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## A Million Person Study Innovation: Evaluating Cognitive Impairment and other Morbidity Outcomes from Chronic Radiation Exposure Through Linkages with the Centers for Medicaid and Medicare Services Assessment and Claims Data

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### Abstract

The study of One Million U.S. Radiation Workers and Veterans, the Million Person Study (MPS), examines the health consequences, both cancer and non-cancer, of exposure to ionizing radiation received gradually over time. Recently the MPS has focused on mortality patterns

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from neurological and behavioral conditions, e.g., Parkinson's disease, Alzheimer's disease, dementia, and motor neuron disease such as amyotrophic lateral sclerosis. A fuller picture of radiation-related late effects comes from studying both mortality and the occurrence (incidence) of conditions not leading to death. Accordingly, the MPS is identifying neurocognitive diagnoses from fee-for-service insurance claims from the Centers for Medicare and Medicaid Services (CMS), among Medicare beneficiaries beginning in 1999 (the earliest date claims data are available). Linkages to date have identified ~540,000 workers with available health information. Such linkages provide individual information on important co-factor and confounding variables such as smoking, alcohol consumption, blood pressure, obesity, diabetes and many other health and demographic characteristics. The total person-level set of time-dependent variables, outcomes, organ-specific dose measures, co-factors, and demographics will be massive and much too large to be evaluated with standard software. Thus, development of specialized open-source software designed for large datasets (Colossus) is nearly complete. The wealth of information available from CMS claims data, coupled with individual dose reconstructions, will thus greatly enhance the quality and precision of health evaluations for this new field of low-dose radiation and neurocognitive effects.

## INTRODUCTION

There is a critical knowledge gap regarding non-cancer detrimental health consequences of exposure to ionizing radiation received gradually over time (1). The epidemiologic study of One Million U.S. Radiation Workers (also called the Million Person Study or MPS) is perhaps the largest radiation epidemiologic study of workers and military veterans in the world aimed to contribute important insights as to the late health effects from chronic<sup>1</sup> radiation exposures (1,2). The study is relevant to current worker populations including nuclear utility plant workers, medical radiation workers, industrial radiographers, aircrews flying at high altitudes, astronauts, cleanup workers of contaminated environments, radioactive waste management workers, emergency responders to nuclear incidents, and military personnel engaged in radiation activities. Findings of the MPS are important input for developing, implementing, and enforcing protection standards and other guidance for the general public and workers (3–6). The study will also provide information to the workers and their families about the potential level of radiation-related health effects incurred during their occupations (7). One specific application of MPS study results is to provide guidance on possible radiation risks for cancer- and non-cancer-related neurocognitive conditions to astronauts who travel on long-duration spaceflight missions (4,8,9).

Overall study aims include investigating chronic low-level radiation exposure and the lifetime risk of disease incidence and mortality, including leukemia, cancers, heart disease, cerebrovascular disease, Alzheimer's disease and related dementias, Parkinson's disease, motor neuron disease primarily amyotrophic lateral sclerosis (ALS), depression, anxiety disorders, neurobehavioral disorders, among other health conditions. Analyses investigate whether exposure to specific types of radiation, e.g., intakes of high-linear energy transfer

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<sup>1</sup>The term chronic exposure refers to protracted and fractionated radiation and is used interchangeably with the terms gradual and prolonged.

(LET) alpha particle radiation or low-LET gamma radiation, affect risk of disease occurrence. Comprehensive radiation dose reconstructions for individual workers enable precise estimates of absorbed dose to organs and tissues for incorporation into dose-response evaluations.

To date, the MPS has evaluated and published the association between radiation exposure and over 40 causes of death among more than 600,000 workers (2,10–19). Efforts continue to evaluate mortality for the approximately 200,000 workers with limited follow-up at large Department of Energy (DOE) facilities such as Hanford and the Savannah River Site as well as approximately 200,000 US Navy personnel such as nuclear submariners and naval shipyard workers. Because death certificate information does not represent a complete assessment of health outcomes, the MPS is now embarking on a large-scale effort to obtain incidence (occurrence or prevalence) data on a wide range of medical conditions, not only cancer and heart disease, but also on neurocognitive conditions such as Parkinson's disease which have been reported to be associated with chronic low-dose radiation exposures (2,20–24).

For persons 65-years and older, identification of neurocognitive outcomes is done by accessing administrative and health insurance claims data from the Centers for Medicare and Medicaid Services (CMS). The MPS recently received all available Medicare fee-for-service claims and enrollment and assessment data for nearly 540,000 radiation workers under study. These data span 1999 (the earliest date of availability) through 2021, as well as nursing home and home health agency assessments for all workers who received care from a Medicare/Medicaid-certified nursing facility or home health agency during the same period. Subsequent linkage with more recent data (2022 onward as they become available) will come shortly and be incorporated into the MPS. The claims data contain dates of medical service and diagnosis codes for services such as hospitalizations, skilled nursing care, emergency department visits, office visits, hospice and home health care. The nursing facility and home health care assessment data include additional measures that capture cognitive impairment and functional status. Importantly, such linkages provide information on important co-factor and confounding variables such as smoking, alcohol consumption, blood pressure, diabetes and many other health and lifestyle characteristics. Medicare Part D claims data provide information about drug prescriptions which can help confirm or point to disease diagnoses. These data are being linked to the MPS employment, military record, dosimetry, and vital statistics follow-up data. This innovative MPS-CMS data linkage will evaluate the potential for late effects of ionizing radiation more fully and accurately than would be possible from mortality data alone.

Ongoing research using the MPS-CMS data linkage aims to support NASA and space exploration (4,9,25). Long missions beyond low-Earth orbit (LEO) will result in meaningful exposures to space radiation that may have potential for increasing the occurrence of central nervous system effects (8). Epidemiologic studies are evaluating cognitive impairment following high-LET alpha-particle exposure to the brain (26). A recent worker study of Mayak workers in Russia reported an association between low-LET gamma radiation and Parkinson's disease (20). Evaluations within five MPS cohorts are consistent with radiation associations for Parkinson's disease (2,14,15,17, 19,22,24, 27). Recent animal experiments

suggest that depression-like behavior may occur after exposure to analogues of space radiation (28). Whether low-level radiation in combination with unique occupational stresses such as isolation and sleep deprivation can contribute to late-term cognitive impairment or depression-like behavior is an important question undergoing rigorous research in animal systems (29). High-level cognitive performance is critically important during space missions which involve environmental, physiological, and psychological stressors. Radiation exposure is a possible stressor that may affect brain function (8,29–32). Employing innovative linkages to CMS data will enable the MPS to evaluate cognition-related outcomes and other chronic condition indications among nearly 600,000 radiation workers who received low-LET gamma-radiation exposure and 200,000 workers with high-LET alpha-particle exposure to brain tissue over a period of years while employed (2,4,25,33).

## METHODS

### Million Person Study Cohorts

More than one million U.S. radiation workers and veterans have been identified through employment records, military records, and regulatory and commercial dosimetry databases. Examples of radiation-exposed cohorts evaluated to date include workers at Los Alamos National Laboratory (14), at the Tennessee Eastman Corporation Y-12 facility (18), U.S. military participants at above-ground nuclear weapons tests (13), nuclear utility workers (15), industrial radiographers (2,19), and medical radiation workers (17). The overall study approach and methods for mortality tracing, analyses, and dose reconstruction have been described (14,34–37). High- and low-LET radiation dose (e.g., from photons, radionuclide intakes, neutrons) to specific organs or tissues are determined for individuals based on employment records, bioassays, and occupational radiation monitoring such as individual film badges, and dose-response analyses conducted to learn of any radiation associations (36,38–41). The approaches set out herein have been used effectively in radiation epidemiology for nearly 50 years, and health studies have improved our understanding of cancer risks following radiation as well as provided the basis for radiation protection standards for workers and the public (7,42–44).

