratory conducted a review of physical and neutronic characteristics of 60 radiation criticality accidents that occurred within the Russian Federation, the UK, Japan and the U.S. (*9*). In most cases, there has been great uncertainty in the physical dosimetry and unknown health effects due to neutron

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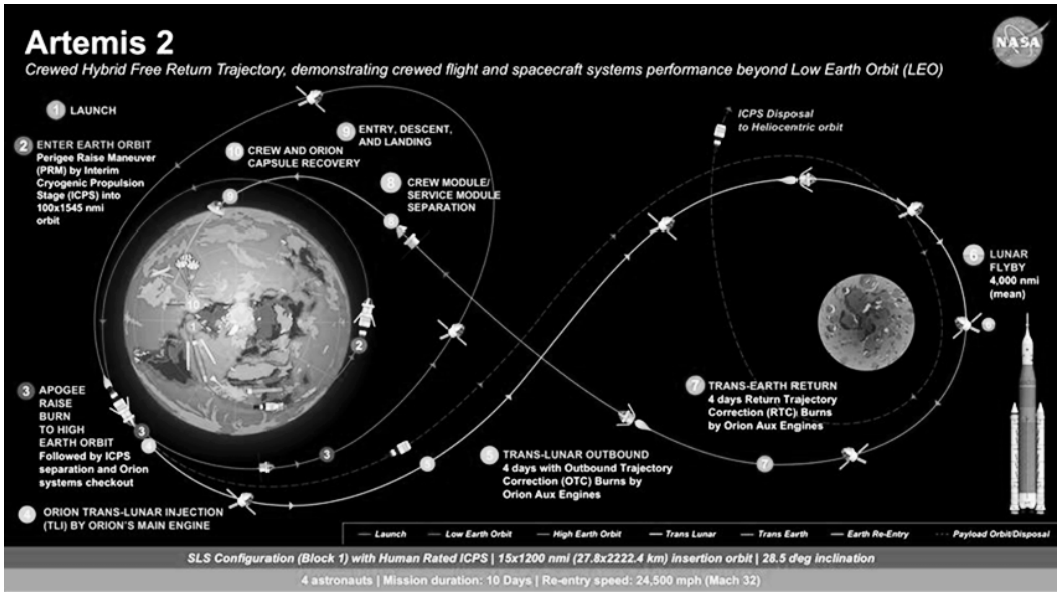

FIG. 1. Artemis 2 will be the first mission to carry astronauts to the Moon for a lunar fly-by. The Orion spaceflight vehicle will carry four astronauts, with the mission expected to last a total of 10 days from launch to landing.

exposure. In fact, the RBE of neutrons in Hiroshima and Nagasaki bombings continue to be studied and debated, underlining the complexity of the issue (*3, 10–12*). Human exposures to ionizing radiation resulting from nuclear incidents differ based on distance to the radiation source and shielding provided by buildings or terrain. Biodosimetry methods, at best, provide an estimate, given the wide variety of energy distributions of gamma rays and neutrons present at a particular location (*3, 12*).

Given the significant role that neutrons could play in a mass casualty radiation scenario, the NIAID/RNCP has funded neutron-focused research, the results of which were presented in the workshop (*7–10*). Furthermore, the NIAID/RNCP recognizes the need to qualify research in this area utilizing appropriate neutron dosimetry, and therefore supports the harmonization efforts of the DoD. Similarly, the NIAID/RNCP has established its own dosimetry assessment across its entire research portfolio. For this reason, the DoD requested the support of the NIAID/RNCP to continue to harmonize neutron and mixed-field dosimetry studies.

NASA requirements. NASA has recently announced the Artemis lunar exploration program (Fig. 1). This ambitious effort outlines a plan to return humans to the Moon by 2024, with the ultimate goal of reaching Mars by the late 2030s. Under the Artemis program, crewed missions carrying four astronauts will begin as early as 2022 and last between 10–30 days. These missions will support the assembly of the Gateway, a space platform in cislunar space that can support crewed missions for 30 days (*13*), a first step to humans setting foot on the lunar surface. A human lunar lander will remain on the Gateway, allowing the crew to perform regular excursions to and from the lunar surface. Dr. Lisa Scott Carnell discussed the potential risk of these missions to astronaut health, warranting the need for NASA to understand the radiation-induced health effects from space radiation exposure. Space radiation is complex and consists of multiple types of radiation, including solar particle events (SPE), galactic cosmic rays (GCRs) and trapped radiation (Van Allen) belts, all of which contribute to the radiation dose astronauts receive during spaceflight missions. Furthermore, there is a concern for albedo neutrons (secondary neutrons directed back towards space, away from the atmosphere) on planetary surfaces (*14*).

Deep space exploration missions will encounter a complex array of space radiation such as GCRs, which are composed of high (H) atomic number (Z) and energy (E) (HZE) particles that can penetrate the spacecraft, making shielding against them difficult. The spacecraft and habitats are designed to reduce radiation exposure; however, the protective shielding modifies the GCR spectrum once it is inside the spacecraft or habitat, resulting in secondary neutrons and light ions, which may have higher RBEs than primary particles. High-energy secondary neutrons are produced by the interactions of the primary radiation field with spacecraft materials and planetary surfaces. These secondary neutrons, along with light ions, tend to dominate the exposure and may contribute up to 30% of the total equivalent dose (*15*). Understanding the radiobiological effects of neutrons will help refine NASA's radiation health risks and determine suitable MCMs to address radiation-induced health effects from spaceflight. Injuries of concern include carcinogenesis, acute and late central nervous system deficits, degenerative tissue changes, and ARS due to solar particle events that may be confounded by additional neutron exposure.

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NASA has funded neutron research over the past two decades, predominately focused on quantifying the neutron spectrum in the space environment. More recently, NASA funded the establishment of a radiation facility at Colorado State University (Fort Collins, CO) that houses a ^{252}Cf neutron source capable of delivering chronic radiation exposure at dose rates expected on a long-duration Mars mission (*16*).[3] The original goal was to develop a radiation resource to examine the effects of chronic exposures to high-linear energy transfer (LET) radiation as experienced in outer space, but serendipitously, NASA has also been able to explore the effects of neutrons in radiobiology studies.

MEETING PROGRAM OVERVIEW

This workshop was an inter-agency effort between the NIAID/RNCP, DOD/DTRA and NASA partners. The target audience included U.S. Government emergency preparedness planning and funding agencies as well as industry and academic researchers engaged in neutron or mixed-field radiation studies developing radiation MCM treatment approaches and biodosimetry tools. To address the stakeholder needs, speakers were invited to provide an overview of neutron radiation dosimetry, historical neutron radiobiology, and ongoing mixed-field research. A robust discussion also ensued regarding the existing research gaps and potential solutions.

