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Estimation of Radiation Doses to U.S. Military Test Participants from Nuclear Testing: A Comparison of Historical Film-Badge Measurements, Dose Reconstruction and Retrospective Biodosimetry

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Retrospective radiation dose estimations, whether based on physical or biological measurements, or on theoretical dose reconstruction, are limited in their precision and reliability, particularly for exposures that occurred many decades ago. Here, we studied living U.S. military test participants, believed to have received high-dose radiation exposures during nuclear testing-related activities approximately six decades ago, with two primary goals in mind. The first was to compare three different approaches of assessing past radiation exposures: 1. Historical personnel monitoring data alone; 2. Dose reconstruction based on varying levels of completeness of individual information, which can include film badge data; and 3. Retrospective biodosimetry using chromosome aberrations in peripheral blood lymphocytes. The second goal was to use the collected data to make the best possible estimates of bone marrow dose received by a group with the highest military recorded radiation doses of any currently living military test participants. Six nuclear test participants studied had been on Rongerik Atoll during the 1954 CASTLE Bravo nuclear test. Another six were present at the Nevada Test Site (NTS) and/or Pacific Proving Ground (PPG) and were believed to have received relatively high-dose exposures at those locations. All were interviewed, and all provided a blood sample for cytogenetic analysis. Military dose records for each test participant, as recorded in the Defense Threat Reduction Agency's Nuclear Test Review and Information System, were used as the basis for historical film badge records and provided exposure scenario information to estimate dose via dose reconstruction. Dose to bone marrow was also estimated utilizing directional genomic hybridization (dGH) for high-resolution detection of radiation-induced chromosomal translocations and inversions, the latter being demonstrated for the first time for the purpose of retrospective biodosimetry. As the true dose for each test participant is not known these many decades after exposure, this study gauged the congruence of different methods by assessing the degree of correlation and degree of systematic differences. Overall, the best agreement between methods, defined by statistically significant correlations and small systematic differences, was between doses estimated by a dose reconstruction methodology that exploited all the available individual detail and the biodosimetry methodology derived from a weighted average dose determined from chromosomal translocation and inversion rates. Employing such a strategy, we found that the Rongerik veterans who participated in this study appear to have received, on average, bone marrow equivalent doses on the order of 300–400 mSv, while the NTS/PPG participants appear to have received approximately 250–300 mSv. The results show that even for nuclear events that occurred six decades in the past, biological signatures of exposure are still present, and when taken together, chromosomal translocations and inversions can serve as reliable retrospective biodosimeters, particularly on a group-average basis, when doses received are greater than statistically-determined detection limits for the biological assays used.

INTRODUCTION

Studies of past ionizing radiation exposures that were received under unexpected or difficult-to-reconstruct conditions are particularly valuable for the purposes of improving methods to retrospectively assess doses that

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may be received in future scenarios, as well as to improve our understanding of the limitations of the available dose estimation techniques. In this work, we studied a group of U.S. military test participants (10 veterans and 2 civilian contractors to the military) who, according to U.S. Department of Defense (DOD) records, received the greatest nuclear test-related radiation exposures of any currently living group of U.S. test participants. These individuals participated in a variety of nuclear testing-related activities in the 1950s and 1960s. The study of these individuals is intended to contribute to a better understanding of three specific dose assessment techniques currently available and to quantify, to the extent possible, the magnitude of the doses received by this high-dose exposure group.

During the 1950s and 1960s, U.S. military personnel and (occasionally) civilians participated in a variety of military-related activities related to the testing of nuclear weapons. Activities of both military and civilian contractors included making weather observations, participating in military ground maneuvers and flying through nuclear debris clouds to obtain samples of radioactive debris. Some of these military and civilian participants were exposed, on occasion, to prompt gamma and neutron radiation, but more frequently, to residual gamma and beta radiation from airborne radioactive debris and deposited nuclear fallout.

Doses to U.S. military test participants have previously been estimated under the Nuclear Test Personnel Review (NTPR)[2] program directed by the Defense Threat Reduction Agency (DTRA) within the Department of Defense. The NTPR program was initiated in 1978 after a series of public laws were implemented due to concerns about radiation exposure of veterans and military test participants during nuclear atmospheric testing. Legislation passed in 1988 by Congress (Radiation-Exposed Veterans Compensation Act of 1988, Pub. Law 100–321; https://bit.ly/2SzfXQV) authorized a compensation program for military test participants and, for some claims, required DTRA to perform a detailed dose reconstruction. These dose reconstructions for compensation tended to overestimate dose, as they were typically based on ''claimant-friendly'' assumptions (*1*).

Efforts in recent years have been made to utilize DOD data on exposure scenarios and available personal dosimetry to estimate unbiased radiation exposures and organ doses to cohorts of exposed military test participants (*2–5*). Till *et al.* (*3*) discuss an approach to dose estimation for military test participants that corrects many of the conservative assumptions in dose estimation procedures previously used for the purpose of compensation. Their methodology attempts to determine the scenario of exposure for each individual military test participant using all available information, and then calculates a dose and an estimated uncertainty without the high-sided bias often present in the compensation programs. Following up on that work, Beck *et al.* (*5*) estimated bone marrow and male breast doses to ~2,000 exposed military test participants, representing a subset of a ~115,000 military participants being studied as part of the One-Million U.S. Workers and Veterans Study of Low-Dose Radiation Health Effects (*4*). The red bone marrow (RBM) doses for the subcohort described in (*5*) averaged approximately 6 mGy and the maximum calculated RBM dose for that study was 108 mGy.

Considerable effort has been put forth in the U.S. and elsewhere to develop strategies for retrospective dose assessments after mass exposure events. Such methods include a range of techniques including physical measurements, devices for monitoring, the use of theoretical modeling and environmental data for dose reconstruction, and uncertainty analysis. The goals of the current study include providing a better understanding of the data requirements and limitations of present-day retrospective dose assessment methods by comparison of three classes of methods and to quantify the doses received by this group of exposed military test participants.

MATERIALS AND METHODS

Study Concepts and Design

Radiation exposures during above-ground military nuclear testing occurred in the mid-1950s and early 1960s, meaning that approximately six decades have elapsed between the time of exposure and the current assessment. The design of the current study includes both historical and contemporary elements. The historical component consists of recorded film badge and other data such as exposure scenarios for various military units that can be used in dose reconstruction models. The contemporary component consists of collection of peripheral blood samples and cognitive interview data, the latter being used to supplement the historical data and to support estimation of other sources of exposure, e.g., from medical procedures and natural background radiation, both of which continued until the time of blood draw in 2015.

Herein we compare findings from three strategies of estimating bone marrow dose for military test participants who participated in nuclear testing-related activities in the 1950s and 1960s: 1. Use of historical personnel monitoring data alone (film badge or surrogate badge data); 2. Dose reconstruction using various combinations of historical data; and 3. Retrospective biodosimetry using two types of radiation-induced chromosome aberrations, specifically, inversions and translocations. Methods 2 and 3 were supplemented with data obtained from cognitive interviews with each veteran. In this work, we focus exclusively on bone marrow dose due to the retrospective nature of the biodosimetry analyses, which directly estimates the dose to stem cells in the marrow. Since the true dose for each military test participant is not known, and because there is no gold standard method for assessing exposures that occurred many decades ago, we studied the level of agreement, or congruence, of estimated doses derived from a suite of alternative methods. To assess congruence of the methods, we examined both correlation and systematic differences of doses from these different methods.

To demonstrate how dose-reconstruction estimates depend on the degree of individual information available, we provide five estimates of external dose, each constructed with varying, but increasing degrees of information. For comparison, we present an estimate of external dose from the DOD Nuclear Test and Review Information System (NuTRIS). We also provide a dose-reconstruction estimate of internal

[2] Nuclear Test Personnel Review (https://bit.ly/2pqNywi).