### Institutional Review Board and CMS Approvals

Human subjects research approval was received from the Vanderbilt University Institutional Review Board and the Oak Ridge Sitewide Institutional Review Board. The aims specific to the MPS-CMS data linkage are covered under the strict terms of a CMS data use agreement (DUA), RSCH-2022-57727, that governs the usage, access to, and data management of the CMS linked files. The DUA requesting organization is the National Council on Radiation Protection and Measurements (NCRP). Vanderbilt University Medical Center serves as the data custodian institution. All data are stored and analyzed on secure Vanderbilt systems, and collaborators from other institutions who receive approval to access the data under the terms of the DUA do so through virtual private network (VPN) access to the Vanderbilt system.

## Million Person Study Linkage with CMS Claims and Assessment Data

The CMS Medicare databases capture all enrollment, medical claims, and nursing home and home health assessments for all Medicare-enrolled persons beginning in 1999 (our current data linkage includes claims data through 2021 with subsequent linkages planned for the future). Because these claims and assessments must report diagnoses, they provide a national source for identifying non-fatal and nonmalignant conditions that do not readily exist elsewhere. Data can be linked at the individual level and over time, allowing for a comprehensive look at a person's health care utilization. The MPS links the CMS data to employment, vital status and dosimetry data of radiation workers. MPS cohorts of radiation workers come from a variety of occupations and begin as far back as 1913, i.e., radium dial painters (45). The initial linkage request consisted of 719,441 workers who were alive in 1999. MPS will follow individual workers over time as they continue as Medicare beneficiaries, become Medicare eligible because of age, or were treated in Medicare/Medicaid certified nursing homes until death or the end of the study period to capture a full range of possible long-term effects of radiation exposure coupled with confounding and co-factor information. The CMS files provide a broad range of diverse health related information including incident diagnoses (e.g., for dementia and Parkinson's disease), prescription drug use (e.g., Levodopa for Parkinson's disease), imaging procedures (e.g., beta-amyloid PET scans for Alzheimer's disease), confounding factors (e.g., smoking, BMI), demographic characteristics (e.g., socioeconomic status), and cognitive and physical function (e.g., standardized Cognitive Function Scale scores, Activities of Daily Living scores) and health care utilization (46).

Radiation dose to the brain and other organs for each individual has already been or will soon be estimated based on a comprehensive program of dose reconstruction that includes radiation monitors such as film badges to measure external radiation and, when available, biological samples, such as urine samples, to estimate intakes of radionuclides during employment (36). The key analyses will contrast the various outcome measures such as dementia and cognitive function by radiation dose to brain to learn if there are any associations (i.e., whether the occurrence of these outcomes or the measures of cognitive function are related to the level of cumulative radiation dose received gradually during employment in years past). The linkages with CMS databases will identify multiple health conditions including, cancer, dementia, Alzheimer's disease, Parkinson's disease, anxiety and behavioral disorders, cardiovascular disease, and cerebrovascular disease. Recently, there has been some discussion that Parkinson's disease may originate with or be associated with the gut rather than or in conjunction with the brain, and we plan to evaluate dose-response with respect to colon dose as well (47).

In addition to insurance claims and enrollment data, the CMS data include federally mandated assessments for individuals receiving post-acute and long-term care from nursing facilities and home health agencies. The Minimum Data Set (MDS) contains assessments for all residents in Medicare and or Medicaid certified nursing facilities, regardless of their individual payor status or their age. Similarly, the Outcome and Assessment Information Set (OASIS) data (48) contain assessments for individuals served by Medicare and or Medicaid certified home health agencies (49–52).

The MDS and OASIS data include comprehensive assessments for each individual at regular intervals to help nursing home and home health agency staff identify needs and develop care plans. The MDS, for example, includes over 400 items to assess residents' physical functioning, communication/hearing problems, behavioral symptoms, mood, care preferences, diagnoses, medication use, and, important to the MPS, cognitive function (50,51,53). MDS assessments are conducted by trained, licensed health professionals upon admission, quarterly, annually, upon discharge, and otherwise whenever the patient experiences a significant change in his or her health status. Approximately 17% of MDS-covered residents are under the age of 65 as Medicare coverage is not a requirement for nursing home care (54). The purpose of these linkages is to examine cognitive functional scores and other indicators for diagnoses and cognitive health outcomes following linkages with the MPS worker and veteran data with a particular interest in workers with radiation dose to brain tissue (4,8,20,24,26,38,39). Prescription drug use for the treatment of depression (e.g., Escitalopram (Lexapro)), dementia, Parkinson's disease and related disorders were obtained via linkages with the CMS Medicare Part D files and are being incorporated into the analyses of relevant outcomes. A description of CMS data files and key variables for the MPS study is provided in Supplemental Table 1.

### **CMS Chronic Conditions and Confounder Indicators**

Diagnosis codes within CMS claims files can be used to identify chronic conditions. CMS provides chronic condition flags for as many as 70 conditions beginning in 1999 through their Chronic Conditions Data Warehouse (CCW). These condition flags are available annually for each Medicare beneficiary with fee-for-service claims and are derived from algorithms that assess the presence of specific diagnoses and procedure codes across Medicare fee-for-service claims for as much as a 3-year look-back period. CMS developed the variables from algorithms validated from the research literature and criteria used by other federal resources as well as CMS-contracted expert panels who refined and enhanced the algorithms (48). The chronic condition flags that are available from CCW in the CMS data are listed in Supplemental Tables 2 and 3. There are two available CCW files, one that covers claims data from 1999–2019 and an updated dataset that covers from 2017 onward (with several overlapping years for both files). It is notable that several flags relate directly to important study outcomes, i.e., cognitive impairment conditions and neurodegenerative diseases (i.e., Alzheimer's disease, Parkinson's disease, dementia, depression, stroke, anxiety disorders, depressive disorders, epilepsy, intellectual disabilities, traumatic brain injury). In addition, there are several flags in the CCW data that relate to potential confounders in epidemiologic health studies (e.g., tobacco use, alcohol use, diabetes, obesity, hyperlipidemia, hypertension, opioid use disorder). Similar algorithms for the chronic conditions will also be run against the claims files for prior years where appropriate (e.g., Parkinson's disease).

