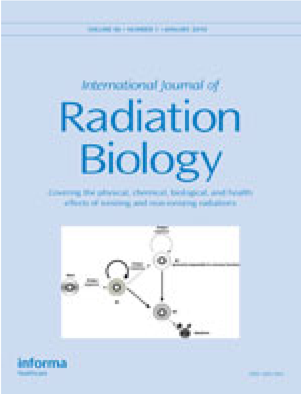

A MILLION PERSONS, A MILLION DREAMS: A VISION FOR A NATIONAL CENTER OF RADIATION EPIDEMIOLOGY AND BIOLOGY

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A MILLION PERSONS, A MILLION DREAMS: A VISION FOR A NATIONAL CENTER OF RADIATION EPIDEMIOLOGY AND BIOLOGY

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ABSTRACT

Background: Epidemiologic studies of radiation-exposed populations form the basis for human safety standards. They also help shape public health policy and evidence-based health practices by identifying and quantifying health risks of exposure in defined populations. For more than a century, epidemiologists have studied the consequences of radiation exposures, yet the health effects of low levels delivered at a low-dose rate remain equivocal.

Materials and Methods: The Million Person Study (MPS) of U.S. Radiation Workers and Veterans was designed to examine health effects following chronic exposures in contrast with brief exposures as experienced by the Japanese atomic bomb survivors. Radiation associations for rare cancers, intakes of radionuclides, and differences between men and women are being evaluated, as well as noncancers such as cardiovascular disease and conditions such as dementia and cognitive function. The first international symposium, held November 6, 2020, provided a broad overview of the MPS. Representatives from four U.S. government agencies addressed the importance of this research for their respective missions: U.S. Department of Energy (DOE), the Centers for Disease Control and Prevention (CDC), the U.S. Department of Defense (DOD), and the National Aeronautical Space Agency (NASA). The major components of the MPS were discussed and recent findings summarized. The importance of radiation dosimetry, an essential feature of each MPS investigation, was emphasized.

Results: The seven components of the MPS are DOE workers, nuclear weapons test participants, nuclear power plant workers, industrial radiographers, medical radiation workers, nuclear submariners, other U.S. Navy personnel, and radium dial painters. The MPS cohorts include tens of thousands of workers with elevated intakes of alpha particle emitters for which organ-specific doses are determined. Findings to date for chronic radiation exposure suggest that leukemia risk is lower than after acute exposure; lung cancer risk is much lower and there is little difference in risks between men and women; an increase in ischemic heart disease is yet to be seen; esophageal cancer is frequently elevated but not myelodysplastic syndrome; and Parkinson's disease may be associated with radiation exposure.

Conclusions: The MPS has provided provocative insights into the possible range of health effects following low-level chronic radiation exposure. When the 34 MPS cohorts are completed and combined, a powerful evaluation of radiation-effects will be possible. This final article in the MPS special issue summarizes the findings to date and the possibilities for the future. A National Center for Radiation Epidemiology and Biology is envisioned.

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INTRODUCTION

The first international virtual symposium was held online on November 6, 2020, on the Study of One Million Radiation Workers and Veterans (MPS) on Low-Level Radiation Health Effects (Boice et al. 2019a). The symposium was co-sponsored by Memorial Sloan Kettering Cancer Center (MSKCC), the National Council on Radiation Protection and Measurements (NCRP), and the Greater New York Chapter, the Baltimore-Washington Chapter, and the New Jersey Chapter of the Health Physics Society. The virtual workshop was attended by more than 300 individuals and included four presentations on the importance of radiation epidemiology to the missions of four U.S. government agencies by their representatives and 12 scientific presentations by collaborating members of the MPS research team, coupled with extensive question and answer sessions. A summary of the presentations, questions and answers, and conclusions, along with citations to other MPS publications, is reported here. Several presentations included preliminary results. Citations to published or submitted manuscripts referring to the formal results are provided to enable readers to seek additional details on specific cohorts, results, and conclusions.

PRESENTATIONS

1. Welcome and Introduction was presented by Dr. Kathryn D. Held (NCRP, and Massachusetts General Hospital / Harvard Medical School).