TABLE 1
Codes for Dose Reconstruction and Assessment Scenarios for Estimating Bone Marrow Doses from Military Service (m) or Personal (p) Exposure Outside the Military

Codes for dose reconstruction and assessment scenarios	Explanation
Location	Rongerik or Nevada test site/pacific proving ground
A	Dose reconstruction (m) based on a generic exposure scenario, i.e., scenario where no personal or individualized data are used.[a]
B	Dose reconstruction (m) based on all data other than interview and personal film badge or cohort film badge data.
C	Film badge only-based dose estimation (m) by substituting individual film badge or cohort film badge data for reconstructed doses in scenario B.
D	Dose estimation (m) based on combining individualized information from interviews with film badge dose data from method C.
E	Dose estimation (m) using all available information including film badge dose information. May differ slightly from method D in that it can include general information on exposure scenario gained from interviews that are not in military records or NuTRIS (includes neutron doses for 2 veterans).
Int	Dose reconstruction (m) for internal dose based on modeling.
Med	Dose reconstruction (p) for external dose from medical radiation based on information derived from personal interviews.
Bkg	Dose reconstruction (p) for external dose from natural background radiation estimate based on age at time of blood draw and typical annual external exposure rate.
Tr	Biodosimetry-based total dose[b] estimation based on chromosome translocation frequency.
Inv	Biodosimetry-based total dose[b] estimation based on chromosome inversion frequency.
Tr/Inv	Biodosimetry-based total dose[b] estimation based on inverse variance-weighted average of chromosome translocation and inversion dose estimates.

[a] Because of the absence of individual information, those individuals sharing the same ''generic'' exposure scenario would be assigned the same dose, characteristic of the general area.

[b] ''Total'' refers to cumulative bone marrow dose from all sources.

dose from test-related activities; an estimate of personal medical external dose based on information derived from individual cognitive interviews, and an estimate of external dose from natural background radiation based on age alone. The latter estimates are included primarily to give context to the magnitude of the military-related exposures.

Table 1 summarizes each dose estimation method and presents codes to identify each method in the findings and discussion. As noted, no single method theoretically qualifies as a gold standard. Therefore, congruence was sought to determine which methods were in best agreement and might, therefore, be useful in future assessments. Implicit in this design was the expectation that as additional information is incorporated, the estimated doses should become closer to the true dose both on an individual and group-average basis.

Study Population Identification

The population studied was derived from a large cohort of over 115,000 U.S. military personnel who participated in at least one of the 230 atmospheric nuclear weapons tests from 1945 through 1962 (*3, 5*). Available information on the military test participants included name, military service number, date of birth, gender, pay grade, rank or rating, unit membership and dates during participation, permanent unit, and dates of entry to and separation from military service.

The goal of the participant identification phase was to identify the nuclear weapons test participants with the highest recorded physical doses who were still alive in 2014. One group identified for possible participation in the study was comprised of military weather observers stationed on Rongerik Atoll for the CASTLE Bravo test in 1954. Rongerik is one atoll in the Marshall Islands, a group of coral atolls that include the Bikini and Enewetak sites that constituted the U.S. Pacific Proving Ground (PPG) during the years of atmospheric nuclear testing. It was known from earlier dose reconstruction efforts that the military men stationed on Rongerik at the time of BRAVO were exposed to unexpected fallout resulting in estimated air kerma doses of approximately 940 mGy (*6–8*). It has long been suspected that exposures of the military weather observers on Rongerik were the highest of any group of U.S. military participating in weapons testing. These exposures were of special interest since, despite the high exposures, there have been no confirmatory biological assays conducted to assess individual exposures.

Based on information available from the DOD and public records, we identified 28 weather observers exposed on Rongerik as well as 31 military test participants who took part in activities at the Nevada Test Site (NTS) and/or the Pacific Proving Grounds (PPG) but for Rongerik. All had recorded badge doses $>$200 mSv (Fig. 1). This minimum dose requirement was chosen to maintain a reasonably high likelihood that the dose for each military test participant could be evaluated by chromosome aberration analysis (*9, 10*).

The 16 of these 59 military test participants who were known to be alive in 2010 were contacted in 2014 to determine their willingness to participate in the study, to be interviewed and provide a blood sample. Two died before the blood draw could be performed, one refused due to ill health and one could not be located. Overall, 12 servicemen agreed to participate. Those who agreed to participate included the six living veteran weather observers (Air Force and Army) stationed on Rongerik in 1954 and another six, comprised of two close-in test observers, two ''cloud samplers'' (men whose mission was to fly through nuclear debris clouds and capture air and debris samples) and two civilian contractors providing specialty technical or research services.

Because chromosomal translocation frequencies are known to increase with age (*11*), we enrolled a group of age-matched veterans who had been exposed to very minimal or no radiation in the military, to establish baseline aberration rates among a similar group of individuals. These ''control'' participants represented a group close in age and experience to the exposed military test participants, except with little or no radiation exposure from military activities. Thus, the purpose of the control participants was to establish baseline frequencies for chromosomal translocations and inversions to more accurately evaluate excess rates among the exposed military test participants. The control subject group was selected to be as similar as practical to the exposed group, i.e., they were military test participants, of the same average age (85 years) with the same smoking frequency (0.58 proportion of ''ever-smokers''). For this analysis, we assumed that exposures to medical radiation were similar for both the exposed and control subjects, approximately quantifying medical exposure

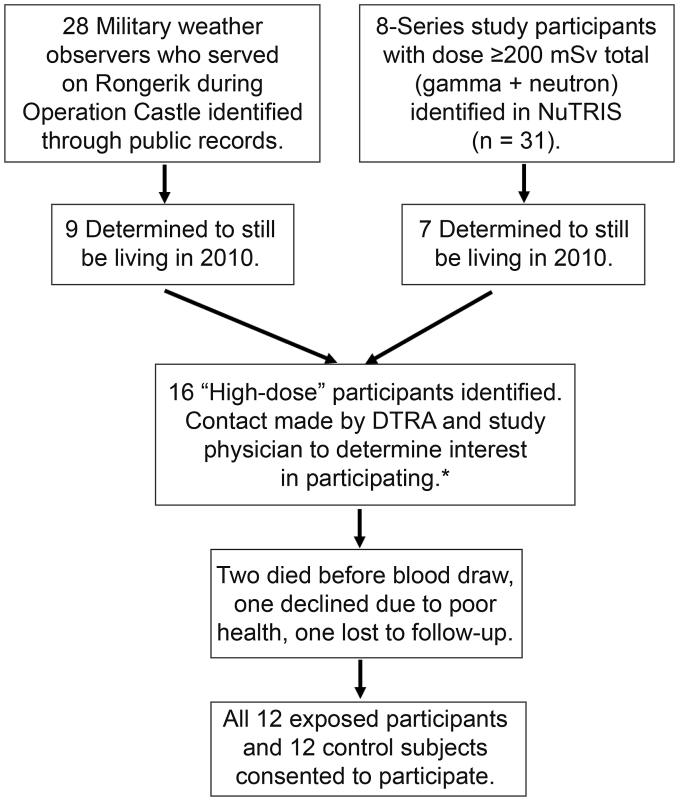

FIG. 1. Flowchart of steps leading to selection and enrollment of 24 participants for interview, blood draw and chromosome analysis.

based on interview data about the number of radiological procedures received. No participant in either group reported having chemotherapy or radiation therapy for cancer. We also assumed that exposure to background radiation was similar among both groups due to their near-equal ages. Although the same number of controls as exposed subjects were selected (12 of each), and they were approximately age-matched and gender-matched, control subject values were not applied in the analysis on a one-to-one basis. Rather, the control subjects were used to derive average values of baseline translocation and inversion rates, separately, for ''never-smokers'' and ''ever-smokers.'' Finally, six younger adult males (~25 years of age) were selected from the student body at Colorado State University (via response to a newspaper advertisement) to provide a blood sample from which *ex vivo* exposure calibration curves could be constructed for radiation-induced translocations and inversions. The age of the young adult controls was chosen to approximate the age of the military test participants at the time of their exposure [see (*12*)]. None were reported to be smokers.

Table 2 summarizes the populations studied, the data and sample collection activities and their purposes. All activities of this study were conducted under the review and approval mechanisms of the Special Studies Institutional Review Board (SSIRB) of the National Institutes of Health/National Cancer Institute, the Reliance Agreement between the Vanderbilt Institutional Review Board (IRB) and the National Institutes of Health/National Cancer Institute (NIH/NCI) IRB, and through a waiver on interview requirements by the Federal Office of Management and Budget (OMB).

Population Tracing

Tracing and determination of vital status was challenging because the Social Security number was not used as the military identification number until 1968 and was not readily available for every test participant. Thus, we also used mortality linkages based on military identification number and name and date of birth. The VA Beneficiary Identification Record Location Subsystem (BIRLS system) was a primary source of vital status information, supplemented with the Social Security Administration (SSA) Death Master File (DMF) and the National Death Index (NDI) (*13*). The SSA Service for Epidemiological Researchers confirmed alive status as did current records within VA BIRLS. Credit Bureau and online searches were also employed to confirm that a military test participant was living and to find their residential address.