### **Cognitive Scores Available in Nursing Home Minimum Data Set.**

All residents, regardless of payer status or age, who enter a Medicare and/or Medicaid-certified skilled nursing facility have an MDS assessment at admission. Prior to October 2010, patients' cognitive function was assessed with the MDS 2.0-derived cognitive performance scale (CPS2.0) (55). The CPS2.0 score is calculated using a complex algorithm

that assigns residents a score between 0–6 based on five MDS items (i.e., daily decision making, eating self-performance, ability to make oneself understood, short-term memory, whether or not the resident is comatose). The CPS2.0 scale corresponds closely with scores generated by the Mini-Mental State Examination and the Test for Severe Impairment, nursing judgments of disorientation, and neurological diagnoses of Alzheimer’s disease and other dementias (55). The MDS 3.0, introduced in October 2010 changed the calculation substantially by including the Brief Interview for Mental Status (BIMS) to assess residents’ cognitive function (56–58). For residents unable to complete the BIMS, assessors complete two items: short term memory and *cognitive skills for daily decision making* that enable calculation of the CPS3.0. The MDS 3.0 cognitive function scale (CFS) is a four-point scale that integrates the BIMS and the CPS3.0 (53,55,57). The CFS has high levels of construct validity (53). To reconcile the change in cognitive scoring over time, residents with a CPS2.0 score greater than 2 and a CFS score greater than 1 will be categorized as “cognitively impaired”; and residents with a CPS2.0 score of 5–6 or a CFS score of 4 categorized as “severely impaired.” These available quantitative measures of cognition among radiation workers with and without radiation dose to brain tissue will provide a powerful and unbiased assessment of whether low-dose rate exposures can cause clinically recognized memory loss and cognitive decline.

### **Cognition As Reported in the Home Health OASIS.**

To assess cognitive function among patients receiving health care at home, items M0610 in OASIS A, B, and B1 and M1740 in OASIS C, C1, and D are used. While M0610 and M1740 are named differently, they assess the same factors over time. Specifically, assessors evaluate behaviors and or cognitive, behavioral and psychiatric symptoms that are demonstrated at least once a week (either reported or observed). These include: 1) memory deficit; 2) impaired decision-making; 3) verbal disruption; 4) physical aggression; 5) disruptive, infantile, or socially inappropriate behavior; or 6) delusional, hallucinatory, or paranoid behavior. This concludes the descriptions of the comprehensive health care data that are available, and the extensive listings of outcomes and diagnoses related to cognitive disfunction and neurological and behavioral maladies. The wealth of information available on neurological outcomes and cognitive scores, coupled with radiation dose assessment, will lead to an evaluation that hitherto has never been attempted on such a large scale and on such a unique and large population.

### **Organ Dose Estimates**

Estimation of absorbed radiation dose to brain tissue and other organs are performed as described in NCRP Report No. 178 and other reports (36,38–40,59,60). The absorbed radiation dose to brain tissue from high-LET radiation is calculated using new and modified approaches developed by NCRP in Commentary No. 31 (26,61).

### **Brain Dose Reconstruction**

The overarching goal for dose reconstruction for neurobehavioral analysis is to quantify occupational brain doses from external radiation and internal radionuclides. Brain doses and associated uncertainties are based on the guidance published by NCRP in Report No. 178 (36). Under this approach, the brain is assumed to be the organ of interest

for neurodegenerative diseases, depression and cognitive dysfunction. Accordingly, brain doses for each cohort worker is reconstructed on an annual basis beginning from the first occupational radiation exposure until death, incidence of an outcome of interest, or end of follow-up. Initially, the total absorbed organ dose will be partitioned into low- and high-LET components without any assumptions about the biological effectiveness of any radiation types. Regarding external irradiation, the personal dose equivalent  $H_p(10)$  for workers is often available based on federally-required personnel monitoring. A substantial part of the dose reconstruction and uncertainty estimation is devoted to estimating the organ doses based on the records of  $H_p(10)$  as outlined by NCRP (36) and is considered in all aspects of dosimetry such as missing dose, multi-facility career dose, irradiation geometry, radiation spectra associated with likely types of external irradiation scenarios, and partial organ irradiation. External exposures include both photon and neutron exposures.

The MPS benefits from collaboration with the United States Transuranium and Uranium Registries (USTUR), a research program established as the National Plutonium Registry in 1968 by the Atomic Energy Commission (62). Designed as a program to improve radiation protection of nuclear workers, the USTUR studies the biokinetics and internal dosimetry of actinides (uranium, plutonium, and americium) in occupationally exposed workers (63–65). These workers voluntarily donated portions of their bodies, or their whole bodies, for scientific use posthumously. Today, the USTUR is one of the few programs worldwide that can comprehensively study biokinetics and dosimetry of internally deposited actinides. Currently, the USTUR and associated National Human Radiobiology Tissue Repository (NHRTR) hold data and tissue samples from 48 whole-body and 317 partial-body donors. Since 1993, USTUR/NHRTR has housed collections of tissue materials and records obtained from the Radium Worker study conducted at Argonne National Laboratory (65,66). The USTUR/NHRTR is a unique scientific resource (<https://ustur.wsu.edu>) that includes information on brain activity deposition, and biokinetics valuable for improving and refining the estimates of cognition-related tissue and organ doses (61).

## Data Analysis

Epicure, a software package frequently employed for radiation epidemiology studies, is functionally capable of analyzing datasets with millions of rows of data; however, the computational demand for MPS is so large that alternative software is being developed (67). With the very large size of the input data for a million or more workers, each worker with annual radiation doses for multiple years, outcomes, confounding and co-factor data, other demographic and occupational data, and information for uncertainty analyses, new software is being developed to handle fitting risk models and perform uncertainty analyses. This need for new software is being met by creating a library in open-source R statistical programming language (68) that will be optimized to handle input on the scale of over 20 million records and upwards of a billion data variables. The new software, called Colossus (69,70), can fit Cox regression models and Poisson regression models, similar to the PEANUTS and AMFIT programs within Epicure, respectively (71–73).

Work to develop such tools to run partial likelihood methods (such as Cox regression) and Poisson regression is underway using code written for the open-source R statistical

programming language and incorporating novel methods for speeding up the model fitting runtime on multi core, modern fast computers. The basis of the software approach is that R has the desired statistical tools and C++ can load and operate on large datasets. The software uses R for finding summary statistics and uses C++ to perform more intensive computations. The survival library (74,75) and stats library in R can perform Cox proportional hazards and Poisson regression modeling effectively on data with millions of person-years. Comparison with smaller datasets can be done with Statistical Analysis System (SAS) and Epicure. Development of R software is being accomplished by using the Rcpp library to transfer the data into C++ and then using the RcppEigen library to integrate the capabilities of the Eigen library and treat the calculation as a series of optimized matrix operations. Validated and documented statistical software packages will be deposited in public repositories (i.e., data at the individual level of one person year at risk) (76).

Data analysis will be based on fitting risk models to combined datasets, to estimate radiation-related risks for specific outcomes, either as a function of the relevant organ/tissue dose, e.g., brain, or risk per unit dose. The risk models will initially be based on linear dose-response models in which the radiation risk either adds to the baseline risk (excess absolute risk) or multiplies the baseline risk (excess relative risk). A further step in the software development will be to consider Multi Model Inference, which allows risk estimates to be based on several plausible dose-response models rather than relying on one single model of choice, the most common being the linear non-threshold (LNT) model (44, 77, 78). Both Cox and Poisson risk analysis methods will be included to fully characterize both the baseline risk and the excess risk due to radiation. Further, ensemble models (79, 80) and other methods (81) for addressing uncertainties will be considered.