The critical evaluation of the health effects of low dose and low dose rate radiation exposures in healthy U.S. populations being conducted through the MPS[1] is of great value for providing an enhanced understanding of the science needed for sound radiation protection policy and recommendations (Boice et al. 2019b). In partnership with numerous U.S. government agencies and other organizations, the NCRP has been involved in the MPS under the directorship of Dr. John Boice, for over a decade. NCRP is a Congressionally-chartered, non-government, non-profit organization that has the mission to support radiation protection by providing independent scientific analysis, information, and recommendations that

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[1] also known as the Million U.S. Workers and Veterans Study (MWS), and earlier as the Atomic and Nuclear Energy Worker (ANEW) Study [http://anewstudy.org/]

represent the consensus of leading scientists. Hence, the NCRP has supported and fostered the conduct of the MPS epidemiology and dosimetry studies and helped disseminate the important findings of those scientific efforts through NCRP Reports (NCRP 2018a), Commentaries (NCRP 2020a), and other published works (Boice et al. 2019a, 2020, 2021a), as well as at scientific meetings. This virtual symposium was a superb opportunity to further disseminate findings and information on the importance of the MPS.

2. A Million Persons, A Million Dreams – Overview of the MPS was presented by Dr. John D. Boice Jr. (NCRP, and Vanderbilt University School of Medicine) and Dr. Lawrence T. Dauer (MSKCC).

The MPS is designed to address the major unanswered question in radiation risk understanding: What is the level of health effects when exposure is gradual over time and not delivered briefly (Boice et al. 2019a; Boice and Dauer 2021)? Over a million healthy American workers and veterans are being studied to evaluate cancer and non-cancer mortality following low-level low-linear energy transfer (LET) and high-LET exposure; rare cancers; intakes of radioactive elements; and differences in risks between women and men.

The MPS consists of seven categories of persons exposed to radiation from 1913 to the present Table 1). Over 30 individual radiation cohorts are included in these broad groupings. The U.S. Department of Energy Health and Mortality study began over 40 years ago and is the source of upwards of 300,000 workers (Ellis et al. 2018). Over 25 years ago, the U.S. National Cancer Institute (NCI) collaborated with the U.S. Nuclear Regulatory Commission to effectively create a registry of radiation workers from which cohorts of nuclear power plant workers (n=135,193) and industrial radiographers (n=123,556) were drawn (Hagemeyer et al. 2018). For over 60 years, the U.S. Department of Defense collected data on aboveground nuclear weapons test participants (n=114,270) (Boice et al. 2020). At the request of NCI in 1978, Landauer, Inc., a dosimetry service provider, began preserving their dosimetry databases which subsequently provided the exposure data used to identify a cohort of 109,019 medical workers as well as to identify supplementary workers at nuclear power plants and workers who were industrial radiographers (Yoder et al. 2018, 2021; NCRP 2020a). The U.S. Navy has recorded dosimetry information since the 1950s on nuclear submariners (~113,000) and nuclear shipyard workers (~96,000) (Mueller et al. 2020). The study of radium dial painters (n=3,276) began in the 1920s and was recently reactivated (Martinez et al. 2021). The MPS is a U.S. national effort and relies on the active cooperation and support of federal agencies (US GAO 2017). The key to high-quality epidemiology is comprehensive dose reconstructions for individuals within each of the seven MPS components (NCRP 2018a; Dauer et al. 2018).

The MPS vision is to provide broad scientific understanding of health effects following prolonged exposure to radiation. Such understanding will improve guidelines to protect workers and the public; improve input to compensation schemes for workers, veterans, and the public; provide guidance for policy and decision-makers; and provide evidence for or against the continued use of the linear non-threshold dose-response model in radiation protection to manage low doses.

3. Dosimetry is Key to Excellent Epidemiology was presented by Dr. R. Craig Yoder (Landauer, Inc., retired).

Dosimetry enables the quantitative stratification of those workers receiving the most radiation exposure from those receiving the least. It permits epidemiologists to relate disease incidence with a radiological quantity and develop response functions. In the case of the MPS, dosimetry aims to estimate the mean or average absorbed dose to an organ or tissue (organ dose) usually abbreviated as D_T. This quantity cannot be measured and must be estimated using a combination of mathematical models and data from measurable quantities. Uncertainties arise from the differences between the real-world radiological exposure environments and the idealized conditions depicted in the models. Reconstructing workers' doses becomes an exercise of identifying the most appropriate models that predict organ dose and converting a large assortment of measured data into the inputs required by the models. Complexity arises from the large variety of exposure conditions that influence this process and changes in these conditions over the nearly 70 years of observation relevant to the MPS. Epidemiological analyses require organ doses to be expressed in both annual and lifetime accumulated values. Changes in the metrological methods and radiation safety quantities introduce issues affecting the comparability of lifetime data. Changes in regulatory requirements on radiation measurements and record-keeping, e.g., monitoring to assess the maximally exposed part of the body, impart additional challenges to compiling lifetime organ absorbed dose values.