Cohort Recruitment and Enrollment

Each of the 12 exposed and 12 control participants were initially contacted via telephone by a military manager from the NTPR program of the DTRA to explain that the NIH would be contacting them about a research study. This pre-study communication was intended to provide assurance to each potential participant about the study's legitimacy and importance. Each of the exposed and control participants was then contacted by phone from the study's physician collaborator (ABB), as agreed with the NIH IRB, to provide an explanation about the study and its general purposes and to determine individual interest in participating. All 24 of the potential participants

TABLE 2
Summary of Study Groups and Data Collection Purposes

	Group			
	Military weather observers (Air Force and Army)	Four military nuclear test participants plus 2 civilian contractors	85-year-old veteran controls (non-exposed)	25-year-old males
No. of participants	6	6	12	6
Location of direct or indirect exposure to nuclear testing radiation	Rongerik	NTS and PPG	na	na
Individual interview	✓[a]	✓[a]	✓[b]	✓[b]
Blood sample collection	✓	✓	✓	✓
Biodosimetry (translocations + inversions)	✓	✓	✓	✓
Analytic dose reconstruction	✓	✓	na	na
Use blood sample to establish baseline aberration rates	na	na	✓	na
Use blood sample for *in vitro* dose calibration curve	na	na	na	✓

Note. Rongerik = Rongerik Atoll, Marshall Islands; NTS = Nevada Test Site; PPG = Pacific Proving Ground.

[a] Individual interviews were performed to obtain information for dose reconstruction (military and personal medical exposure).

[b] Individual interviews were performed only to ascertain that the participant was never diagnosed or treated for cancer and to obtain smoking history.

TABLE 3
Summary of Exposure Sources and Available Data for Reconstructing Individual Doses of 12 Veterans Studied

Subject(s)	Exposure sources	Tests/years/ locations	Personal film badge? (Y/N)	Surrogate film badge? (Y/N)	Reconstructed exposure rates?[a] (Y/N)	Military Records available? (Y/N)	Personal interviews available? (Y/N)	Times and locations of potential radiation exposures available? (Y/N)
Six Air Force and Army weather observers	Fallout exposure[b] and decontamination activities.	BRAVO test/1954/ Rongerik	N	Y (one badge from deceased member of group)	Y	Y	Y	Y
Cloud sampler no. 1	In-cloud exposure.	PLUMBBOB series/1957/NTS	N	Y	N	Y	Y	Y
	Flew contaminated planes back to base.	1957/ NTS	N	Y	Y	Y	Y	Y
	Fallout exposure.	na						
Cloud sampler no. 2	Cloud exposure.	Multiple tests/ 1956, 1957, 1958	Y (36 badges for same individual)	Y	Y	Y	Y	Y
	Fallout exposure.	1956, 1958/PPG	N	Y	Y	Y	Y	Y
Observer no. 1	Direct gamma-ray exposure[c] + fallout.	SIMON/1953/NTS	Y (1 badge)	Y	Y	Y	Y	Y
	Direct neutron.	SIMON/1953/NTS	N	N	Y	Y	Y	Y
Observer no. 2	Direct gamma + fallout.	NANCY, BADGER, SIMON/1953/ NTS	N	Y	Y	Y	Y	Y
	Direct neutron.	NANCY, BADGER, SIMON/1953/ NTS	N	N	Y	Y	Y	Y
Civilian no. 1	Gamma-ray exposure from miscellaneous activities.	1953–1962/NTS and PPG	Y (14 badges)	N	N	Y	Y	Y
Civilian no. 2	Gamma-ray exposure from miscellaneous activities.	1951–1962/NTS and PPG	Y (~90 badges)	N	N	Y	Y	Y
	Fallout exposure.	1951/PPG	N	Y	Y	Y	Y	Y

Note. Rongerik = Rongerik Atoll, Marshall Islands; NTS = Nevada Test Site; PPG = Pacific Proving Ground.

[a] Reconstructed exposure rates refer to the time-dependent exposure rates originally estimated by the DOD from either measurements or models [revised in (*3*)] that were used to estimate total exposure for each individual from direct radiation and/or fallout based on known or assumed intervals of time when exposure occurred.

[b] Fallout exposure refers to exposure to gamma and X rays emitted from radioactive debris created by the detonation, either during or after deposition. The source of the radiation is usually beta decay but can include alpha decay.

[c] Direct gamma-ray exposure refers to exposure to prompt gamma rays emitted from the detonation itself.

agreed to receive a visit from a licensed phlebotomist who, at the time of the visit, administered a consent form, obtained a signature and performed a blood draw according to study protocol. A third-party contractor to the NCI again contacted each of the 12 exposed participants to schedule a date and time for a visit from NCI staff to conduct an individual cognitive interview. Interviews were held at the home of each of the 12 exposed participants, who resided in nine states from California to New York. A diagram of the participant selection process is provided in Fig. 1.

Interviews and Data Collection

Cognitive interviews are a reliable method to gather details about previous experiences (*14, 15*) and were used here to ascertain details about the exposures. The specific purpose of the cognitive interview in this study was to collect individual retrospective information about the situation and conditions under which exposure occurred for each participant, as a means of gathering information for dose reconstruction. Information on health conditions and some individual habits, e.g., smoking, was also collected. Prior to the start of each interview, the purposes and means of conducting the interview were explained to the subject, and a signed consent form obtained. Individual cognitive interviews were conducted by an experienced interviewer (SIS), accompanied by a senior radiation physicist (SLS), and used a NIH/ NCI SSIRB-approved interview guide. Interview data were recorded in duplicate and the audio was recorded when the subject gave written consent. Interviews were conducted in the home of each participant and took up to 1.5 h to allow the subject to recollect as much specific information about the exposure conditions as possible. A summary of collected data for each of the 12 veterans including exposure locations, sources and types of monitoring information available is provided in Table 3.

Personnel Monitoring Data: Film-Badge Data (Method 1)

Film badges were used extensively for personnel monitoring during the 18-year period of atmospheric nuclear testing (*16*). Film badge technology improved throughout the period of nuclear testing and was shown to be reliable for measurement of exposure greater than 0.1 R (Roentgen). The measurement of exposure by a film badge inherently has limitations, including energy sensitivity, changing sensitivity to variations in angle of exposure and limits of detection. Nevertheless, a film badge measurement associated with an identified soldier is a valuable type of data, particularly for individual retrospective dose assessment.

Depending on the specific nuclear test, branch of the military, and task assigned, film badges for personnel monitoring were either assigned and available on an individual basis, or one or more badges were issued for an entire company of men assigned to the same task. As discussed by Till *et al*. (*3*), for a large study of more than 115,000 atomic military test participants, approximately 25% of the military personnel had film badge records that accounted for 80% or more of their individual military dose. Those records, when available, can be used for making dose assignments to the individuals wearing the badge.

In the case of military test participants without an individual badge, there are several possibilities to derive and subsequently impute a surrogate dose value. First, film badge measurements for a soldier who performed similar duties can be used. An extension of that strategy is one in which all members of a unit are assigned similar duties, and a single ''cohort'' film badge is issued and used for personnel monitoring. In some of those cases, the measured value can assist in estimating dose to individuals in the cohort, e.g., for the SMOKY nuclear test (*2*). The issuance of a single badge for a unit did not, however, guarantee that the measurement would reflect the exposures of all individuals. This was particularly the case for Operation CASTLE in the Marshall Islands in 1954 (*3*).

Dose Reconstruction (Method 2)

The term ''dose reconstruction,'' as used here, pertains to applications of theory and measurements and may, but not necessarily, include personnel dosimetry measurements. While dose reconstruction has been used rarely for occupational and military exposure, it has been used extensively for civilian dose reconstruction after nuclear tests and detonations in Japan during WWII (*17*), Nevada (*18, 19*), Utah (*20, 21*), Kazakhstan (*22*), Marshall Islands (*23*) and New Mexico for the Trinity nuclear test.[3] Types of measurement data needed include environmental measurements of exposure rate, shielding factors and other parameters that might be used to estimate individual dose. Commonly used techniques include converting measurements of exposure rate in air (R per unit time) to air kerma and integrating over a known exposure period while accounting for radioactive decay and shielding of the individual by buildings or protective clothing or devices. The final step is to multiply by a conversion coefficient that relates air kerma to absorbed dose to bone marrow.