## RESULTS

While the conceptual design discussed herein is being implemented, there are several results-related analyses that can be shared now. There are 26 cohorts of the MPS that were included in a linkage request to CMS; the cohorts, the numbers in the eligible populations, and those sent for CMS claims data linkage are listed in Table 1. The 26 MPS cohorts consisted of 934,075 workers, of whom 698,666 (74.8%) were eligible to be sent to CMS based on age and vital status as of 1999. There were 539,958 (77.3%) matches for these eligible workers. Some workers may have switched or joined Medicare Advantage, obtained insurance solely from the Veterans Health Administration, or only utilized private health insurance and thus did not appear in the CMS data for some intervals. The cohorts with the largest number of eligible workers were nuclear utility workers (n = 124,033 submitted), nuclear submariners (n = 112,727), medical workers (n=96,001), naval shipyard workers (n=77,128), industrial radiographers (n=73,986), and atomic veterans (n=65,023). These workers were exposed primarily to low-LET external radiation. The cohorts with the largest number of eligible workers with potential exposure to internal emitters and possible brain dose from high-LET radiation were workers at Hanford (n=27,982), LANL (n=18,340), Savannah River combined cohorts (n= 17,778), X-10 (n=15,408), Y-12 (n=13,511), and K-25 (n=11,512). These results indicate a large pool of workers (539,958) have the potential for claims-based clinical and demographic information. The earliest cohorts, with the oldest workers as of 1999, were the ones most likely to have high linkage rates over 93% for those

eligible, i.e., atomic veterans, radium dial painters, and workers at Mallinckrodt, Rocky Flats, Mound and Hanford. The cohorts with the youngest workers in 1999, as expected, had the smallest linkage rates, i.e., medical workers, industrial radiographers and nuclear submariners. In addition, MPS workers had an enrollment rate of between 20–25% from 2011–2015, and below 20% from 1999–2010, for Medicare Advantage, the managed care program for Medicare (also known as Medicare Part C). In the future, we plan on obtaining linkages to Medicare Advantage encounter data to obtain additional information for these groups.

Table 2 provides the linkage results for Parkinson's disease for the eligible workers from the 26 MPS cohorts. Parkinson's disease was selected for this first evaluation because of the increasing evidence that low-dose and low-dose rate exposure may be associated with increased risk (2,15,22,24). Currently, the algorithms to identify Parkinson's disease within CMS claims data cover the years 2017–2019 and thus only a fraction of diagnoses that are available back to 1999. For Parkinson's disease there were 6,104 (0.9 %) of eligible workers with CMS claims data covering the years 2017–2019 (Table 2). These incidence numbers for only three years can be contrasted with the 3,176 deaths attributed to Parkinson's disease among all cohorts over all calendar years followed, from the 1940s to the present, i.e., up to 80 years. The cohorts with more than 600 workers with indications of a Parkinson's disease diagnosis were nuclear utility workers, nuclear submariners, atomic veterans, medical workers, and nuclear shipyard workers. The cohorts with the potential for intakes of radionuclides and brain dose from high-LET alpha particles, with more than 200 incident matches for Parkinson's disease, include Hanford, LANL, X-10, Y-12, and K-25. The cohorts with more than 100 workers having died from Parkinson's disease include atomic veterans, Hanford, LANL, industrial radiographers, nuclear utility workers, and workers at X-10, Y-12, K-25, Savannah River and naval shipyards. There were 2,944 more claims data for Parkinson's disease for a three-year period than deaths over an 80-year period, i.e., the CMS linkage has already identified substantial numbers of workers with clinically meaningful disease that, as expected, exceed the number of workers dying of Parkinson's disease.

Each of the 23 specific CMS files and years requested and approved for linkage as part of this project are listed in Supplementary Table 4. It is noted that the data in Table 2 for Parkinson's disease, do not represent the full range of information available to obtain and confirm diagnoses. For example, Part D claims will be searched to identify specific drugs used to treat this condition, (e.g., Levodopa). Further, any eligible worker admitted to a nursing facility will have an MDS assessment at admission, which includes a cognitive assessment that produces the MDS 3.0 CFS (53,55,57). Table 3 provides the number of MDS assessment matches enabling the calculation of a CFS score for the years 1999–2019 among the eligible workers from the 26 MPS cohorts. A total of 161,139 (23.1%) workers have been identified as likely to have cognitive function scores with the highest numbers from the atomic veterans (n=26,459), the nuclear utility workers (n=16,744), and the naval shipyard workers (n=9,152).

Radiation absorbed doses to brain have been estimated for workers in 10 MPS cohorts. Table 4 provides mean, standard deviation (SD), median, percent  $\geq 100$  mGy, and maximum values

of brain dose in mGy. For the 10 MPS cohorts with individual estimates of brain dose, the mean cohort values ranged from 6.9 to 47.6 mGy and the maximum brain dose values ranged from 297 to 2,654 mGy.

## DISCUSSION

The linkages with CMS data are unique to epidemiologic occupational studies and provide an innovative approach to examining associations with neurodegenerative diseases while accounting for co-factor and confounding variables, such as smoking, alcohol consumption, blood pressure, obesity, and diabetes. No similar investigation to our knowledge has been conducted of this scale that involves over a million workers, followed for a period up to 80 years, with comprehensive radiation dose reconstructions, exquisite outcome ascertainment, and time-dependent assessment of multiple outcomes and multiple clinical and demographic factors. The initial goal is to learn whether neurological and behavioral conditions, depression, anxiety and cognitive function are related to brain disruption linked to radiation dose to brain. The initial linkages with 23 CMS data files identified 539,958 workers with claims-based data, i.e., who were Medicare beneficiaries. Parkinson's disease was evaluated among the 26 MPS cohorts for linkages based on age and vital status as of 1999 when CMS records became available. There were nearly twice as many diagnoses of Parkinson's disease in a three-year period, 2017–2019, than there were deaths in an 80-year period from the early 1940s to the present. A broad range of individual radiation dose to brain has already been estimated for over 500,000 workers in 10 MPS cohorts. The wealth of information available from CMS claims data, coupled with the epidemiologic foundation of the MPS, which has been ongoing for twenty years, will substantially enhance the quality and precision of these health evaluations for this new field of low-dose radiation and neurocognitive effects.

This innovative approach to radiation epidemiology is relevant to astronaut crew on long-term missions beyond earth orbit (4,25) and is built on a firm foundation: the MPS has been ongoing for over 20 years, has more than 100 scientific publications to date (82), and is overseen by radiation scientists around the nation (2,33,83); animal experiments indicate that neurological and behavior conditions result from GCR exposures (29); epidemiologic studies indicate radiation associations with Parkinson's disease (24); linkages with CMS data have been used in non-radiation epidemiologic studies of Alzheimer's disease, dementia, and cognitive impairment (53,84); existing CCW algorithms for chronic conditions provide validated outcome data on morbidity, confounding, and descriptive clinical and demographic information (85); new dose reconstruction approaches have been developed for brain tissue for both low-LET and high-LET exposures (26,39); and specialized software utilizing modern computational power have been developed to efficiently handle over a million workers with billions of data points including multiple time-dependent variables, while contributing to an in depth assessment of uncertainties (69).