Neutron Exposure Scenarios

Nuclear incidents. DTRA enables the DoD and the U.S. Government to prepare to combat weapons of mass destruction and improvised threats as well as ensure nuclear deterrence. Within this mission space exists DTRA's Human Survivability Research and Development (HSRD) Program, which uses modeling to determine immediate health effects in nuclear weapon environments. As previously discussed, a nuclear detonation results in prompt radiation exposure from gamma-ray and neutron particles. The protracted radiation exposures occur due to neutron activation products and radioactive fallout. The blast and thermal injuries and inhalation hazards will play a role in the health effects. Ultimately, in an urban environment, complex injuries with potentially survivable doses of radiation exposure can occur.

Dr. Daniela Stricklin provided an overview on the significance of neutrons in nuclear detonation scenarios and reactor accidents in an effort to answer the question: Do neutrons matter? The answer depends on the device characteristics, the height of burst and the urban environment, which can affect the neutron-to-gamma ratio. The neutron RBE is dictated by the neutron dose and energy, and generally increases with decreasing neutron energy (*6*). In addition, the neutron RBE can vary for different organ systems (*17*). Historically, most casualty estimation codes estimate an RBE of 1 based on supra-lethal doses, which does not account for neutron effects. In contrast, the 2013 Lawrence Livermore National Lab Hotspot Code employs an RBE of 3 for estimates of a 10-kT surface burst. This code is based on rodent studies, which do not necessarily correlate to the human condition.

The HSRD program has embarked on a systematic and three-pronged approach to determine the RBE of neutrons (*5*), which includes: 1. Environment modeling to examine the energies and doses to which survivors would be exposed; 2. Neutron radiobiology review to determine the appropriate RBE for acute effects to neutron exposures; and 3. Scenario analyses to decide if the impacts are sufficient to require updating codes. The program determined that survivors will be exposed to a spectrum of energies, with neutron dose contribution ranging from 24–51% of the total radiation dose received, depending on the individual location in the urban environment. In addition, the HSRD program reviewed large animal survival studies and found a range of observed RBEs from 0.9 to 2.9 (*5*); however, the variability between experimental parameters made it difficult to make comparisons between studies. Since RBE is dose-dependent and organ-dependent, studies were broken down by LD_{10}, LD_{50}, and LD_{90} data. Although dose-response trends were observed, the slopes were not statistically significant due to animal variability. Overall, after much interpretation, a single RBE value of 2 was proposed. A radiation blast scenario set in Washington, DC with an RBE of 2 was predicted to result in a 40% increase in fatalities. Further examination of this scenario showed that approximately 69% of the surviving population would receive a neutron dose. Clearly, the neutron component will be a factor in a nuclear detonation scenario. Moving forward, the DoD needs to determine the best neutron RBE integration strategy and consider revising DoD policy (*18*) and DoD code to address the biological effects of neutrons. Furthermore, the DoD should examine target organ doses from computational studies and revisit organ-specific RBEs. All of this information should be used in mechanistic models to estimate the true biological effect.

These HSRD analyses demonstrate the gaps in knowledge for nuclear detonation scenarios. Importantly, neutron exposure will likely be dependent on a specific scenario and each will yield variable neutron energies (sub-MeV), doses and neutron-to-gamma ratios. One example of this is in nuclear power plant scenarios, where there are uncertainties in historical physical dose reconstructions due to the variability of exposures. Workers in the immediate range of a radiation source may have an acute high dose, while surrounding populations may have low-dose exposures and overall neutron activation may be significant. In all cases, an appropriate RBE for immediate tissue reactions or acute

[3] Space radiation: CSU studies risks for astronauts going to Mars. Fort Collins, CO: Colorado State University; 2015. (https://bit.ly/3pVGMfp)

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TABLE 2
Neutrons Classification by Initial Energy (*24*)[a]

	Energy range	Dominant interactions
Cold	0–0.025 eV	Scattering
Thermal	~0.025 eV	Scattering
Epithermal	~0.025–100 eV	Elastic
Slow	~100 eV to 0.5–1 MeV	Elastic
Fast	~0.5 to 10–20 MeV	Collisions

[a] https://go.nasa.gov/3bjNU1a.

TABLE 3
Comparison of Existing and Proposed Radiation Weighting Factors from ICRP 60 and the Recommended Approach in ICRP 103 (*23*)

	Radiation weighting factor	
Neutron energy	ICRP 60	ICRP 103
10 keV	5	A continuous curve as a function of neutron energy ranging from 2.5–20.
10 keV–100 keV	10	
>100 keV–2 MeV	20	
>2 MeV–20 MeV	10	
>20 MeV	5	

effects is needed to extrapolate animal data to humans and to better understand how neutrons affect ARS.

Space. Astronauts are exposed to a complex array of radiation types during exploration missions on the International Space Station (ISS) and will endure even harsher exposure scenarios during deep-space, long-duration missions to the Gateway, the lunar surface or Mars. Dr. Mark Christl explored the significant role that neutrons play in the absorbed biological dose in space. On the ISS and Gateway, the shielding from the structures generates secondary neutrons as HZE ions pass through the materials, resulting in nuclear interactions. Although shielding may slow HZE particles, neutrons are very penetrating and can go through shielding without interacting, since they have no charge. These neutrons elicit significant biological damage as a result of indirect ionizations that occur due to elastic or inelastic scattering interactions. The energy of the neutrons can be as high as several tera electron Volts (TeV) in magnitude, affecting the dose and damage exerted on biological tissue in space, thus making it difficult to study and understand radiobiological effects. To quantify the neutron field inside the ISS, a fast neutron spectrometer (FNS) has been installed that is capable of measuring the energy and flux of the neutron spectrum to refine the radiation models. On planetary surfaces, albedo neutrons are also generated as a result of HZE particles and SPE rays interacting with the surface. Once these rays strike the lunar surface, they scatter up to a meter in depth and reflect back out as much as 15% of the absorbed dose. Exploration missions that plan to establish habitats on planetary surfaces will need to incorporate albedo radiation contributions in radiation risk models, since the varying thickness and type of shielding for the habitat will impact the overall radiation dose to the astronauts due to the penetrating albedo neutrons (*19*).

Neutron Dosimetry

Dr. Lawrence Heilbronn discussed the physics of neutrons and how their interactions with matter allow for detection and quantification of energy deposition associated with neutron exposures. Neutron interactions depend on the initial energy of neutrons (Table 2) and the nature of the matter in which they interact. Each interaction results in a change in the neutron energy. Research on neutron biological interactions requires an understanding of the physics of neutrons and the relevant variables that can influence the biological result of that interaction. Adding to the complexity of understanding the effects of the biological response is the introduction of mixed-field exposures. Any research done with a mixed-field must be defined clearly and include neutron flux, spectrum of the neutron flux, photon energy, neutron/photon ratio, and tissue composition exposed.