Note that the above definition for dose reconstruction contrasts with dose reconstruction for compensation in which historical film badge data, if available, is the starting point of the estimation process, and other information made available through military resources is used to refine the dose estimate. Even given the film badge data, complications can arise, e.g., the need to extrapolate measurements to the soldier of interest from sources not directly applicable, e.g., a group film badge or data from another soldier with similar job responsibilities. This latter step requires familiarity with military operations as well as dosimetry and physics. Note that in the current work, the more restrictive definition of dose reconstruction (theory and measurements with or without film badge data) was used because it was our intention to simulate possible real-world scenarios, i.e., situations where only environmental radiation data are available, or where only film badge or surrogate film badge data are available (either partially or fully complete).

Two important resources were available for the military records needed: the NTPR and NuTRIS. Film badge results and/or NTPR generic dose reconstructions for each military unit were often available as a starting point for estimating both external and internal exposure and organ doses. The NuTRIS database includes detailed information on individuals who participated in nuclear testing activities, including their military rating and military unit, where and when they participated, and their estimated external dose at those locations during those times. In addition to NuTRIS, other DTRA documents contain information on each of the 230 atmospheric detonations and estimated exposures for specific military units. Other data and reference material are available on military unit locations and activities including ships logs, photographs of facilities and maneuvers at the NTS and the PPG. Much of the detailed information available had been compiled to support estimation of dose for compensation programs for exposed military test participants (*24, 25*).

The general dose reconstruction approach is described elsewhere (*3*), and detailed procedures for estimating external dose to the RBM have also been published (*5*). For each of the external dose scenarios considered by dose reconstruction, the RBM dose was estimated by applying an exposure (R) to an RBM conversion of 6.5 mGy/R (*26* that assumes 2/3 of the radiation was incident rotationally and 1/3 isotopically). This approach accounts for unknown exposure geometries, and individual variability, and is reflected in the estimate of uncertainty, which, according to Beck *et al*. (*5*), can be characterized by a geometric standard deviation (GSD) of approximately 1.2.

Minor dose components. Internal dose was estimated by relatively simple modeling that primarily depended on the types of activities each exposed military test participant was involved in and the potential in those activities to ingest or inhale substantial amounts of radioactive material. The assessment of the internal RBM doses was based on our understanding of intakes of fallout radioactivity among the Rongerik weather observers (*27*). The intakes in that group were estimated from a measurement of ^{131}I in urine. The intakes of ^{131}I and other radionuclides were assumed to be predominantly due to the ingestion of fallout particles and this concept was used to estimate the intakes of other radionuclides using the relative radionuclide composition of fallout (*28*). The RBM doses per unit activity intake were calculated for each important radionuclide using the ICRP models recommended for adults and the fractional uptakes to blood from the gastrointestinal tract (*29*). Assumptions varied depending on a description of duties for veterans. For example, we assumed that cloud samplers were inside an airplane cabin with a source of purified air, which in those years was confirmed by whole-body counting to rule out internal contamination.

Doses to bone marrow from personal medical radiation were estimated based on the number and types of radiology examinations reported in each interview; however, restricted ability to completely recall all lifetime examinations limited the precision of each estimated medical dose. In general, the cohort of veterans all reported various kinds of routine X rays, barium screenings, and other types of diagnostic tests with no large systematic differences between the exposed and control groups (based on their interviews). For this work, medical radiation was not explicitly used in the methods intercomparison, since it was assumed that the exposed test participant and control participant experienced approximately the same level of medical care and related exposure over the years. Interviews with each test participant confirmed that none had chemotherapy or radiation therapy that might have induced chromosome aberrations.

Like estimated medical doses, doses from natural background radiation were not explicitly used in the comparison of methods but were assessed to give a context for comparing the level of military

[3] Study to Estimate Radiation Doses and Cancer Risks Resulting from Radioactive Fallout from the Trinity Nuclear Test (https://bit.ly/2WQepBI).

exposure received. Assuming the test participants had received approximately 1 mSv per year whole-body dose from natural radiation, each had received on the order of 85 mSv by the time of their blood draw.

Biodosimetry (Method 3)

Chromosome aberration analysis for retrospective biodosimetry is a well-established approach for estimating dose from exposures received at times long in the past (*30*). Historically speaking, the dicentric chromosome assay is the gold standard for estimating unknown radiation doses to individuals; however, dicentrics are lost relatively quickly over time, and so would not be informative here. Reciprocal translocations are more persistent with time (*31*); however, increases in translocation background frequencies due to age, lifestyle (smoking) and non-radiation environmental factors (exposure to pesticides) can make their analyses problematic (*32*).

More recently, chromosomal inversions (inverted segments within chromosomes) have been proposed as potential retrospective biodosimeters (*33*). Here, for the first time, they were investigated for reconstructing past exposures [see (*12*)]. Like the case for reciprocal translocations (rearrangements between chromosomes), inversions are symmetrical (i.e., they are balanced); therefore, they also persist with time. The strand-specificity of the cytogenomics-based methodology of directional genomic hybridization (dGH) enables detection of inversions at much higher resolution than previously possible (*34*), while simultaneously also detecting translocations. Indeed, inversions are induced at a greater rate per unit dose than are translocations, and further, high-linear energy transfer (LET) particles are more efficient at inducing inversions than gamma rays (*33*).

Here, we hypothesized *a priori* that inclusion of inversions could improve retrospective biodosimetry for estimating exposures that took place over six decades in the past, reasoning that their persistence and higher induction rate per unit dose would be favorable for retrospective dose estimation. Furthermore, we hypothesized that changes in telomere length [e.g., shortening, see (*35*)] might also reflect these past radiation exposures, thereby providing insight into potential long-term biological and overall health implications [see (*12*)]. These considerations were the basis for the design of an assessment based on both inversions and translocations.

To identify inversions and translocations, dGH was employed using single-color whole chromosome 1, 2 and 3 paints (KromaTiD Inc., Ft. Collins, CO), and performed as described elsewhere (*12, 34*). Over 200 metaphase spreads per military participant and 300 metaphase spreads per young adult volunteer were imaged and analyzed to establish aberration rates. Clonal rearrangements that appeared two or more times were scored as one event.

To allow the assessment of individual doses from measurements of chromosome aberration rates, dose-response curves for inversions and translocations were established by exposing whole peripheral blood *ex vivo* from six male volunteers in their mid-20s (similar age of exposure as the military test participants) to a range of ^{137}Cs gamma-ray doses and the aberration rates were assessed as a function of dose. Linear relationships were evident in all derived calibration curves [see (*12*)]. In simple terms, the dose to bone marrow from measurements of translocation and inversion frequencies was individually assessed using Eq. (1).

$$D_i = \left(AF_i - \overline{BF}\right)/CF, \tag{1}$$

where,

D_i is absorbed dose (mGy) to bone marrow of individual i;

AF_i = measured aberration frequency (translocations or inversions) in peripheral blood lymphocytes from exposed subject i;

$\overline{BF}$ = average baseline aberration frequency derived separately from both ''ever-smoker'' or ''never-smoker'' control subjects and assigned according to the smoking status of individual i;

CF = calibration factor equal to the slope of derived dose-response curve (aberration frequency/mGy).

Biodosimetry estimates were derived from: 1. translocations alone; 2. inversions alone; and 3. a weighted-average of translocations and inversions. The purpose of deriving the weighted average was to explore the possibility that the two biodosimetry assays combined might be a more useful metric of RBM dose. For the latter case, the weighted average, $D_{Tr/Inv}$, was derived based on inverse-variance weighting (*36*) to account for the relative degree of uncertainty in each assay [Eq. (2)].

$$D_{Tr/Inv} = \left[\left(1/\sigma_{Tr}{}^2\right)/\left(1/\sigma_{Tr}{}^2+1/\sigma_{Inv}{}^2\right)\right] * D_{Translocation} + \left[\left(1/\sigma_{Inv}{}^2\right)/\left(1/\sigma_{Tr}{}^2+1/\sigma_{Inv}{}^2\right)\right] * D_{Inversion} \tag{2}$$

Uncertainty Assessment

As there is no known true value of dose for each test participant, an assessment of uncertainty of doses estimated by each method is a necessary step to determining reliability and is also useful in the determination of congruence between methods.