NCRP Report 178, Deriving Organ Doses and Their Uncertainty for Epidemiological Studies (NCRP 2018a; Dauer et al. 2018), provides a framework for the dose reconstruction process to be used for the various worker and atomic veteran cohorts forming the MPS. The key steps in this framework that influence the dosimetry are the construction of the pathways for internal and external exposure, and the selection of the irradiation geometries for external exposure and of the biokinetic models for internal exposure. Each cohort presents unique considerations regarding the types and energies of radiation leading to dose along with the approaches to radiological monitoring and availability of lifetime exposure data. Influences that create conditions leading to inhomogeneous irradiation of the body, such as leaded aprons and other shielding fixtures, present special challenges for tissues distributed widely in the body. Less scientific or technical difficulties arise from identifying the completeness of an individual's dose history and uncertainties affecting the ability to relate radiation safety monitoring results to a specific individual. These issues affect both internal and external dosimetry efforts and vary in importance depending on the specific worker cohort.

The recently published NCRP Commentary No. 30, Using Personal Monitoring Data to Derive Organ Doses for Medical Radiation Workers, with a Focus on Lung (Yoder et al. 2018, 2021; NCRP 2020a), details the external dosimetry process for medical workers. This cohort was primarily exposed to x and gamma rays and includes large numbers of women from which to examine possible sex-related differences in disease mortality or incidence, depending on the health effect of concern. NCRP Commentary No. 30 gives examples of both the technical and administrative challenges involved in providing annual doses that add up to a lifetime organ dose value.

4. *Importance of Radiation Epidemiology: CDC Perspective* was presented by Dr. Armin Ansari (Centers for Disease Control and Prevention).

The practice of radiation protection is based on application of scientific data, together with consideration of ethical principles and societal factors, to provide for health and safety of workers and members of the public, including at-risk populations. During the last hundred years, we have learned a great deal about the biological effects of radiation on cellular and animal models. Radiation's mutagenic and carcinogenic effects are characterized in these experimental systems (NRC 2006; NCRP 2018b; UNSCEAR 2020). However, what informs our radiation protection and public heath practice concerning the long-term effects of human exposures to ionizing radiation comes primarily from epidemiologic data on cancer and non-cancer diseases – most notably from the Life Span Study (LSS) of Japanese atomic bomb survivors. Except for occupational accidents, medical overexposures, or some acts of terrorism, most environmental exposures (including radon and technologically enhanced naturally occurring radioactive material [TENORM]), medical exposures, and occupational exposures (including nuclear workers and aircrews) are low doses accumulated from protracted low dose-rate exposures. Even in the aftermath of a major nuclear or radiological emergency, critical public health decisions in response and recovery (IAEA 2011; US EPA 2017; ICRP 2020) are informed by what we know about the risk of exposure at low doses and low dose-rates, and uncertainties of those estimates. These critical decisions include evacuation, relocation, the embargo of food and agricultural products, waste management, remediation, and long-term monitoring of exposed population. While direct observation of human health effects by epidemiologic means at low doses remains highly challenging, use of biologically based dose-response models can supplement epidemiological data and enhance the estimation of health (NCRP 2020b). Ultimately, while a multitude of factors can modulate the health effects of radiation exposure, we depend on reliable epidemiological studies to inform our radiation protection and public health practices (Ansari et al. 2019; Boice et al. 2019b).

5. *MPS Cohort: Medical Worker Study* was presented by Dr. Lawrence T. Dauer (Memorial Sloan Kettering Cancer Center).