### NASA Relevance

NASA evaluates nervous system risks in two categories: acute central nervous system (CNS) risk that could lead to in-mission performance decrement with a risk of mission loss and or

crew loss, and late CNS risk such as the development of neurodegenerative diseases post mission. NASA uses data from computational models, preclinical animal and cell models, and human data to characterize, manage, and quantitatively assess radiation risks (32,86–88). There are several limitations of the existing data for evaluating neurodegenerative diseases within spaceflight crews, specifically the small number of astronauts who have accumulated relatively high doses and their short follow-up for outcome evaluation (86–89). Furthermore, future missions that operate outside of LEO will experience prolonged exposures with increased cumulative doses from the complex radiation environment of GCR, including the energetic high-LET heavy ions found therein (79). Therefore, the data from the present study of terrestrial workers will provide important information from human cohorts to inform the NASA risk models for space radiation and approaches to risk mitigation, especially for long duration missions including trips to the Moon and Mars (2). Mars mission-related doses are expected to be of the order of 300–450 mGy (870–1200 mSv) (1,90–93) and are consistent with the radiation exposures in the MPS (2), in which exposures occurred over many years and not over minutes or weeks as in previous animal experiments or in the Life Span Study (LSS) of the atomic bomb survivors. Information from high-LET and low-LET brain exposures in humans, in combination with other computational and preclinical models, will aid in the NASA assessment and management of radiation risks (26,94–96).

However, it is recognized that no human terrestrial radiation exposures are ideal analogues to space radiation exposures as the doses, dose-rates, and radiation quality characteristics differ. No human terrestrial exposure can replicate the scenario of space radiation where heavy ions are traveling near the speed of light, and no terrestrial environment is comparable to a space station or vehicle (4). Nonetheless, when assessing energy deposition patterns in cell nuclei, there are overlaps between GCR versus terrestrial alpha emitting particles showing potential relevance for high-LET doses (95–96) (Fig. 1).

NASA has supported the development of tests that assess multiple domains of neurocognitive functions applicable to space flight including assessment of working memory, stability of sustained attention, and risk decision making. The Cognition Test Battery (COGNITION) has replaced the WinSCAT cognitive performance battery of tests (97–99). COGNITION uses multiple, brief, neurobehaviorally orthogonal tests, is neuroimaging based, and has been validated and normed on astronauts and other high performers (100). It is primarily used to assess changes in cognitive function (pre-mission, in-mission, and post-mission) and was used in the NASA Twin Study (101–102). However, long-term cognitive impairment, and risk for neurodegenerative diseases in astronauts, remains understudied (100). Using the CMS data that contain diagnoses and assessments of cognition – for MPS radiation workers receiving care from nursing facilities and home health agencies – combined with data detailing chronic radiation exposure in a terrestrial occupational environment will provide baseline data to inform risk assessments for space travel. Estimates of health effects related to cognition, behavioral changes, dementia and depression will be possible, and this human experience should help decision-makers in assessing radiation risks and setting radiation protection guidance.

## CMS Linkages - Conceptual Justifications

Medicare claims data are frequently used to identify prevalence and incidence of health conditions among older adults. For example, by comparing claim-based identification of Alzheimer's disease and related dementia to results from cognitive assessment tests, researchers have established that Medicare claims data for adults aged 65 and over can identify most cases of Alzheimer's disease or dementia but is less successful at identifying mild cases of dementia and is more likely to identify dementia among White adults than Black or Hispanic adults (103–104). Claims-based identification of Alzheimer's disease and related dementia has been used to explore differences in prevalence or incidence related to race and ethnicity, lifestyle factors, and statin use, among others (84,105, 106). Thus, procedures are in place to identify large numbers of workers with incident cases of Alzheimer's disease and related dementia, along with important demographic and clinical co-factor data, and evaluate associations with radiation dose to brain. Alzheimer's disease is of importance because of animal models suggesting an increase in cognitive impairment and  $\alpha\beta$  plaque accumulation following galactic cosmic radiation (107).

## Uncertainty Approaches

Quantification and propagation of uncertainties is crucial (1) for understanding the precision in outcome risk estimates obtained through analysis of the CMS datasets and (2) for later use when estimating risks and the associated uncertainty for individuals exposed to an annual series of doses (80, 86). Typically, excess risk parameterization includes an implicit assumption that the subject-specific covariates, including doses, are exact, and so the calculated confidence intervals do not include uncertainty contributions from these variables. While dosimetric uncertainty is always important to characterize, it is especially crucial when analyzing longitudinal series of low annual doses such as those considered in the MPS cohorts, where the uncertainty associated with annual doses may vary as a function of any number of dosimetric variables, including time.

The MPS is exploring ways to implement uncertainty approaches similar to those described in Federal Guidance Report (FGR) No. 13 (108) that tabulates cancer risk coefficients for internal or external exposure of the U.S. population to each of more than 700 radionuclides in environmental media such as air and drinking water. FGR 13 characterizes the expected reliability of individual risk coefficients in terms of broad, semi-quantitative uncertainty categories identified by letters A-E (109). Category A represented the most narrowly determined risk coefficients, Category E represented the least well characterized coefficients, and Categories B, C, and D represented intermediate, increasing levels of uncertainty. The latest available biokinetic models as described in NCRP Commentary No. 31 (26) are being used to predict uptake and retention of absorbed activity by the brain. The uncertainty in brain dose estimates for intake of any of the dosimetrically dominant radionuclides encountered so far at MPS sites (e.g., U or Pu isotopes, Ra-226, Po-210, and Am-241) are usually assigned to Category B or lower categories.

Recently, the NCRP published Commentary 34 (81) on dose uncertainties in radiation epidemiologic models which will be carefully considered. One possible method of dosimetric uncertainty propagation being considered is to use Monte Carlo sampling to

generate alternative, plausible realizations of annual dose series for each subject in the study using known or estimated probability density functions for each annual dose, and then reanalyze the entire dataset to generate the corresponding excess hazard function and associated confidence intervals for the corresponding realization. The Monte Carlo sampling process is repeated until statistical convergence of the mean excess hazard function is achieved and the construction of a joint probability density function for all excess hazard function model parameters is enabled. This method for dosimetric uncertainty propagation is computationally extensive and the regression must be performed hundreds or possibly thousands of times. Use of analysis code purpose-built for processing large datasets that employs extensive parallelization could make such an approach tractable. Model form uncertainty has historically not been considered in radiation epidemiology studies but could be included in a manner similar to dosimetric uncertainty. Here, probability density functions for the relative contribution to a linear combination of each of the proposed model forms could be defined, possibly informed by analyses of other cohorts and expert judgment (110–1127). A large number of realizations of the overall dose response form could be generated and used for regression. Propagation of covariate uncertainty (i.e., dosimetric uncertainty) and model form uncertainty could occur simultaneously since these are independent contributors to the overall uncertainty in excess hazard function.

## LIMITATIONS

The limitations associated with mortality data are recognized, including underrepresentation of health conditions that infrequently lead to death, the accuracy of coded information, and the inability to fully evaluate neurological and behavioral conditions (113,114). Thus, linkages with the CMS datasets will add appreciably to the quality and informativeness of the MPS. Over 700,000 workers and veterans were alive in 1999 and eligible for coverage by Medicare. Such a large number of radiation-exposed workers coupled with the wealth of information to be gleaned from the CMS datasets will be uniquely informative.

One limitation of the CMS data is that it will not provide complete lifetime coverage of all workers and veterans. Medicare coverage is available to adults aged 65 and older and adults under the age of 65 with significant disabilities who have at least 10 years of Medicare payroll taxes through their own work history or their spouses' work history. Except in instances where individuals received care from Medicare/Medicaid-certified nursing homes or home health care agencies, we will not have access to health outcome information prior to their Medicare eligibility. These data availability considerations may introduce potential bias: among individuals under the age of 65, we have information on history of diagnoses only for people who have significant disabilities or who use nursing home or home health services. For example, someone who qualifies for Medicare at age 55 due to dementia can be observed in CMS datasets; someone who is healthy at the same age will not be observed in CMS datasets until age 65. Without accounting for these differences in data availability that are correlated with health status, our estimates of relative risk may be biased. However, serious health conditions leading to death would be picked up in mortality analyses that will be contrasted with the CMS claims data. Thus, we have the opportunity to evaluate the level of potential bias related to CMS data availability. Further, we will continue linking over

the years with the CMS data when the worker reaches age 65 so that another evaluation of potential bias will be possible.