The technique for estimating uncertainty of each of the three assessment strategies differed. The uncertainty for film badge measurements is discussed in a National Research Council report (*16*) as was the continual improvement in film badge materials over the years during which it was used for personnel monitoring. The National Research Council (*16*) suggested that the uncertainty for film badge-estimated exposures resulted in upper (and lower) 95% confidence intervals less than 2× the measured exposure, and typically, within 1.5×. Film badge uncertainties, however, do not fully capture the reliability of the doses estimated from film badge measurements, as there are other limitations. For example, individual film badge measurements are not always available for all military test participants; therefore, extrapolation from others with similar job responsibilities is sometimes necessary. That requirement, in itself, contributes to an increase in the overall uncertainty. The additional uncertainty due to basing the dose on a cohort badge is still less than that, had the dose been based on a dose reconstruction. An additional uncertainty arises from converting exposure, as measured by a film badge, to organ dose. In cases where there is little information to quantify the uncertainty, some subjective judgment may be required to estimate confidence limits. Uncertainty estimation for dose reconstruction made use of such judgement where necessary, but primarily relied on analysis of empirical data coupled with standard analytical error propagation. In contrast, uncertainties for the biodosimetry assays were derived by applying Monte Carlo simulation to Eqs. (1) and (2), using probability density functions (PDFs) specified for each parameter, and the calculation repeated 50K times using random selections from the PDFs. Quantifying uncertainty for assumed values or imputed values, whether they be for dose reconstruction or biodosimetry, is a particularly difficult analytical problem. The assigned uncertainties for imputed values were developed using a mathematical propagation of errors approach, using all quantifiable information, the same as for other samples.

RESULTS AND DISCUSSION

Interviews and Data Collection

Cognitive interviews with the military test participants were an important component of this study. The cognitive interview methodology has proven effective with long-term recall and reconstruction of past experiences (*14, 15*). Memory aids of the period, including photographs of military field exercises, airplanes used for cloud sampling

and images of Rongerik Island, served as tools for facilitating recall of experiences. Interviews provided confirmatory personal information on disease and treatment history including exposure to medical radiation, smoking history, the location(s) and times of exposure in the military, type of duties and activities engaged in that were pertinent to radiation exposure scenarios, types of protections used (e.g., clothing and respiratory protections), conditions during meals, decontamination activities and whether individual or group monitoring was used. The Rongerik veterans, for example, provided useful information about the buildings they worked in during the fallout, including the locations of the buildings, information not available in military records.

Many specifics relative to the actual exposure conditions were clearly difficult for participants to recall with detail six decades after exposure; information on disease history, smoking history and locations of exposure and duties conducted appeared to be recalled with the greatest certainty.

Estimated Doses

Derivation and reporting of estimated doses by these various methods required consideration of several factors in addition to the source and exposure scenarios, including radiation weighting factors [W_R; see (*37, 38*)] for neutron exposures and determination of the minimum detectable dose for biodosimetric assays. Each are briefly discussed in turn.

Doses estimated in this work are to RBM as a single organ. All dose reconstruction scenarios (A–E) represent external dose calculations with generally increasing degrees of information on which the assessment was based. Only scenario C represented film badge data (and/or surrogate film badge data) exclusively. Internal dose was estimated because the biodosimetric assays would presumably reflect the combined external and internal exposure of the bone marrow. Scenarios A + Int through E + Int represent the sum of reconstructed nuclear testing-related external and internal dose. Medical dose (from X rays) and natural background radiation (gamma radiation) are presented only to illustrate general magnitude.

While all estimated doses from exposure to gamma ray are estimated as absorbed dose (mGy), neutron exposure requires multiplication of the absorbed dose by a weighting factor to account for the high LET of neutrons. The radiation weighting factor W_R (*37*), normally appropriate for stochastic effects, could be used to derive equivalent dose (mSv), or a relative biological effect (RBE) value could be used, resulting in radiation-weighted absorbed dose (RBE * D), normally appropriate for tissue reactions. Here we use the W_R value, though the same numerical value of the adjustment factor would be used for the RBE. While only two of twelve military test participants are known to have received neutron exposures, to make doses among all participants comparable, all are reported as equivalent dose (mSv) by using a W_R (=1.0) for gamma-ray exposures. The W_R for stochastic effects due to neutron exposures is recommended to be a function of energy (*37*). In this work, three values of W_R for neutrons were compared; 1, 10 and 20, although only two veterans exposed at the NTS received neutron exposures.

TABLE 4
Minimum Detectable Dose (MDD) in mGy from Biodosimetry for 80- to 90-year-old Male Veterans by Smoking Status and Certainty Level

	80- to 90-year-old males			
	Never-smokers		Ever-smokers	
	95%	99%	95%	99%
Translocations	210	270	310	400
Inversions	160	210	180	240

Biodosimetry dose estimates can vary considerably among individuals who experienced very similar exposure levels because of the inherent variation between individuals to form and repair aberrations, as well as due to the probability of observing aberrations among the finite number of cells scored. These variations can be used to derive a minimum detectable dose (MDD) which, in simple terms, is the minimum dose that can be said to differ from ''no exposure'' at a specified confidence level. MDDs are typically estimated for 95% or 99% confidence. Using the variability described by McKenna *et al*. (*12*) for aberration rates among the 12 non-exposed control subjects, we separately derived the MDD (see Table 4) for translocations and inversions using the procedure described by Tucker and Luckinbill (*10*), a method similar to that routinely used in radioactivity analysis (*39*). For the weighted translocation and inversion dose, an average of the MDD for the individual assays was used. Because the standard deviation of the translocation or inversion rate was found to vary according to smoking status, the MDD also varies according to smoking status. For purposes of comparison, MDD values are presented in Table 4, with the 99% level used in all subsequent analyses. MDD values (Table 4) derived for translocations in this work (approximately 270 mGy for never-smokers at 99% certainty) were comparable to published values [approximately 240 mGy (*10*)] derived from a review of translocations obtained internationally (*11*). No estimates of the MDD for inversions has been previously reported.

Group-average doses to the Rongerik veterans, the NTS/PPG test participants, and both groups combined, are shown in Table 5 for dose reconstruction and dose estimation scenarios of greatest import to the design of this study, i.e.: A (generic exposure scenario), C (film badge and/or surrogate film badge), E (dose reconstruction based on the most complete information), E + Int (E scenario plus internal dose) in mSv (equivalent dose to bone marrow) and for the biodosimetric assays (Tr, Inv, Tr/Inv) in mGy

TABLE 5
Group Attributes and Group-Average Red Bone Marrow Dose Estimates

	Group			
	Rongerik (n = 6)	NTS/PPG (n = 6)	All (n = 12)	Controls (n = 12)
Attributes				
No. of ever-smokers	5	2	7	7
No. of subjects with neutron exposure	0	2	2	na
No. of Tr/Inv estimates <MDD at 95% certainty level	3	4	7	na
No. of Tr/Inv estimates <MDD at 99% certainty level	4	4	8	na
Group-average dose estimates[a] by assessment method				
A (mSv)	550	250	400	
C (mSv)	340	160	250	
E[b] (mSv)	370	200[b]	280	
Int (mSv)	11	3.6	7.2	
E[b] + Int (mSv)	380	200[b]	290	
NuTRIS[c] (mSv)	398	398	398	
Med (mGy)	5.6	5.3	5.4	
Bkg (mGy)	84	90	87	
Tr (mGy)	480	65	270	
Inv (mGy)	240	280	260	
Tr/Inv (includes <MMD measured values in average) (mGy)	290	91	190	
Tr/Inv (with imputation[d] for <MDD measurements) (mGy)	310	230	270	

Note. NTS = Nevada Test Site; PPG = Pacific Proving Ground.
[a] All derived mean values are reported to two significant digits.
[b] Scenario E for two NTS/PPG veterans includes adjustment for neutron exposure using a $W_R = 20$.
[c] NuTRIS value is presented as reported by the DOD.
[d] One half of MDD imputed for measurements <MDD (smoking status and related MDD value considered on an individual basis).

(absorbed dose to bone marrow). For context, the medical and background radiation doses (mGy) as well as the NuTRIS doses (mSv) are also shown by group average.

Table 5 also includes other relevant information about the exposed groups including the smoking frequency in each and the proportion of those exposed to neutrons. Estimates of dose for eight of the 12 veterans by biodosimetry were <MDD at 99% certainty (Table 4). For the biodosimetry estimates that were <MDD, one half the MDD (Table 4) (considering smoking status and related MDD) was imputed as an unbiased proxy consistent with recommendations of National Research Council (*16*). Figure 2 shows the individual dose estimates using the three primary assessment methods: 1. film badges; 2. dose reconstruction for scenario E + Int; and 3. biodosimetry (Tr/Inv) after imputation for <MDD values. The equal values of the film badge readings for the Rongerik veterans are due to substitution of a single badge reading from a deceased Rongerik veteran as a surrogate. After imputation for <MDD values, the Tr/Inv values for the Rongerik veterans were within, on average, 14% of the E + Int dose reconstruction value, 8% of E + Int for NTS/PPG participants and 11% of E + Int for both groups combined. As shown in Table 5, depending on the assessment method, group-average military exposures appear primarily to be within the range of approximately 300–400 mSv for Rongerik veterans and approximately 250–300 mSv for NTS/PPG participants.