Neutron interactions are classified into different categories: key interactions include elastic scattering, inelastic scattering, and capture reactions (*20*). For elastic scattering events, neutron interactions can result in recoil nuclei or heavier charged particles of different energies, and therefore result in variable doses. Collisions with nuclei dominate, leading to scattering, capture or fission. For inelastic reactions, the neutron can be captured by a nucleus and result in, for example, high-LET alpha particles. The probabilities of each interaction, together with the energy and direction of resulting charged particles, are used to calculate absorbed dose. The dose is a function of the number of neutrons, their energy, and the type of atoms in the material exposed. The amount of energy transferred to the resulting charged particles must be included in the calculation of absorbed dose. The kinetic energy released per unit mass, or kerma, is the basis for estimating absorbed dose and is defined as the sum of all initial kinetic energies of all charged particles created in matter from photons and neutrons (uncharged radiation) per unit mass (*21*). The kerma is specific to matter, due to the dependence of the calculation on the constituent elements. Neutron energy-dependent dose conversion factors are used to estimate dose from the neutron fluence (*22*). Absorbed dose is the amount of energy deposited by radiation in a given mass (such as a tissue or organ), and the equivalent dose is a measure of the radiation dose to a tissue or organ that accounts for the RBE of different types of ionizing radiation, such as neutrons. Equivalent dose uses the absorbed dose, together with an appropriate radiation weighting factor (w_R), which accounts for the differential impact that various types of radiation can have, even when the absorbed dose is the same (*23*). Both equivalent dose and the radiation weighting factors (Table 3) are terms developed for radiation protection (*24*). As such, these terms are aimed to be protective for stochastic, long-term health effects rather than acute health effects. Their application in risk assessment has been debated (*25*).

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In some of the scenarios described previously, neutron detectors would need to have real-time responses and be able to detect a wide range of neutron energies within a mixed radiation field. Examples of these kinds of detectors include neutron rem detectors, parallel plate fission chambers, tissue equivalent proportional counters (TEPC) and paired ionization chambers. While some knowledge exists for lower-energy neutrons and their detection is possible, more data are needed from the neutron energy region above 20 MeV that will be encountered in space radiation environments. Additional data are also needed to understand resulting neutron doses in shielded environments from fission neutrons. Although limitations and gaps in neutron detection exist for some scenarios, in other circumstances, passive detectors are still widely useful and provide low-cost, reliable estimates for neutron personal dosimetry (*25*).

Neutron Radiobiology

Dr. Marco Durante focused on the radiobiological effects exerted by neutrons. Two fundamental ways that ionizing radiation affects biological tissue are through cell killing, which can result in immediate tissue injury or acute effects, and through genetic alterations that can lead to stochastic or late effects. Neutrons are neutral in charge and interact with the nuclei of the absorbing material, but not with orbital electrons. The neutron interactions give rise to densely-ionizing particles (recoil protons, alpha particles and heavier nuclear fragments), and the result is a high concentration of ionizations as they pass through material. Therefore, neutrons are classified as high-LET and are considered to be indirectly-ionizing rather than directly-ionizing radiation. The concentration of ionizations and the degree to which ionizations occur depends on neutron initial energy, as well as the matter in which they interact. Because of the high density of ionizations, neutrons are capable of inducing a larger number of complex and non-repairable DNA lesions compared to low-LET radiations such as photons. The type of interaction and the amount of dose deposited in the body is strongly dependent on the neutron energy and the nature of the absorbing material. The human body is composed primarily of hydrogen, carbon, nitrogen and oxygen (*26*). In neutron-carbon nucleus interactions, three alpha particles can be produced, whereas a neutron-oxygen nucleus interaction could result in four alpha particles. Alpha particles produced are highly ionizing and can damage sensitive living cells and tissue.

Relative biological effectiveness (RBE). The RBE is defined as the ratio of the doses required by two radiation exposures to cause the same level of effect. RBE depends on the dose, dose rate, and the biological end point under consideration. The term, RBE_M, which refers to the maximum RBE value with decreasing dose, is used to guide the selection of radiation weighting factors for low-dose stochastic or late effects, as shown in Table 3 (*27*). The term RBE_m is used to describe the maximum RBE values for deterministic or acute effects such as cell killing. Some studies report doses as a Gray-Equivalent (Gy-Eq) when an RBE_m has been applied for deterministic effects. When an absorbed dose is modified by a radiation weighting factor, equivalency is denoted by the Sievert (Sv). The differential biological impact of neutrons should be expressed in terms of RBE, as compared to photons. The RBE of neutrons depends on a number of biological and physical factors as shown in Table 4; however, the RBE will vary depending on the specific type of tissue, its volume, and the depth of the tissue within the organism (*28*). The complexity of establishing RBEs, given the variety of factors that impact biological effects, as well as the difficulty in differentiating stochastic (late) and deterministic (acute) effects, are being considered (*29*); this is the topic of research by a European consortium (*30*).

TABLE 4
Biological and Physical Factors that Impact Neutron RBE

Biological	Physical
Biological end point	Linear energy transfer
Tissue type (sensitivity)	Energy
Tissue volume and depth	Dose
Microenvironment	Dose rate
Cell-cycle phase	Tissue or material composition

A significant amount of knowledge has been collected on the radiobiology of neutrons. Experiments on cell survival curves illustrate the increased cell-killing effectiveness of neutrons, in particular, fission spectrum neutrons, as compared to 250-kVp X rays (*31*). These studies also demonstrate the dependence of this effect on neutron energy, since cell killing per unit dose is diminished as neutron energy increases from 3 to 15 MeV. Similar studies show that lower doses in fractionation experiments increased the observed RBEs (*32*). Several published studies on acute myeloid leukemia suggest an approximate RBE of 10 for carcinogenesis (*33–35*). *In vitro* studies of chromosomal aberrations provide well-defined neutron energy-dependent relationships to dicentric yields, where aberrations per unit dose increase with decreasing neutron energy in the range from 0.37 to 2.3 MeV (*36*).

Considerations for stochastic effects. Stochastic effects, generally late effects such as carcinogenesis, are probabilistic in nature. Although the impact of neutrons on stochastic effects is not clear, the stochastic effects of neutrons and mixed-field exposures are being studied, as demonstrated by the available literature on carcinogenic effects of neutrons (*37–40*). However, further research is needed to improve understanding of the risk associated with exposures below the level at which deterministic effects occur. Stochastic effects can happen at any dose, but effect probability increases with dose. A neutron radiation weighting factor is used in low-dose exposures for radioprotection to define the stochastic risk associated with exposure and to determine

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equivalent dose from the absorbed dose averaged over a tissue or organ. The resulting weighted dose establishes the estimated organ or tissue-equivalent dose. Since dose and effect of neutrons can differ based on the nature of exposure, it is important to note from the outset whether the effects in question are deterministic or stochastic and whether the doses of interest have been adjusted, either with an RBE or weighting factor for neutrons (*27*).