In addition, CMS data are only available to researchers beginning in 1999 with limited exception. Any MPS worker or veteran who died prior to 1999 are not eligible for CMS linkage; although we will have information on relevant conditions that caused the death. These workers who are not eligible for linkage are cohort specific and there is sufficient overlap to be able to evaluate the impact, if any, on the estimates of radiation-related risk. We also recognize that we have limited Medicare claims data for MPS participants who enroll or switch to Medicare Advantage, the managed care program for Medicare (also known as Medicare Part C), or whose healthcare was not billed to Medicare, such as those receiving healthcare exclusively from the Veterans Health Administration or other military or private health insurance. We note that over 98% of the atomic veterans eligible for Medicare, had at least one beneficiary claim, whereas for the younger cohort of nuclear submariners the match rate was lower, 63%, because of the age requirements for Medicare eligibility. Medicare Advantage enrollment has increased more in recent years among Black and Hispanic beneficiaries compared with White beneficiaries and among beneficiaries in disadvantaged neighborhoods, which will affect how representative traditional Medicare data are of these populations (115). The MPS study consists primarily of White workers and veterans who were employed for many years so that these important racial and ethnic issues may be relatively minor but will be evaluated.

On the plus side, we will have access to fee-for-service claims for Medicare Advantage beneficiaries in the CMS files associated with hospitalizations, skilled nursing (MedPAR includes inpatient and skilled nursing) drugs, and hospice use, as well as the assessment data from the nursing home MDS and home health OASIS claims. Future work is planned to examine the Medicare Advantage encounter data and Medicaid claims to potentially identify additional diagnoses and MPS participants. Additionally, there are limitations to the ascertainment of diagnoses in Medicare claims data. Even when Medicare claims data are available for MPS participants, there are limitations to how reliably claims data capture the participants' health conditions (106,116,117). Nonetheless, the unique worker and veteran populations studied in the MPS, their lengthy employment histories and known demographic features, will minimize many of these perceived limitations. It is important to realize that we have been conducting mortality dose-response analyses. For specific causes of death, such as a leukemia with a relatively high fatality rate, we will evaluate whether the CMS claims data provides the same or different estimates of radiation risk. We will evaluate any differences to obtain a sense of bias.

The CCW has performed validation efforts associated with currently developed algorithms for chronic and other conditions (85), and it will be important to assess the strength and validity of these algorithms for specific chronic conditions in this study. An assessment will include understanding if a CMS claims-based algorithm has been validated against a reliable gold standard (i.e., includes a standardized clinical assessment, based on a large cohort that is representative of the population, and includes identification of people with and without the disease of interest to enable sensitivity and specificity evaluations). Less reliable standards might include clinical assessments from medical charts or records that

include patients from only one provider or health system or a limited geographic region and include patients with and without the outcome condition of interest. Least reliable standards are based on comparisons to other administrative data sources instead of clinical assessments or do not include participants without the disease for assessing specificity. Other considerations include assessing the population used for chronic condition validation studies against the MPS populations (e.g., similar demographics, health insurance coverage, or health providers). Additional understanding of how well an algorithm performs with both ICD-9 and ICD-10 codes is key since prevalence rates in claims data could change for some conditions depending on codes employed (84–85). Claims algorithms vary in how accurately they predict the presence of a disease, a factor that will be taken into consideration (118). As we have begun, and presented here, Parkinson's disease will be one of the first chronic conditions carefully evaluated and validated. Alzheimer's disease and associated dementias will be a close second.

## CONCLUSIONS

The unique, challenging and innovative linkages of CMS claims data to employment characteristics, military databases, and dosimetry records enables the MPS to evaluate a wide range of both fatal and nonfatal chronic conditions, including neurobehavioral diseases and measures of cognition, among radiation workers who received exposure from low-LET gamma-radiation and/or high-LET neutron or alpha-particle exposure to brain tissue from intakes of radionuclides over a period of years while employed (and in later years from incorporated radionuclides). It is unique to capture clinical and behavioral information on important confounding and co-factor information such as smoking, alcohol, blood pressure, obesity, and diabetes over time. This ability to assess morbidity outcomes and chronic condition information represents an innovative and important step forward for occupational radiation epidemiology with the potential to provide additional insights on major questions about late health effects from chronic radiation exposures with substantial statistical precision. If there are provocative results, future possibilities include the potential for personal interviews to update cognitive scores for individuals, blood genetics on molecular/biological aging and markers of cognitive decline, amongst other radiation biology and epidemiology integrations. The MPS coupled with CMS appears limited only by the imaginations of the investigators (2).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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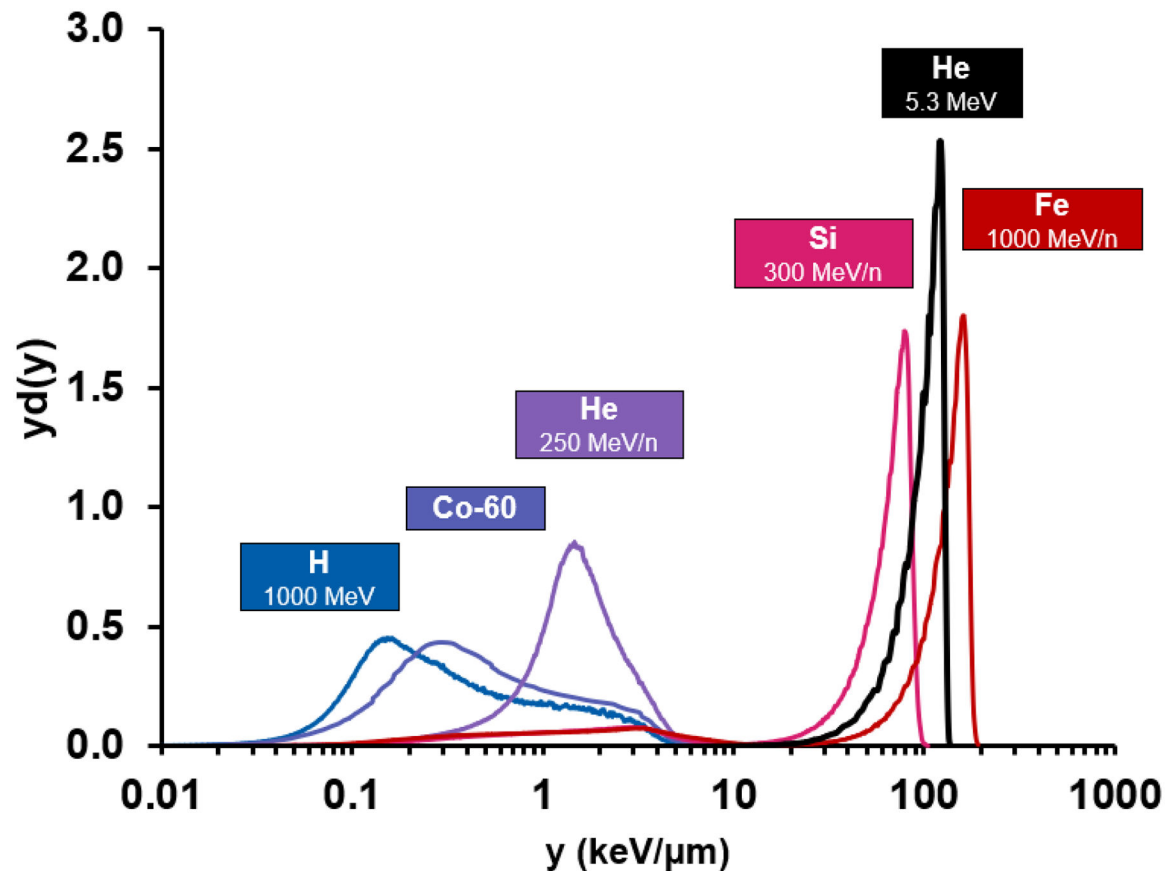