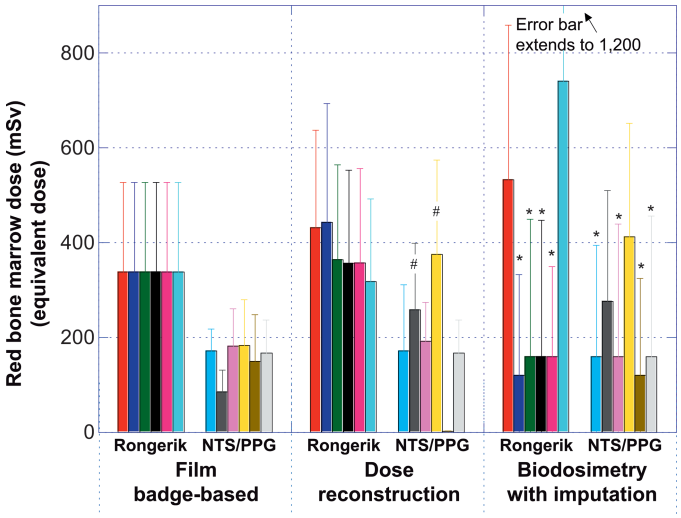

FIG. 2. Comparison of bone marrow dose estimates, mSv equivalent dose, to six Rongerik and six NTS/PPG veterans (color-coded vertical bars correspond to individual veterans) by three estimation methods: 1. film badge-based dose estimates (using individual or "cohort" badges, see Table 3); 2. dose reconstruction (scenario E + Int); and 3. biodosimetry (Tr/Inv): weighted translocation and inversion doses with imputation. Dose reconstruction data points with hash marks (#) indicate those estimates adjusted for neutron exposure (using radiation weighting factor $W_R = 20$). Biodosimetry data points with asterisks (*) indicate those measurements <MDD as determined by individual smoking status (see Tables 4 and 5) and that were subsequently imputed with one-half minimum detectable dose (MDD) for smoking category. Error bars are estimated ± 2 sigma uncertainty.

TABLE 6
Spearman Correlation Coefficients between Biodosimetry-Based Dosed Estimates (Tr, Inv and Tr/Inv) and Dose Reconstruction Estimates for Three Different Values of Radiation Weighting Factor ($W_R > 1$ Used Only for Two NTS Veterans with Neutron Exposures)

Codes for assessment methods[a]	$W_R = 1$[b]			$W_R = 10$[b]			$W_R = 20$[b]		
	Tr	Inv	Tr/Inv[c]	Tr	Inv	Tr/Inv[c]	Tr	Inv	Tr/Inv[c]
Location	–0.40	0.06	–0.39	–0.40	0.06	–0.39	–0.40	0.06	–0.39
A	0.39	–0.04	0.39	0.43	0.08	0.47	0.45	0.22	0.55
B	0.29	–0.08	0.32	0.33	0.05	0.43	0.36	0.22	0.54
C	0.39	–0.22	0.36	0.39	–0.22	0.36	0.39	–0.22	0.36
D	0.28	0.00	0.36	0.31	0.14	0.46	0.32	0.30	0.55
E	0.30	0.02	0.41	0.33	0.16	0.50	0.34	0.31	**0.58**
Int	0.51	–0.04	**0.59**	0.51	–0.04	**0.59**	0.51	–0.04	**0.59**
Med	–0.02	–0.52	–0.37	–0.02	–0.52	–0.37	–0.02	–0.52	–0.37
Bkg	–0.12	0.16	0.09	–0.12	0.16	0.09	–0.12	0.16	0.09
A + Int	0.39	–0.04	0.39	0.43	0.08	0.48	0.45	0.22	0.56
B + Int	0.30	–0.08	0.33	0.34	0.05	0.44	0.37	0.21	0.54
C + Int	0.39	–0.21	0.37	0.39	–0.21	0.37	0.39	–0.21	0.37
D + Int	0.28	–0.01	0.37	0.32	0.13	0.47	0.33	0.29	0.55
E + Int	0.31	0.02	0.41	0.34	0.15	0.51	0.35	0.30	**0.58**

Note. Statistical significance ($P < 0.05$) indicated in bold face.
[a] See Table 1 for code definitions of assessment scenarios.
[b] W_R is the ICRP radiation weighting factor for neutrons used in the dose reconstruction of two NTS veterans where neutron exposures were evident.
[c] Inverse variance weighted average of biodosimetry chromosome translocation dose estimate and chromosome inversion dose estimate.

One interesting outcome involved the dose assessment for one of the three participants with a military record as a ''cloud-sampler.'' Although this individual originally had a reported NuTRIS dose of 219 mSv, two separate and independent interviews confirmed that the participant never flew a mission through a nuclear debris cloud and, thus, had a surrogate film badge dose assigned of <90 mSv. His dose reconstruction based on a subsequent search of his records by the DOD resulted in a best estimate of approximately 2 mSv only, and his biodosimetry estimate was <MDD.

Correlations

The strength of linear relationships among all exposure assessment methods (film badge-based, each dose reconstruction method and each biodosimetry variation) was examined using Spearman correlation coefficients (Table 6). Correlations greater than 0.5 were used as an *ad hoc* screening level for potentially important relationships, while correlations >0.57 were statistically significant ($P < 0.05$) for the sample size.

As discussed, two of the six NTS/PPG participants were exposed to neutrons. When the additional biological damage from neutrons is accounted for in the dose reconstruction by a radiation weighting factor, W_R, those few neutron-exposed individuals can have a significant impact on the correlations between the dose reconstruction and the biodosimetry estimates. We found that dose reconstructions using W_R values of 1.0 or 10 resulted in no statistically significant correlations between dose reconstructions and any of the biodosimetric assays. In contrast, we found that a W_R value of 20 applied in the dose reconstruction for the two neutron exposures resulted in statistically significant correlations between Tr/Inv with E and E + Int (see Table 6, column 10). While this finding may be merely serendipitous, it is interesting and provocative, considering that a W_R of 20 is predicted in the ICRP Report 103 (*37*) energy-based model for W_R using a neutron energy of approximately 1.0 MeV, a value relevant to the range of neutron energies emitted from nuclear detonations (*40*).

Note that we did not include medical or background radiation dose in further analytical comparisons between dose reconstruction and biodosimetry because of the absence of any significant correlations as noted in Table 6.

Systematic Differences

The second measure of congruence among methods was based on assessment of systematic differences between group-average doses. While significant correlations were found between internal dose and the biodosimetry, because the internal dose is so small (Table 5), there are obvious large systematic differences between those two assessments. In that case, the correlation reflects only the extent to which those variables increase or decrease in parallel. Because of the large known differences in magnitude, no formal evaluation of systematic difference was needed to demonstrate lack of congruence between internal dose and biodosimetry.

To characterize the presence of systematic differences in average dose among methods, Table 7 shows the average ratio of Tr/Inv to E + Int for the Rongerik veterans, the NTS/PPG participants and the combined groups. The comparison based on the biodosimetric measurements showed that, on

TABLE 7
Average Ratios between Assessment Methods C, E + Int and Tr/Inv as an Indication of Systematic Differences

Average ratios	Group		
	Rongerik (n = 6)	NTS/PPG (n = 5[c])	All exposed (n = 11)
C to (E + Int)[a]	0.91	0.74	0.83
Tr/Inv (with no imputation for <MDD measurements) to (E + Int)[a]	0.79	0.38	0.61
Tr/Inv (with imputation[b] to correct for <MDD measurements) to (E + Int)[a]	0.86	0.92	0.89

Note. NTS = Nevada Test Site; PPG = Pacific Proving Ground.

[a] Includes adjustment in dose reconstruction for neutron exposure of two NTS veterans using $W_R = 20$.

[b] Imputation consisted of replacing measured values of Tr/Inv less than the assessed minimum detectable dose (MDD) (at 99% certainty) with one half of assessed MDD.

[c] One case eliminated because subsequent record search by DOD and personal interviews confirmed veteran was not exposed in the military.

average, Tr/Inv values, as measured, were smaller in magnitude to E + Int, particularly for the NTS/PPG participants. The reason, primarily, was due to the numerous measurements <MDD, which are not reliable and can fluctuate at random from zero to the MDD. However, the imputation of one half the MDD for values <MDD resulted in improved agreement of Tr/Inv with the dose reconstruction, i.e., within 14% of the dose-reconstructed E + Int value for Rongerik veterans, within 8% for NTS/PPG participants, and within 11% for both groups combined.