Neutron Effects in Biological Systems

A significant amount of radiobiological research has been conducted with neutrons in various exposure scenarios. Dr. Polly Chang provided an overview of a special issue of *Radiation Research* (*41*) as well as other historical *in vitro* and small animal model neutron radiobiology studies. Between 1970 and 1992, nearly 50,000 studies using B6CF1 male and female mice were conducted using fission neutrons; the publicly available dataset is hosted at Northwestern University (Evanston, IL).[4] A neutron dose range of 13.5 to 40 cGy was used, with a focus on overall mortality or life shortening, and particular emphasis on renal, pulmonary, vascular and liver function (*42, 43*). Other neutron radiobiological studies included examination of effects using different *in vitro* cell systems, as well as a variety of *in vivo* whole animal studies in a range of species. This *in vivo* research examined a wide variety of exposure scenarios such as prompt high dose, fractionated, and chronic lower doses (*44*). The range of biological end points studied using *in vitro* cell systems included cytogenetic damage, genomic instability, gene expression, mutations and apoptosis (*45, 46*). The RBEs observed were dependent on neutron energy and the specific biological end point measured. For some end points such as apoptosis, cellular response to neutrons was similar to photons. Tissue-dependent responses and the mutational profile of neutrons resembled that of other high-LET radiation (*47–51*).

Small animal model studies have shown that lifespan is significantly decreased after neutron exposure in a dose rate- and energy-dependent manner (*46*). A significant and dose-dependent increase in cataract formation has been observed in rodents and other species (*52*). Other health effects studied in rodents include cardiovascular end points, with observed neutron RBEs from 3–4, and with evidence of sex-specific differences in response. Other important end points examined in rodents were differences in central nervous system (CNS) and behavioral effects. Significant increases in sensitivity to neutrons (*53*), as well as decreased neurogenesis (*54*) were observed in rat hippocampal cells. In behavioral studies, neutron compared to photon exposure of rats resulted in decreased taste aversion, but neither gamma-ray nor neutron exposures resulted in CNS-mediated task aversion and learning disabilities (*55*).

[4] Paunesku D. Janus Tissue Archive. Evanston, IL: Northwestern University. (https://bit.ly/38q1mOQ)

History of neutron exposure research. Animal studies aimed at determining the biological effects of neutrons and photons have revealed a differential response on lethality and damage to tissues and organ-specific cells. An overview and rich resource for early neutron radiobiology research, conducted at the Armed Forces Radiobiology Research Institute (AFRRI; Bethesda, MD) and other laboratories, both national and international, can be found in the 1990 *International Colloquium on Neutron Radiation Biology* report (*41, 56*). The colloquium focused on the status of neutron radiobiology and dosimetry at the time. While these earlier studies provided valuable information on the effects of neutrons on lethality and injury to animals, there are still other key variables that must be considered. Variations seen between animal species, radiation sources, dose, dose rates, exposure geometries, neutron energies and neutron-to-gamma ratios could impact the relevance of actual outcomes from an IND and the subsequent human biological response. Researchers strive to model problems that radiation emergency response planners have developed. As possible exposure scenarios are more clearly defined, study designs will need to adapt.

Archived data of radiobiology studies conducted from 1952 to 1992 at Argonne National Laboratory (Lemont, IL) were also analyzed (*57*). The intent was to determine if there was an increase in mortality due to cardiovascular disease (CVD) after exposure. In those studies, B6CF1 mice received ^{60}Co gamma rays or fission neutrons in either a single dose or 60 protracted weekly doses. CVD mortality increased in a dose-dependent manner from both gamma rays and neutrons. The RBE for neutrons was estimated to be 4 or 5, with females being more susceptible than males. The CVD mortality appeared to be increased when the dose was protracted in females, with a dose and dose-rate effectiveness factor (DDREF) range of 0.4–0.45 for neutron and gamma-ray exposures (*58*). In a more recently published study, differential responses to neutrons were observed when fast neutrons, produced by bombarding a beryllium target with 65-MeV protons, were delivered to female BALB/c mice (*59*). This study focused on spleen cell sensitivity after exposure to either 65-MeV neutrons or 15-MV X rays from a linear accelerator (LINAC). The timed kinetics (6, 24, 48 and 72h) of spleen weight and cellularity loss after exposure to 1 Gy fast neutrons or X rays showed that spleen weight and cellularity were lower, as a function of time, in animals that received neutrons compared to those exposed to X rays (*59*).

In addition to rodent studies, mixed neutron-gamma studies have also been conducted in canines and NHP models. Dr. Thomas MacVittie presented a systematic overview of mixed-field studies in both large animal models. Using a canine model for hematopoietic-ARS (H-ARS), male and female canines were irradiated with a neutron-to-gamma ratio of 5.4:1 using the 1.1 MW Training, Research, Isotopes, General Atomics (TRIGA) Mark-F research reactor, which delivers a mixed LET field

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of fission spectrum neutrons and gamma rays and is a unique resource to AFRRI. Exposure of 40 cGy/min with an average neutron energy of 0.85 MeV was delivered bilaterally (simultaneous) to the midline, resulting in mortality of 50% of the exposed population within 30 days or an $LD_{50/30}$ of 153 cGy when no medical support was administered. However, medical support consisting of fluids, antibiotics and fresh irradiated platelets/whole blood increased the $LD_{50/30}$ to 185 cGy. The resultant $LD_{50/30}$ values for bilateral ^{60}Co gamma rays alone, without and with medical support, were 260 and 338 cGy (*60*).

NHP dose-response relationship (DRR) curves after single radiation exposures to ^{60}Co gamma rays, X rays, or neutrons were presented and the $LD_{50/30}$ estimates were calculated to be 644, 520, and 385 rads, respectively. Comparisons of LD_{50} values in these studies were used to gain insight into a neutron RBE for lethality in NHP models of the H-ARS; at nearly one half the dose, neutrons have a greater negative biological impact (*61*). A retrospective dataset was published that provided a comparison of the mixed neutron-to-gamma radiation exposure in a canine model of acute GI- and H-ARS relative to ^{60}Co gamma rays (*45*). Additionally, a systematic review of the mixed neutron-to-gamma radiation-induced H-ARS in canines and NHPs relative to reference quality radiations was also conducted (*62*). In studies performed from the 1950s to the 1990s, investigators examined mixed-field exposures derived from reactors, or in some cases, actual nuclear weapon exposures. Studies used dose rates with variable steady-state pulse or prompt exposures and different geometries (unilateral, bilateral and rotational). The neutron energy range for the studies varied from 14.6 to 1 MeV. Reference radiations were 250-kVp or 1–2-MeV X rays or ^{60}Co photons. The neutron-to-gamma ratios varied among the experiments. A review of the dose-response curves, and comparison of $LD_{50/30}$ values observed in the studies, suggested increased mortality in mixed-field studies. Bilateral exposures generally resulted in greater mortality than unilateral exposures, with all mixed-field effects being dependent on dose, dose rate and neutron energy. The neutron RBE for acute lethality based on the $LD_{50/30}$ observed in canines were generally less (1.2) compared to NHPs (1.7–2). Some studies indicated that an acute tissue injury RBE for GI-ARS may be as high as 3 for mixed-field exposures; however, not all studies collected data on GI end points, so a reliable assessment could not be obtained.