**Figure 1.**

Standard representation of a microdosimetric spectrum using a spherical target with a radius equal to  $4\ \mu\text{m}$  for ions of different LET. The x-axis displays lineal energy ( $y$ ) in  $\text{keV}/\mu\text{m}$  on a logarithmic scale and the y-axis is the dose distribution ( $d(y)$ ) multiplied by  $y$ . The spectrum for a Po-210 alpha particle, He at 5.3 MeV, is shown in black. The space radiation environment consists of both high and low-LET radiation. Alpha emitters, such as Po-210, more closely mimic the high-LET components of space radiation compared with photons (as shown for Co-60 gammas).

**TABLE 1**

Radiation Workers and Veterans in 26 MPS Cohorts Submitted to CMS and Results of the Beneficiary Matches indicating Available Claims Data for Study

| <b>MPS Cohort</b>                   | <b>Category</b>          | <b>Total number of workers</b> | <b>Sent to CMS for linkage</b> | <b>Number of beneficiary matches</b> | <b>Match rate (%)</b> |
|-------------------------------------|--------------------------|--------------------------------|--------------------------------|--------------------------------------|-----------------------|
| Atomic Veterans                     | Military and Veterans    | 114,270                        | 65,023                         | 63,983                               | 98.4%                 |
| Fernald                             | DOE Workers              | 7,406                          | 5,009                          | 4,423                                | 88.3%                 |
| Hanford                             | DOE Workers              | 44,157                         | 27,982                         | 26,256                               | 93.8%                 |
| Industrial Radiographers            | Industrial Radiographers | 123,401                        | 73,986                         | 48,518                               | 65.6%                 |
| K-25                                | DOE Workers              | 17,210                         | 11,512                         | 10,783                               | 93.7%                 |
| Los Alamos National Lab-Zia         | DOE Workers              | 26,328                         | 18,340                         | 16,994                               | 92.7%                 |
| Linde                               | DOE Workers              | 1,551                          | 431                            | 388                                  | 90.0%                 |
| Mallinckrodt                        | DOE Workers              | 2,514                          | 1,261                          | 1,221                                | 96.8%                 |
| Medical Workers                     | Medical Workers          | 109,019                        | 96,001                         | 64,303                               | 67.0%                 |
| Middlesex                           | DOE Workers              | 738                            | 144                            | 132                                  | 91.7%                 |
| Mound                               | DOE Workers              | 7,267                          | 4,728                          | 4,459                                | 94.3%                 |
| Naval Shipyard                      | Navy Shipyard Workers    | 95,698                         | 77,128                         | 54,813                               | 71.1%                 |
| Nuclear Submariners                 | Military and Veterans    | 112,727                        | 107,030                        | 67,451                               | 63.0%                 |
| Nuclear Utility Workers             | Nuclear Workers          | 135,193                        | 124,033                        | 99,781                               | 80.4%                 |
| Paducah                             | DOE Workers              | 5,731                          | 4,470                          | 4,082                                | 91.3%                 |
| Pantex                              | DOE Workers              | 5,427                          | 4,180                          | 3,804                                | 91.0%                 |
| Portsmouth                          | DOE Workers              | 8,453                          | 6,639                          | 5,951                                | 89.6%                 |
| Radium Dial Painters                | Radium Dial Painters     | 3,276                          | 822                            | 809                                  | 98.4%                 |
| Rocketdyne                          | DOE Workers              | 5,801                          | 4,260                          | 3,882                                | 91.1%                 |
| Rocky Flats                         | DOE Workers              | 9,397                          | 7,264                          | 6,971                                | 96.0%                 |
| Savannah River Site (SRS)           | DOE Workers              | 9,860                          | 6,209                          | 6,166                                | 99.3%                 |
| SRS Supplement                      | DOE Workers              | 12,952                         | 11,569                         | 7,278                                | 62.9%                 |
| Tennessee Eastman Corporation (TEC) |                          |                                |                                |                                      |                       |
| TEC Women                           | DOE Workers              | 13,951                         | 7,946                          | 7,352                                | 92.5%                 |
| TEC Men                             | DOE Workers              | 18,819                         | 3,780                          | 3,476                                | 92.0%                 |
| X-10                                | DOE Workers              | 22,746                         | 15,408                         | 14,060                               | 91.3%                 |
| Y-12                                | DOE Workers              | 20,183                         | 13,511                         | 12,622                               | 93.4%                 |
| Total                               |                          | 934,075                        | 698,666                        | 539,958                              | 77.3%                 |

TABLE 2

Parkinson's Disease CMS Matches for the Years 2017–2019 among 698,666 Eligible Workers Within 26 MPS Cohorts Contrasted with the Number of Deaths Due to Parkinson's Disease (PD) for All Years of Follow-Up Beginning in the 1940s