Statistical analysis was performed to discern if there were significant systematic differences between E + Int and Tr/Inv, with and without imputation (for <MDD values). The non-parametric Mann-Whitney test was not able to identify significant differences, and it appears likely that the large variations within each group prevented a finding of significance. Despite not being able to reject the null hypothesis of no difference, the substitution of one half the MDD values for those <MDD resulted in much closer agreement of the mean values, particularly for NTS/PPG participants (see Table 7).

Overall Assessment of Congruence

Together, the statistically significant correlation between dose reconstruction (method 2, scenario E + Int) and TR/Inv (method 3), coupled with the absence of large systematic differences (after correction for <MDD), are strong suggestions for congruence. Because the dose reconstruction scenario E + Int and the measurement Tr/Inv are two completely independent methods for estimating dose, the congruence suggests a degree of validity, at least on average, for those two sets of dose estimates. Under the assumption that E + Int and Tr/Inv are both legitimate estimates of dose in terms of magnitude, we used these values as the basis to assume a range of best estimates of doses received.

Uncertainty

Dose uncertainty plays a role in the determination of congruence since individual doses are subject to both random (and possibly systematic) errors. As shown in this section, we found, in general, an improvement in the congruence between dose reconstruction scenarios with smaller individual dose uncertainties (e.g., found in E + Int) and the biodosimetry (Tr/Inv). In this section, we illustrate the general improvement in dose reconstruction as additional information is incorporated, as well as the general magnitude of dose uncertainties observed in this study.

The uncertainties on individual dose estimates can be presented either as coefficients of variation (CV = standard deviation/mean) or absolute error in mGy. In general, typical CVs for individual doses were 0.35 for scenario A, reducing to approximately 0.28 for scenarios with more information (C–E). The decrease in uncertainty in scenario C–E generally supports preconceived notions that the addition of individual information will decrease the uncertainty and improve the dose estimation. Both the change in estimated dose and the magnitude of the uncertainty in successive scenarios (A–E) are compared for a single Rongerik veteran with the NuTRIS value and the weighted biodosimetry (Tr/Inv) estimate (Fig. 3). Note that the NuTRIS value is shown without uncertainty, as it is

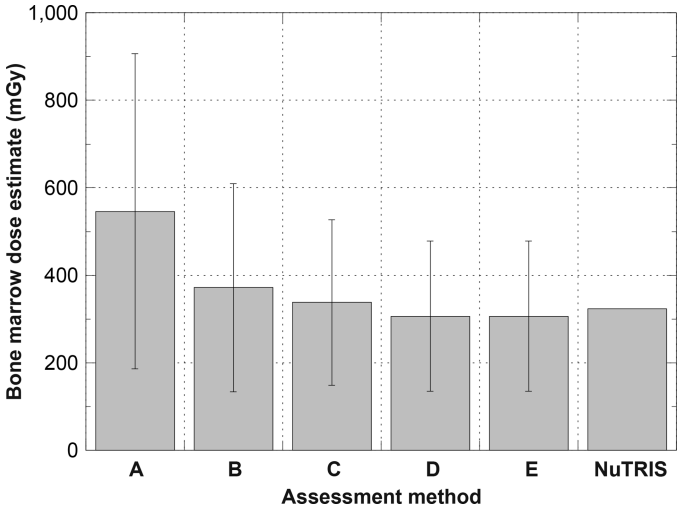

FIG. 3. Example of reduction in uncertainty with increasing information: estimated external bone marrow dose for a single Rongerik veteran dose reconstruction. Error bars are ±2 sigma. NuTRIS dose (for comparison) is without error bar, as it is an assigned dose value.

an assigned value. The weighted biodosimetry estimate (Tr/Inv) in Fig. 3 is shown with a CV comparable to the dose reconstruction, approximately 0.26. For the case of biodosimetry measurements, the CV is a strong function of the number of observed aberrations (equivalently, a function of dose). Biodosimetry estimates close to the MDD had CVs of approximately 0.35, while values <MDD had CVs as large as 1.0 (not shown).

It is apparent that the large uncertainty associated with some biodosimetry assessments is a consequence of interindividual variability in the aberration rates, the individual rates at which those aberrations are repaired or disappear over the decades, the variation of baseline rates among the non-exposed controls and statistical limitations imposed by the scoring of a finite number of cells (in this case, 200 cells).

CONCLUSIONS

Assessment of radiation doses to U.S. military test participants provides useful information to inform servicemen of past exposures, but also serves to improve our understanding of the limitations and requirements of retrospective dose estimation. An improvement in our future capability to reliably estimate past doses received is also one intended outcome of this research.

In this work, we estimated bone marrow dose by review of film badge dose estimates, dose reconstruction that we conducted using several methodological variations, each with increasing information, and retrospective biodosimetry using chromosomal translocations and, notably for the first time, chromosomal inversions. Our biodosimetry results confirm that even for exposures that occurred six decades in the past, cytogenetic evidence of exposure is still present. Moreover, our results suggest that although translocations and inversion frequencies can be metrics of exposure independently, a combined approach provides a more reliable estimate of past radiation exposure.

From this investigation, we deduce 11 valuable lessons and conclusions:

1. Recruitment of potential study subjects for participation after exposures that occurred many decades earlier can be impaired due to deaths in the cohort, illness and inability to locate or contact the subjects. These constraints fall under the general category of ''loss to follow-up'' and considerably weaken the power of a study to draw firm conclusions.
2. Minimum detectable dose (MDD) by chromosome aberration assays complicates comparisons between dose reconstruction and biodosimetry, especially when dose to bone marrow is less than approximately 250 mSv. The MDD, while directly dependent on the variation of the baseline aberration rate, is also influenced by the number of cells scored, age and smoking status.
3. This research confirms that it is still possible, at more than 60 years since exposure, to detect chromosome damage in excess of that caused by age and related factors. However, the success in making estimates of past exposure by chromosome aberrations depends on the magnitude of the dose(s) received and other, possibly unknown, variables that result in variations in baseline rates.
4. The value of including analysis of chromosomal inversions for retrospectively assessing radiation exposures was assessed. We found in this study that the additional assessment of inversion frequencies improved the biodosimetric dose assessment compared to translocations alone, which was generally consistent with our expectations.
5. Dose reconstruction and biodosimetric assays were shown to be, on average, well correlated and had small systematic differences between them under the following two conditions: 1. The dose reconstruction must have considerable information available on the exposure scenario; 2. The true dose received must be above a threshold such that the biodosimetry operates in a range where there is reliability in assessing the aberration frequency relative to the baseline frequency.
6. Congruence among methods was demonstrated by a combination of statistically significant correlations and small systematic differences. The two methods most congruent were E + Int and Tr/Inv.
7. Scenario C (film badge alone) was not significantly correlated with E + Int or with Tr/Inv (not shown) despite the fact that there was a small average systematic difference between the methods. On average, the film badge-based assessment (scenario C) was 17% less than E + Int, while Tr/Inv was approximately 11% less than E + Int after imputation for <MDD values. However, E + Int was significantly correlated with Tr/Inv, which is one important attribute of the congruence determination.
8. Biodosimetry is the only method we tested that uses biological markers of exposure from the subject for reconstructing the individual's dose. Determination of individual dose by biodosimetry with a moderate- to high degree of certainty is exceedingly difficult for exposures that were received decades in the past, though group-average doses can be assessed with much greater confidence.
9. It may be possible to quantitatively assess the radiation weighting factor (W_R) for particulate radiations (e.g., neutrons) by comparison of the reconstructed dose with the assessment of chromosome aberration frequency. This research, based on sparse findings, suggested a W_R of 20, consistent with international recommendations for neutron energies approximating a few MeV.
10. Rongerik veterans who participated in this study appear to have received, on average, bone marrow equivalent doses on the order of 300–400 mSv, while

NTS/PPG participants who participated in this research appear to have received approximately 250–300 mSv. The exception to these findings was one NTS/PPG participant who was determined to have received a military-related dose of only a few mSv at most and for whom a NuTRIS dose had been erroneously assigned based on a job description. While this research attempted to compare three methods to deduce generalizable findings about congruence between methods, it should be noted that the subjects of this study were the highest exposed (living) veterans. For that reason, they may not be typical of all other veterans and our findings should be generalized with caution.