In a study published in 1978, Broerse and colleagues assessed the potential risks of ionizing radiation exposure of humans by performing an NHP survival study using total-body, 300-keV X rays and fission neutrons (*63*). In this study, a survival benefit was observed for NHPs who received autologous bone marrow cells a few hours after doses of fission neutrons up to 440 rads (4.40 Gy), or 300-keV X rays up to 860 rads (8.6 Gy). However, doses above these levels, approximately 470 rads (4.7 Gy), reduced mean survival time and initiated development of GI-ARS in the animals that received fission neutrons. Animals that received X rays only were markedly delayed in the development of GI-ARS (*63*).

Despite the vast amount of data available on neutron radiobiological effects, the complexity of neutron interactions with biological tissues is difficult to interpret. Together with the large number of parameters that impact biological responses, the varied radiation exposures, and in some cases the inconsistent reporting of radiation quality, dose and dose rate, make it difficult to query the data for the specific needs of today. Therefore, prominent gaps in knowledge, in terms of understanding human health risks in the context of current neutron exposure scenarios, still exist. While RBEs for ARS and lethality in humans have been estimated (*64*), more work is needed to reduce the uncertainty of the estimate. In particular, the energy- and dose dependence of the neutron RBE for acute effects in humans remains to be delineated. While some data point to differential effect of neutrons in key target organs, there is not yet a clear understanding of the effect neutrons have in humans, making it necessary, but challenging, to establish organ-specific RBEs. This will require knowledge of depth-dose distribution of mixed neutron-to-gamma radiations relative to critical organ volume and the expected exposure geometry in established radiation-effects scenarios.

Current Research

Biodosimetry and diagnostics. In any realistic situation involving a nuclear detonation, the types of radiation exposures experienced would range from short-term to long-term, partial- to whole-body, with beta and photon only, neutron and photon only, or some variation. To assess exposure in a meaningful way, there is a need to understand the complexities of the event, the details of the exposures, and, most importantly, the biological response that must be taken into consideration. Biodosimetry and diagnostics could potentially provide critical information to medical personnel and decision-makers working to assess risk to personnel during an emergency response. These tools can be used to understand clinical severity or determine stochastic risks of radiation exposure. Most of the biodosimetry work to date has focused primarily on understanding the effects of photon exposure. Several challenges were revealed through this work, including the fact that individual and organ responses can vary based upon the percentage of the body exposed or time after exposure. When mixed-field radiation exposures are added to the equation, there is even greater complexity.

The mechanism of neutron damage is not just more extensive, but unique (*65*). Dr. David Brenner focused on high-throughput biodosimetry systems being conducted at Columbia University, which demonstrate that both photons and neutrons produce the same biomarkers, but neutrons do so more efficiently, making it nearly impossible to discern

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between the two. Chromosome-based biomarkers allow for distinction between photons and neutrons, but only at a low throughput (*66*). Therefore, the need exists for a high-throughput system that allows for distinction, and for more work on biomarkers specific to neutron exposure.

Current high-throughput, micronuclei-based biodosimetry systems already measure the number of micronuclei in each binucleated cell (*66*). Based on machine learning, it may be possible to identify a neutron component in a mixed field, based on the distribution of micronuclei numbers in binucleated cells. Through the evaluation of the distribution of micronuclei per binucleated cell, some insight on photon to neutron doses has been obtained. Photons produce a Poisson distribution of micronuclei; however, neutrons result in an over-dispersion of binucleated cells with high numbers of micronuclei which are not Poisson-distributed. As such, parametric analysis was used to evaluate micronuclei distributions to predict the type of exposure (*66*).

Transcriptomics research has also shown that while some genes are unaffected by a 3 Gy photon dose, the introduction of as little as a 5% neutron component causes an altered gene response (*67*). Certain pathways such as ubiquitin were affected by all radiation types and doses, while other pathways such as the eukaryotic initiation factor 2 signaling pathway were affected by neutron radiation and not X-ray exposure. These finding could potentially allow for distinction between neutron and photon exposures.

Dr. Evagelia Laiakis highlighted the effects that neutrons can have on metabolomics, and its subcategory lipidomics, demonstrating that a snapshot of metabolomic perturbations can be used to explore the biochemical differences that take place after radiation exposure (*68*). When a specific amount and type of radiation exposure is administered, it produces a defined biological response that can be evaluated using blood and urine samples. Significant qualitative and quantitative differences between the radiation qualities can be identified using variations in biomarkers and different tissues, with some responses changing based on time elapsed after exposure. Metabolomics studies detect small molecules ($<$1 kDa) present in biofluids (e.g., blood, serum, saliva, urine, etc.) or tissues, to provide a snapshot of the metabolomic profile of an organism (*68*). Changes can be tracked based on specific stressors or exposures. To understand the effects of neutrons on metabolites, simulations can be conducted in an accelerator-based neutron irradiation facility, such as the Columbia University Radiological Research Accelerator Facility (RARAF) (*69*). In fact, this facility was designed to produce a neutron spectrum similar to that estimated in the Hiroshima neutron spectrum (*70, 71*). Using this facility, C57BL/6 mice received either 1 Gy neutron or X-ray irradiation, with samples collected at day 1 or 7 postirradiation (*68*). Using volcano plots, clear differences were found in urine, serum and lipid metabolites. Neutron irradiation led to the identification of four omega-6 and omega-3 free fatty acids that decreased at day 1 after neutron irradiation, compared to control or X-ray-irradiated cohorts. At day 7, the identified metabolites between neutrons and X rays were difficult to distinguish. While the effects were small, changes were noted in the neutron irradiated samples that were not seen in X-ray irradiated samples, compared to control. This study demonstrated that neutrons increase metabolic dysregulation compared to X rays. It is important to note that these exposures were comprised of neutrons or X rays, so the effects of mixed fields are unknown.