| MPS Cohort                  | Total number of workers | Submitted to CMS for linkage | Number of CMS PD matches | Match rate (%) | Number of PD deaths | Percent PD deaths for each cohort (%) |
|-----------------------------|-------------------------|------------------------------|--------------------------|----------------|---------------------|---------------------------------------|
| Atomic Vets                 | 114,270                 | 65,023                       | 741                      | 1.14%          | 861                 | 0.75%                                 |
| Fernald                     | 7,406                   | 5,009                        | 60                       | 1.20%          | 43                  | 0.58%                                 |
| Hanford                     | 44,157                  | 27,982                       | 317                      | 1.13%          | 301                 | 0.68%                                 |
| Industrial Radiographers    | 123,401                 | 73,986                       | 414                      | 0.56%          | 235                 | 0.19%                                 |
| K-25                        | 17,210                  | 11,512                       | 219                      | 1.90%          | 115                 | 0.67%                                 |
| Los Alamos National Lab-Zia | 26,328                  | 18,340                       | 246                      | 1.34%          | 273                 | 1.04%                                 |
| Linde                       | 1,551                   | 431                          | <11                      | <2.5%          | <11                 | <0.71%                                |
| Mallinckrodt                | 2,514                   | 1,261                        | 18                       | 1.43%          | 24                  | 0.95%                                 |
| Medical Workers             | 109,019                 | 96,001                       | 657                      | 0.68%          | 87                  | 0.08%                                 |
| Middlesex                   | 738                     | 144                          | <11                      | <7.6%          | <11                 | <1.49%                                |
| Mound                       | 7,267                   | 4,728                        | 76                       | 1.61%          | 44                  | 0.61%                                 |
| Naval Shipyard              | 95,698                  | 77,128                       | 626                      | 0.81%          | 111                 | 0.12%                                 |
| Nuclear Submariners         | 112,727                 | 107,030                      | 793                      | 0.74%          | 87                  | 0.08%                                 |
| Nuclear Utility Workers     | 135,193                 | 124,033                      | 984                      | 0.79%          | 140                 | 0.10%                                 |
| Paducah                     | 5,731                   | 4,470                        | 51                       | 1.14%          | 39                  | 0.68%                                 |
| Pantex                      | 5,427                   | 4,180                        | 34                       | 0.81%          | 37                  | 0.68%                                 |
| Portsmouth                  | 8,453                   | 6,639                        | 90                       | 1.36%          | 61                  | 0.72%                                 |
| Radium Dial Painters        | 3,276                   | 822                          | <11                      | <1.39%         | <11                 | <0.34%                                |
| Rocketdyne                  | 5,801                   | 4,260                        | 45                       | 1.06%          | 36                  | 0.62%                                 |
| Rocky Flats                 | 9,397                   | 7,264                        | 80                       | 1.10%          | 57                  | 0.61%                                 |
| Savannah River              | 9,860                   | 6,209                        | 99                       | 1.59%          | 112                 | 1.14%                                 |
| Savannah River Supplement   | 12,952                  | 11,569                       | 64                       | 0.55%          | 14                  | 0.11%                                 |
| TEC Men                     | 18,819                  | 3,780                        | <11                      | <0.29%         | 98                  | 0.52%                                 |
| TEC Women                   | 13,951                  | 7,946                        | 20                       | 0.25%          | 80                  | 0.57%                                 |
| X-10                        | 22,746                  | 15,408                       | 215                      | 1.40%          | 160                 | 0.70%                                 |
| Y-12                        | 20,183                  | 13,511                       | 242                      | 1.79%          | 132                 | 0.65%                                 |
| Total                       | 934,075                 | 698,666                      | 6,104                    | 0.87%          | 3,160               | 0.34%                                 |

**TABLE 3**

Minimum Data Set (MDS) Assessment Matches indicating the Potential for Cognitive Performance Scores for the Years 1999–2019 among 698,666 Eligible Radiation Workers within 26 MPS Cohorts

| <b>MPS Cohort</b>           | <b>Total number of workers</b> | <b>Number submitted to CMS for linkage</b> | <b>MDS assessment matches</b> | <b>Match rate (%)</b> |
|-----------------------------|--------------------------------|--------------------------------------------|-------------------------------|-----------------------|
| Atomic Vets                 | 114,270                        | 65,023                                     | 26,459                        | 40.7%                 |
| Fernald                     | 7,406                          | 5,009                                      | 1,603                         | 32.0%                 |
| Hanford                     | 44,157                         | 27,982                                     | 7,706                         | 27.5%                 |
| Industrial Radiographers    | 123,401                        | 73,986                                     | 8,910                         | 12.0%                 |
| K-25                        | 17,210                         | 11,512                                     | 3,347                         | 29.1%                 |
| Los Alamos National Lab-Zia | 26,328                         | 18,340                                     | 4,867                         | 26.5%                 |
| Linde                       | 1,551                          | 431                                        | 231                           | 53.6%                 |
| Mallinckrodt                | 2,514                          | 1,261                                      | 500                           | 39.7%                 |
| Medical Workers             | 109,019                        | 96,001                                     | 7,099                         | 7.4%                  |
| Middlesex                   | 738                            | 144                                        | 83                            | 57.6%                 |
| Mound                       | 7,267                          | 4,728                                      | 1,608                         | 34.0%                 |
| Naval Shipyard              | 95,698                         | 77,128                                     | 9,152                         | 11.9%                 |
| Nuclear Submariners         | 112,727                        | 107,030                                    | 7,802                         | 7.3%                  |
| Nuclear Utility Workers     | 135,193                        | 124,033                                    | 16,744                        | 13.5%                 |
| Paducah                     | 5,731                          | 4,470                                      | 1,167                         | 26.1%                 |
| Pantex                      | 5,427                          | 4,180                                      | 1,040                         | 24.9%                 |
| Portsmouth                  | 8,453                          | 6,639                                      | 1,727                         | 26.0%                 |
| Radium Dial Painters        | 3,276                          | 822                                        | 608                           | 74.0%                 |
| Rocketdyne                  | 5,801                          | 4,260                                      | 1,217                         | 28.6%                 |
| Rocky Flats                 | 9,397                          | 7,264                                      | 2,080                         | 28.6%                 |
| Savannah River              | 9,860                          | 6,209                                      | 2,144                         | 34.5%                 |
| Savannah River Supplement   | 12,952                         | 11,569                                     | 656                           | 5.7%                  |
| TEC Men                     | 18,819                         | 3,780                                      | 1,898                         | 50.2%                 |
| TEC Women                   | 13,951                         | 7,946                                      | 4,860                         | 61.2%                 |
| X-10                        | 22,746                         | 15,408                                     | 4,458                         | 28.9%                 |
| Y-12                        | 20,183                         | 13,511                                     | 3,952                         | 29.3%                 |
| Total                       | 934,075                        | 698,666                                    | 161,139                       | 23.1%                 |

TABLE 4

Radiation Absorbed Dose to Brain among Workers in 10 MPS Cohorts<sup>a</sup>

| MPS cohort                                  | Total number of workers | Mean (mGy) | SD (mGy) | Median (mGy) | Percent $\geq 100$ mGy | Maximum (mGy)      |
|---------------------------------------------|-------------------------|------------|----------|--------------|------------------------|--------------------|
| Low-LET exposure                            |                         |            |          |              |                        |                    |
| Nuclear Power Plant Workers                 | 135,193                 | 33.2       | 45.5     | 17.2         | 6.58                   | 834                |
| Industrial Radiographers                    | 123,401                 | 11.9       | 31.2     | 1.1          | 2.10                   | 977                |
| Medical Radiation Workers                   | 109,019                 | 18.9       | 27.7     | 9.8          | 1.15                   | 1,080              |
| Atomic Veterans                             | 113,806                 | 6.9        | 17.7     | 2.6          | 0.05                   | 2,654 <sup>d</sup> |
| High-LET and Low-LET exposures              |                         |            |          |              |                        |                    |
| Los Alamos National Laboratory <sup>b</sup> | 26,328                  | 11.6       | 39.4     | 0.8          | 1.78                   | 760                |
| Rocky Flats <sup>b</sup>                    | 9,397                   | 47.6       | 89.0     | 13.2         | 11.7                   | 831                |
| Mound <sup>c</sup>                          | 4,954                   | 26.1       | na       | na           | na                     | 937                |
| Rocketdyne <sup>c</sup>                     | 5,801                   | 13.5       | na       | na           | na                     | 1,000              |
| Mallinckrodt <sup>b</sup>                   | 2,514                   | 35.0       | 61.0     | 13.8         | 8.79                   | 746                |
| Fernald <sup>b</sup>                        | 6,170                   | 11.2       | 24.5     | 1.1          | 1.26                   | 297                |

<sup>a</sup> Brain doses represent the latest study compilations and may differ slightly from previously published values.<sup>b</sup> Dose weighting factor of 1 applied for plutonium and uranium.<sup>c</sup> Personal dose equivalent, mSv.<sup>d</sup> This relatively high maximum dose was due to radiation exposures received by a veteran at places of employment other than during nuclear weapons testing.

na denotes not available