11. This study illustrates how the accuracy and presumed reliability of individual dose estimates depends on the amount of data available and generally improves as additional information is incorporated. The reliability of dose assessments for military test participants, or other exposed populations, can be optimized in the future by use of all available data, including the types of data studied in this research: 1. individual personnel monitoring; 2. data on exposure conditions; 3. cognitive interviews; and 4. biodosimetric assays.

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REFERENCES

1. Radiation dose reconstruction: principles and practices. NCRP Report 163. Bethesda, MD: National Council on Radiation Protection and Measurements; 2009.
2. Caldwell GG, Kelley D, Zack M, Falk H, Heath CW Jr. Mortality and cancer frequency among military nuclear test (SMOKY) participants, 1957 through 1979. JAMA 1983; 250:620–24.
3. Till JE, Beck HL, Aanenson JW, Grogan HA, Mohler GJ, Mohler SS, Voilleque PG. Military participants at U.S. Atmospheric nuclear weapons testing-methodology for estimating dose and uncertainty. Radiat Res 2014; 181:471–84.
4. Bouville A, Toohey RE, Boice JD Jr, Beck HL, Dauer LT, Eckerman KF, et al. Dose reconstruction for the million-worker study: Status and guidelines. Health Phys 2015; 108:206–20.
5. Beck HL, Till JE, Grogan HA, Aanenson JW, Mohler HJ, Mohler SS, et al. Red bone marrow and male breast doses for a cohort of atomic veterans. Radiat Res 2017; 187:221–8.
6. Lessard E, Miltenberger R, Conard R, Musolino S, Naidu J, Moorthy A, et al. Thyroid absorbed dose for people at Rongelap, Utrik and Sifo on March 1, 1954. Report BNL 51882. Upton, NY: Brookhaven National Laboratory, Safety and Environmental Protection Division; 1985.
7. Goetz J, Klemm J, Phillips J, Thomas C. Analysis of radiation exposure - service personnel on Rongerik Atoll, Operation Castle - Shot Bravo. DNA-TR-86-120. McLean, VA: Science Applications International Corp.; 1987.
8. Simon SL, Beck H, Land C, Bouville A. Radiation doses and cancer risks in the Marshall Islands associated with exposure to fallout from Bikini and Enewetak nuclear weapons tests: Summary. Health Phys 2010 99:105–23.
9. Tucker JD. Low-dose ionizing radiation and chromosome translocations: a review of the major considerations for human biological dosimetry. Mutat Res 2008; 659:211–20.
10. Tucker JD, Luckinbill LS. Estimating the lowest detectable dose of ionizing radiation by FISH whole-chromosome painting. Radiat Res 2011; 175:631–7.
11. Sigurdson AJ, Ha M, Hauptmann M, Bhatti P, Sram RJ, Beskid O, et al. International study of factors affecting human chromosome translocations. Mutat Res 2008; 652:112–21.
12. McKenna M, Bailey S, et al. Chromosome translocations, inversions, and telomere length for retrospective biodosimetry on exposed US Atomic Veterans. Radiat Res 2019; 311–22:191.
13. Page WF, Mahal CM, Kang HK. Vital status ascertainment through the files of the Department of Veterans Affairs and the Social Security Administration. Ann Epidemiol 1996; 6:102–9.
14. Davies G, Thomson DM. Memory in context: context in memory. New York: Wiley; 1987.
15. Tulving E, Thomson D. Encoding specificity and retrieval processes in episodic memory. Psychological Review 1973; 80:352–73.
16. National Research Council. Film badge dosimetry in atmospheric nuclear tests. Washington, DC: National Academies Press; 1989.
17. Young RW, Kerr GD. Reassessment of the atomic bomb radiation dosimetry for Hiroshima and Nagasaki-Dosimetry System 2002 (DS02); Vols. 1 and 2. Hiroshima, Japan: Radiation Effects Research Foundation; 2005. (http://rerf.or.jp/libra.ry/index_e.html)
18. Anspaugh, LR, Church BW. Historical estimates of external exposure and collective external exposure from testing at the Nevada Test Site. I. Test series through Hardtack II, 1958. Health Phys 1986; 51:35–51.
19. Anspaugh LR, Wheeler DL, Church BW, Ricker YE. Historical estimates of external gamma exposure and collective external gamma exposure from testing at the Nevada Test Site. II. Test series after Hardtack II, 1958, and Summary. Health Phys 1986;59:525–32.
20. Lloyd R, Gren DC, Simon SL, Wrenn ME, Hawthorne HA, Stevens W, et al. Assigning individual exposures from Nevada Test Site fallout for Utah leukemia cases and controls. Health Phys 1990; 59:723–37.
21. Simon SL, Till JE, Lloyd RD, Kerber RL, Thomas DC, Preston-Martin S, et al. The Utah leukemia case-control study: dosimetry methodology and results. Health Phys 1995; 68:460–71.

22. Gordeev K, Shinkarev S, Ilyin L, Bouville A, Hoshi M, Luckyanov N, et al. Retrospective dose assessment for the population living in areas of local fallout from the Semipalatinsk Nuclear Test Site. Part I: External exposure. J. Radiat Res 2006; 47:A129–36.
23. Bouville A, Beck HL, Simon SL. Estimation of doses from external irradiation to Marshall Islanders from nuclear testing. Health Phys 2010; 99:143–56.
24. National Research Council. A review of the dose reconstruction program of the Defense Threat Reduction Agency. Committee to Review the Dose Reconstruction Program of the Defense Threat Reduction Agency. Washington, DC: National Academies Press; 2003.
25. Blake PK, Komp GR. Radiation exposure of U.S. military individuals. Health Phys 2014; 106:272–8.
26. Petoussi-Henss N, Bolch WE, Eckerman KF, Endo A, Hertel N, Hunt J, et al. ICRP Publication 116. Conversion coefficients for radiological protection quantities for external radiation exposures. Ann ICRP 2010; 40: 1–257.
27. Harris PS, Simon SL, Ibrahim SA. Urinary excretion of radionuclides from Marshallese exposed to fallout from the 1954 BRAVO nuclear test. Health Phys 2010; 99:217–32.
28. Hicks HG. Calculation of the concentration of any radionuclide deposited on the ground by off-site fallout from a nuclear detonation. Health Phys 1982; 42:585–600.
29. Ibrahim S, Simon SL, Bouville A, Melo D, Beck HL. Transfer of fallout radionuclides through the human alimentary tract: recommendations and justifications for f_1 values to be applied in the reconstruction of internal doses from local and regional fallout from nuclear tests. Health Phys 2010; 99:233–51.
30. Simon SL, Bailiff I, Bouville A, Fattibene P, Kleinerman RA, Lloyd DC, et al. Consensus committee report on biodosimetric methods to evaluate radiation doses at long times after exposure. Radiat Meas 2007 42:948–71.
31. Tawn EJ, Whitehouse CA. Persistence of translocation frequencies in blood lymphocytes following radiotherapy: implications for retrospective radiation biodosimetry. J Radiol Prot 2003; 23:423–30.
32. Ramsey MJ, Moore DH, Briner JF, Lee DA, Olsen LA, Senft JR, et al. The effects of age and lifestyle factors on the accumulation of cytogenetic damage as measured by chromosome painting. Mutat Res 1995 338:95–106.
33. Ray FA, Robinson E, McKenna M, Hada M, George K, Cucinotta F, et al. Directional genomic hybridization: inversions as a potential biodosimeter for retrospective radiation exposure. Radiat Environ Biophys 2014; 53:255–63.
34. Ray FA, Zimmerman E, Robinson B, Cornforth M, Bedford J, Goodwin E, et al. Directional genomic hybridization for chromosomal inversion discovery and detection. Chromosome Res 2013; 21:165–74.
35. Sishc BJ, Nelson CB, McKenna MJ, Battaglia CL, Herndon A, Idate R, et al. Telomeres and telomerase in the radiation response: Implications for instability, reprograming, and carcinogenesis. Front Oncol 2015; 5:257.
36. Hartung J, Knapp G, Sinha BK. Statistical meta-analysis with applications. Hoboken: John Wiley & Sons, Inc.; 2008.
37. The 2007 recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP 2007; 37:1–332.
38. Wrixon AD. New ICRP recommendations. J Radiol Prot 2008; 28:161–8.
39. Definition and procedure for the determination of the method detection limit, Revision 2. EPA 821-R-16-006. Washington DC: Environmental Protection Agency; 2016. (https://bit.ly/2BnKOpU)
40. Publicly released prompt radiation spectra suitable for nuclear detonation simulations, Revision 1. Report No. DTRA-TR-17-026 (R1). Fort Belvoir: Defense Threat Reduction Agency; 2017. (https://bit.ly/2ROzB7r)