Another study showed that a small percentage of neutrons in a mixed field can cause perturbations in the metabolome, shifting it towards a pro-inflammatory state (*72*). Mice were exposed to a mixed-field of neutron and gamma-ray doses, where the neutron fractions spanned 5–25%. Serum samples were collected at day 1 and 7 postirradiation and a lipidomic analysis was conducted. Increases were noted for triacylglycerides (TGs), phosphatidylserines (PSs), lysophosphatidylethanolamines (LPEs), and lysophosphatidylcholines (LPCs) at day 7 rather than day 1, whereas phosphatidylcholines (PCs) remained largely unchanged. Diacylglycerides (DGs) decreased in mixed-field compared to photon-only irradiated samples. In addition, highly unsaturated lipid molecules exhibited the greatest changes in mixed field compared to photon-alone irradiated samples. Understanding when changes occur can help predict the outcome of an individual exposure, such as alterations in the LPC to PC ratio that can be indicative of inflammation. Tracking this ratio over time and between different neutron exposures can provide insight into the effects neutrons may have on the lipidome. Studies are still ongoing, and differences have been found based on the radiation quality. Network analysis using the Kyoto Encyclopedia of Genes and Genomes (KEGG) has revealed distinct changes in DNA damage, amino acid, and energy-related metabolite-protein interactions. Finally, tissue analysis of heart, lung and spleen are also being conducted.

MCMs and treatments. As described above, the ever-increasing threat of nuclear terrorism is not only a national security concern but a critical public health issue for people across the globe. Detonation of an IND would inflict damage and result in significant mortality and injuries from acute radiation exposure for a large number of people (*4*). An additional concern is the biological impact of neutrons produced during a detonation. As discussed above, high-energy photons (gamma rays) are likely to contribute a major portion (80–90%) of the dose received, but neutrons will likely contribute much more than 10–20% to the overall health risks. Research in the field has illustrated that neutrons elicit a more complex biological response and the extent of their influence on the efficacy of current treatments for ARS is not yet fully understood.

Both past and present incidents compel the radiation research community to continue to better understand the life-threatening effects of acute radiation exposures, and in particular, mixtures of fission neutrons and gamma-ray photons. Tactical or strategic use of nuclear weapons, possible terrorist detonation of such weapons or radiation

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dispersal devices (RDDs), the nuclear disasters at Chernobyl and Fukushima, and use of atomic bombs in Hiroshima and Nagasaki, all underscore the gravity of this work. Neutron research being conducted at AFRRI includes both *in vitro* and *in vivo* mixed-field radiation studies to elucidate their effects on immune cells. In addition, both small and large animals have been used to identify MCMs that might be useful against a combination of neutron and gamma radiation.

Dr. Lynnette Cary presented the dose radiation response data for a CD2F1 mouse mixed-radiation model. Mice received total-body irradiation (TBI) at 1.5 Gy–6.08 Gy of neutron-to-gamma ratio of 67/33%, at a dose rate of 0.01 Gy/s (0.6 Gy/min) using a TRIGA nuclear reactor. Sublethal administration (<4.5 Gy) of mixed-field radiation (67% neutron exposure) preferentially led to a reduction in the number of circulating peripheral blood cells, bone marrow cells (with reduced function), T cells in the spleen and lung (but not in the liver), and an altered circulating cytokine profile. Mixed-field radiation also resulted in an altered bacterial milieu and bone marrow cellularity. Using this mixed-field model, a number of MCMs were tested to date; Neupogen, Neulasta, CDX-301, and ALXN4100TPO showed promise in mitigating injuries during mixed-field radiation scenarios (*73*).

Dr. Juliann Kiang presented data from a radiation combined injury B6D2F1 mouse model (skin wound and radiation) with gamma-ray (^{60}Co) and mixed-field irradiation; with mixed-field exposures, the median wound closure time increased from 7 days (no radiation exposure) to 12 days (gamma-ray; 7 Gy), 16 days (neutron/neutron + gamma rays = 0.95; 2.5Gy), and 18 days (neutron/neutron + gamma rays = 0.7; 3.5Gy), respectively (*74, 75*). Male and female B6D2F1 mice received TBI consisting of a neutron-to-gamma ratio of 67%/33%, with increasing doses (0, 3, 6, 12 Gy) of gamma rays and dose rates of 0.6 Gy/min and 1.9 Gy/min. Serum cytokine analysis revealed that G-CSF and IL-18 levels increased in a dose rate-dependent manner in gamma-ray irradiation alone, but not with mixed-field irradiation. Both cytokines were observed to be radiation dose-dependent in mixed fields but were not sex-dependent (*76*).

Long-term health effects. NASA recently funded a study to investigate the efficacy of a low-dose aspirin regimen against high-LET radiation-induced hepatocellular carcinoma.[5] This study was conducted at the Colorado State University neutron facility and included a chronic exposure of 0.4 Gy of ^{252}Cf neutrons. Studies were performed using a panoramic irradiator loaded with 80 μg (1.6 GBq) of ^{252}Cf housed in a concrete shielded building (Fig. 2). The facility has a set-up of 18 racks that hold 10 cages with 5 mice per cage. The racks form an arc 180 cm from the source, providing capacity for up to 900 mice to be studied simultaneously. The mixed-field fluence is from a combination of neutrons and photons directly from the source as well as scattered particles from the concrete walls and floor. Photon dosimetry was performed using a neutron-insensitive GM counter and CaF_2 TLDs. TEPC were used for neutron dosimetry, and radiation quality determination and measurements were made with a full set of racks, cages and 900 mouse phantoms. The photon contribution was set to 20% of the total dose and the instantaneous dose rate (mGy/h) was configured to keep the daily dose at 1 mGy/d by adjusting exposure times gradually from 8 h/day initially to 21 h/day after 400 days. The uncertainty for the total dose rates delivered to mice was estimated to be ±20%, taking into account rack-to-rack variations and random positions of mice in each cage. The measured distribution of dose versus LET in tissue, using the TEPC, revealed that 95% of the dose from the neutrons was delivered by recoil protons, and the dose average LET was found to be 68 keV/μm. C3H male mice received 6 or 18 months of chronic neutron irradiation. Results are being analyzed to determine the efficacy of low-dose aspirin to reduce tumor initiation and proliferation when given prophylactically.

Dr. Marjan Boerma presented studies on the cardiac effects of chronic, low-dose-rate, high-LET irradiation, which were performed in collaboration with the Colorado State University Specialized Center of Research on Carcinogenesis. Both male and female mouse models received chronic low-dose-rate neutron irradiation and the effect on cardiac function was assessed using echocardiography. Echocardiography was performed on female BALB/C mice ~400 days after initiating the chronic neutron irradiations (total dose of 0.12, 0.2 or 0.4 Gy). These studies revealed a significant decrease in left ventricular fractional shortening (indicative of contractile function) and an increase in left ventricular posterior wall thickness in animals that received the high-dose (0.4 Gy) irradiation. These results are suggestive of pathologic overload and hypertrophy. Similar studies were performed on male C3H mice ~400 days after initiating the same chronic irradiations. Echocardiograph results in the males showed a clear impairment in left ventricular fractional shortening and increases in left ventricular wall thickness, consistent with the neutron irradiated female BALB/C mice described above. These results are consistent with the studies performed under the Janus experiments, where cardiac responses to fission spectrum neutrons at a mean energy of 0.8 MeV were evaluated. In these experiments, both single-dose (0.8 or 2.4 Gy) and protracted irradiation regimens (24 weekly fractions to a total of 0.2–2.4 Gy) induced significant radiation injury in the myocardium, coronary arteries and aorta in a mouse model (*77–79*).[6] Others reported that cardiovascular mortality increased in a dose-dependent manner (*58*).

[5] Task book: Biological & Physical Sciences Division and Human Research Program. FY2019. Washington, DC: NASA Research and Educational Support Systems; 2020. (https://bit.ly/3963afe)

[6] Task book: Biological & Physical Sciences Division and Human Research Program. FY2020. Washington, DC: NASA Research and Educational Support Systems; 2020. (https://bit.ly/3rYvrNv)

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FIG. 2. Panoramic irradiator housed in a concrete shielded building (53 m^2) located at Colorado State University. The facility has a set-up of 18 racks that hold 10 cages with 5 mice per cage. The racks form an arc 180 cm from the source, providing capacity for up to 900 mice to be studied simultaneously.

Tissue analysis and echocardiography were also completed in rats that received low-dose-rate neutron irradiations in this facility (*80*). Male Long-Evans rats were evaluated by echocardiography immediately after 400 days of chronic neutron irradiation (total dose of 0.4 Gy). These studies showed no significant effect of radiation on left ventricular function or morphology; however, a small, but statistically significant increase in isovolumic relaxation time (indicative of slower myocardial relaxation) was seen. This finding was thought to represent the early stages of left ventricular stiffening and diastolic dysfunction, which typically precede wall thickening and systolic dysfunction.

Computational studies. Dr. Robert Prins provided an overview of DTRA-funded work using computational human phantoms to estimate neutron dose received from a mixed gamma/neutron radiation spectrum (*81*). The gamma-ray and neutron spectra must be separated or deconvoluted from each other in order to use these to estimate the neutron dose component (*6*). The computational KT-Man2 phantoms used to determine the neutron radiation dose received by specific organs at a survivable distance from ground zero (1–2 kM) were developed by the Radiation Safety Information Computational Center at Oak Ridge National Laboratory (ORNL; Oak Ridge, TN). Monte Carlo N-Particle Transport Code (MNCP6.2) developed at Los Alamos National Laboratory was the computational modeling code used for this study.[7] To model cell fluence (particles/cm^2) and energy deposition (MeV/g), Tally 4 and 6 were used, respectively. Four incident directions were included: anterior-posterior (AP), posterior-anterior (PA), right lateral (RL), left lateral (LL). Environmental parameters were also adjusted to account for atmospheric (i.e., dry vs. wet air) and soil scattering (i.e., Western soil).

Computational modeling showed that the greatest amount of tissue damage occurs immediately after the prompt radiation burst, where the body is exposed to the highest dose ($<$1 s). Beyond the initial burst ($>$1 s), neutron doses are negligible and do not contribute to human tissue damage. Tissue activation was not expected to be a significant contribution to final dose ($<$0.3%), and similarly, computational estimates were not significant for ground scatter. A significant directional dependency to total dose was determined, with the left side facing the detonation having the lowest absorbed dose, particularly for the spleen and small intestinal wall. Organ-specific doses were highly dependent on the position of the phantom, where the doses to the lung and small intestinal wall were proportional and more significant when facing the source. The value of computational studies in examining neutron exposure scenarios was well-illustrated, but also provided insight on

[7] A general Monte Carlo N-particle (MCNP) transport code. Monte Carlo methods, codes, & applications group (Abstract). Los Alamos, NM: Los Alamos National Laboratory. (https://mcnp.lanl.gov/)

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how other computational approaches might be used to better understand and interpret neutron experimental studies by estimating tissue-specific doses.

Dr. Stephen Egbert discussed the details of neutron dose calculations in epidemiology cohorts in Hiroshima and Nagasaki to determine the RBE of neutrons (*82*). The ''Little Boy'' Hiroshima spectrum was iron-moderated with fast neutron energies ranging from 100 keV–1 MeV with a small epithermal component, while the ''Fat Boy'' Nagasaki spectrum was hydrogen-moderated with fast neutron energies ranging from 1–5 MeV with a very large epithermal component. Original dosimetry calculations estimated that the Nagasaki neutron energy was 4 orders of magnitude lower than 1 MeV, with only 1% contribution of fast neutrons. Since it was thought that low-energy neutrons would not pass through air and to the ground, Nagasaki was considered to have a low neutron dose. Furthermore, since Hiroshima was estimated to have 100× the number of fast neutrons, it was believed that the neutron dose was much larger than Nagasaki.

To ensure accurate measurements, new dosimetry systems, DS86, DS02 and DS02R1, were developed to reassess the atomic bomb neutron dosimetry. Using DS02, the largest radiation components were attributed to: 1. Primary delayed gamma rays; 2. Prompt secondary gamma rays; 3. Prompt primary gamma rays; and 4. Delayed secondary gamma rays. At prompt ground range, the estimated neutron dose component was estimated to be 6% at Hiroshima and 1% at Nagasaki. A delayed neutron component was estimated at 0.5% at both Hiroshima and Nagasaki. In 1986, DS86 was developed by the Radiation Effects Research Foundation (RERF) to simulate a multi-component system to account for air transport leakage, shield propagation (i.e., terrain and wooden house shielding) and organ dosimetry. This new dosimetry system showed that terrain shielding varied by radiation source. Gamma-ray doses were significantly reduced by dense obstacles, whereas neutron doses were not affected. In addition, the human body was shown to shield neutron radiation better than gamma rays. Wooden houses were equal at shielding both neutron and gamma-ray sources and since Japanese houses were made of mostly wood, they shielded neutrons more effectively. Ultimately, both cities were unaffected by neutron-produced fission products because the bombs detonated mid-air and the bomb debris remained in the ''atomic cloud,'' which drifted eastward to other locations. Most importantly, neutron dose time of duration is short; for example, fast neutrons (inelastic-elastic collisions) occur around 1 μs, thermalized neutrons are captured between 10–100 μs, and the delayed neutrons emitted from the fission products inside the fireball occur at 0.1–3 s. Normally the delayed neutrons are not considered a significant radiation source, but since they were dispersed mid-air with no shielding, the small neutron dose was enhanced. As a result, the small percentage of delayed gamma-ray and neutron radiation from the ''atomic cloud'' was the largest survivor radiation dose component. While neutrons were certainly a factor, it is important to consider that the gamma-ray dose alters the neutron dose, and the RBE value of neutrons in a mixed field is much lower than in a pure neutron field (*83*). Therefore, RERF showed that the RBE was more dependent on the gamma-ray dose received. Using these refined dosimetry systems, the neutron doses were re-calculated using the DS86 method developed by the RERF and were shown to be much lower in both Hiroshima and Nagasaki than previously thought.

DISCUSSION

The workshop brought to light the many factors of neutron exposure that can impact the biological response, and the importance of detailed and consistent dosimetry approaches. The need for harmonized reporting of exposure and experimental parameters was highlighted. Such parameters are essential to interpreting results across studies and in translating observed effects between species. A selection of conditions essential to reproducibility and interpretation of study results was further discussed during the workshop. These conditions are summarized below.

Recommendations for Reporting Exposure and Dosimetry Specifications

Studies should clearly delineate any radiation parameters when using neutron or mixed-field exposures. The neutron/photon spectra, peak and mean neutron energy, and gamma-ray energies should be reported. For mixed-field reactor exposures, the neutron-to-gamma ratio or the percentage neutron component of dose is essential for contextualizing the results of the study. Pulsed vs. continuous, unilateral vs. bilateral, and whole-body vs. partial-body exposure aspects must be reported and considered when evaluating and translating results. Many radiobiological studies neglect to specify the type of dose reported; however, free-in-air, midline tissue, or bone marrow doses are all commonly reported values, which result in significantly different values, even for gamma-ray exposures. Due to the limited range in tissue, the differences for neutron doses are even more significant and may warrant reporting in terms of each critical target organ dose. Finally, dose rate or fractionation must always be reported, since biological effects may vary with different dose rates.

Animal Model Parameters

The experimental factors that are relevant for consideration in reporting results of neutron and mixed-field animal model studies include: species, age at exposure, sex, number of animals, groups, types of analyses, experimental design, and sampling strategy, such as time(s) after exposure. More recently, measurement of stress responses in control, sham-irradiated animals have highlighted their necessity in experimental studies. If the focus of a study is

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to compare results to another radiation type, details regarding the comparator radiation exposures are required to make a complete and accurate analysis. If a study reports RBEs, the biological end point(s) as well as the radiation spectrum used for the RBE must be specified, and whether its effect is deterministic or stochastic should be considered.

While these experimental details are essential to neutron studies and data reporting, the list is not comprehensive, and other aspects of dosimetry and study design may need to be considered. Researchers in the field can learn from the laboratories that publish details on their dosimetry methodology. This knowledge-sharing across the radiation research community will lay the groundwork for eventual dosimetry harmonization. Researchers should first assess available resources at their institution that will allow them to perform proper quality assurance. Most importantly, reliable oversight by a radiation physicist who can conduct accurate dosimetry and provide guidance to experimental design is necessary, rather than relying on historical dosimetry calibrations or device manufacturer data.

Many historical studies included varying neutron exposures (differences in doses, dose rates, percentage neutron, neutron energy, unilateral or bilateral exposure, etc.) making it extremely difficult to conduct a thorough analysis and interpretation to estimate health effects in humans. It is unclear whether new and highly focused animal studies are warranted, or whether there are methods available to leverage existing data. Regardless, strategically designed, novel experiments, especially in larger animals, could provide a straightforward means of filling specific data gaps. However, examination of dose- and energy-dependent RBE effects would require many studies to be conducted to obtain sufficient data that fully describe those dependencies, thus making the reliance solely on large animal studies inefficient and unfeasible. In addition, neutron facilities are limited and those in existence must be monitored closely using National Institute of Standards and Technology (NIST) standards (*84*).

With the vast amount of radiobiological data available, the need to identify ways to leverage historical data was acknowledged. As such, methods to estimate the organ doses from whole-body irradiation animal studies may provide more insight on organ-specific effects for a given neutron energy and dose. Such organ dose reconstruction might be possible through the use of Monte Carlo simulations and computational phantoms. Furthermore, the same computational approaches, as illustrated in the scenario simulations presented during the workshop, might be able to facilitate the design of relevant *in vitro* studies utilizing innovative technologies, such as 3-D tissue models and organ-on-a-chip technology (*64*). Such *in vitro* studies could be conducted more efficiently, but may require a modified exposure profile, perhaps guided by computational studies, to reflect the actual exposure the specific organ would receive after the neutron component has interacted with other tissues surrounding the organ. Computational human phantoms, created by the National Cancer Institute (NCI; Bethesda, MD), can be used to estimate external exposures, organ depth distributions and dose estimation (*85–87*). Perhaps this technology can be adapted to help with neutron dosimetry, and researchers can learn from the valuable contributions of the radiotherapy community.

CONCLUSIONS

Current global incidents help illustrate the relevance of furthering an understanding of neutron and mixed-field exposures. For example, nuclear-armed neighbors, India and Pakistan, recently pulled back from the brink of a military confrontation over the contested Kashmir region. North Korea's nuclear testing in late 2017 had an estimated yield of 70–280 kT, and that country has been simultaneously testing ballistic missile delivery systems that supposedly can reach the U.S. On August 2, 2019, the United States announced that it would formally withdraw compliance from the Intermediate-Range Nuclear Forces Treaty (INF). This treaty, signed by Presidents Reagan and Gorbachev in 1987, banned the development and deployment of ground-based ballistic and cruise missiles in the 300–3,400-mile range. In addition, with the announcement of the Artemis program comes new concerns regarding radiation health risk for astronauts as the program advances at an accelerated rate to establish a sustainable long-term presence on and around the Moon by 2028. Along with this exciting venture comes additional radiation considerations due to albedo neutrons that astronauts will be exposed to during extended stays on the lunar surface for the first time in the history of human space exploration.

Although multiple neutron radiobiology programs were initiated between the 1940s and 1970s, significant progress has been made in recent years with regard to the importance of experimental design and the number of variables that impact biological responses. Therefore, this workshop intended to revisit what is currently known about the health effects in current neutron exposure scenarios. As such, the complexity of neutron exposures and current understanding of their biological effects were discussed, as were the gaps in knowledge, primarily the lack of dosimetry harmonization in neutron studies, which limits the ability to use these studies to estimate the health effects of neutron exposures. The workshop increased the awareness of the potential effect of neutron exposures in different scenarios and helped identify important factors (dose, dose rate, and the description of radiation spectrum used) when designing neutron exposures in biological experiments. All these factors are essential for the harmonization of neutron dosimetry, which leads to more effective and informative studies. Collectively the workshop and the contributions of the participants will help improve science and preparedness. In due time, it is hoped that these efforts will translate into updates of computer coding for dosimetry estimates, policy, and investments by research funding agencies.

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ACKNOWLEDGMENTS

We express our deep appreciation to all of the speakers listed in Table 1, who provided their valuable insights during the workshop and for their review of this manuscript. Thank you to David Schauer (AFRRI) and Paul Blake (DoD) for ensuring a successful workshop. We also thank NIAID colleagues who reviewed the manuscript prior to submission (David Cassatt, Andrea DiCarlo, Brynn Hollingsworth, Merriline Satyamitra, and Thomas Winters). The opinions contained herein are the private views of the authors and are not necessarily those of the NIAID, NIH, the DoD, NASA, or the U.S. Army.

Received: August 28, 2020; accepted: January 11, 2021

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