The MPS includes a cohort of U.S. workers exposed to radiation as a consequence of performing various medical procedures that involve the use of ionizing radiation (medical radiation workers). Among the different cohort groups studied as part of the MPS, the medical radiation worker group features the highest percentage of female subjects (49%) from which to examine adverse radiation effects that may vary according to sex, particularly the development of lung cancer (NCRP 2020a). NCRP Report No. 178 (NCRP 2018a) developed a framework for external radiation exposures along with tables and figures of conversion coefficients for relating measured approximations of the personal dose equivalent, $H_p(10)$ (the dose equivalent at a depth of 10 mm in the body expressed in units of mSv), to selected tissue and organ doses, D_T expressed in mGy (data essential for epidemiology studies). NCRP Commentary No. 30 (NCRP 2020a) has further and more specifically delineated considerations for deriving organ doses for the medical radiation worker cohort that depend on the development of radiation exposure scenarios to describe the radiological and physical conditions to which specific categories of medical workers may have been exposed. Dose-response analyses are based on organ-specific lung doses estimated for each worker based on his or her job-based exposure scenario and calendar years of monitoring. Four medical exposure scenarios were evaluated: general radiology characterized by low-energy x-ray exposure with no lead apron use; interventional radiologists or cardiologists (lead apron wearers); nuclear medicine personnel; and radiation oncologists (mainly nurses and technologists and some medical doctors) receiving high-energy gamma (photon) doses. Table 2 provides information on the lung doses for the four occupational categories. The lower doses among interventionalists are related to the use of lead aprons which appreciably diminished the absorbed dose to lung. The results of the study of U.S. medical radiation workers have recently become available (Boice et al. 2021a). Overall, the MPS medical workers were at increased risk for lung cancer and risk was higher among men than women. There were no statistically significant radiation-associations with leukemia excluding CLL, ischemic heart disease or other specific causes of death. A positive but not statistically significant dose response was found for Parkinson’s disease.

6. *Importance of Radiation Epidemiology*: The U.S. Department of Energy Perspective was presented by Dr. Joey Y. Zhou (Department of Energy).

The U.S. Department of Energy (US DOE) has supported all aspects of the MPS since the feasibility study in 2009-2010, funded by the Office of Science and now by the Office of Environment, Health, Safety & Security. Twenty-six percent (260,000) of the MPS study population comes from former U.S. DOE radiation workers (Boice et al. 2019a). The U.S. DOE and its predecessors have a long history in conducting and supporting radiation epidemiological studies. Surveillance of radiation exposure and its health effects were implemented shortly after the Manhattan Project began in 1942. The Radiation Exposure Information and Reporting System (REIRS) was established in 1968 to serve as the central repository of occupational radiation exposure records (Hagemeyer et al. 2018; NRC 2020). The feasibility studies of using personnel, employment, medical, radiation exposure, and facility records to conduct epidemiologic mortality studies were completed in the 1960s while the health and mortality studies of radiation workers across U.S. DOE facilities were carried out from the early 1970s (Ellis et al. 2018). The Epidemiological Records Moratorium, "an agency-wide freeze" on the destruction of all epidemiological records, was issued in 1990. The Comprehensive Epidemiologic Data Resource (CEDR) also was created in 1990 to allow researchers to access data from the U.S. DOE epidemiological studies program (US DOE 2020). The CEDR became a major source of data used to extend the follow up U.S. DOE worker cohorts for the MPS. The U.S. DOE has data for over 650,000 former radiation workers and about 75,000 current radiation workers. The MPS can provide valuable research findings to improve U.S. DOE former worker medical screening and compensation programs, and to enhance the protection of current radiation workers.

7. *MPS Cohort: Mortality among Workers at the Los Alamos National Laboratory, 1943-1984* was presented by Dr. Sarah S. Cohen (EpidStrategies).

Los Alamos National Laboratory (LANL), established in 1942 during the Manhattan Project, continues operations today to solve national security challenges. This MPS study (Boice et al. 2021b) includes 26,328 male and female workers who worked at LANL between 1943-1980 and were employed by LANL or Zia, the LANL maintenance contractor for the site. Vital status was determined through December 31, 2017. External radiation monitoring data were available from 1944 through 1990. The greatest potential for elevated doses from internal emitters arose from ^{238}Pu and ^{239}Pu. Doses to the 6,499 workers monitored for plutonium were based almost entirely on plutonium urinalyses for which there were over 158,000 (or 24.3 samples per worker on average). External doses also were received at facilities other than at LANL and were available from the U.S. DOE Radiation Exposure Monitoring System (REMS); U.S. Nuclear Regulatory Commission (NRC) REIRS; Landauer, Inc.; U.S. Navy Dosimetry System and other military databases; and the Nuclear Test Personnel Review Program. All dose estimates from photons, neutrons, tritium, ^{238}Pu, and ^{239}Pu were combined to obtain organ-specific doses received by each worker for each calendar year. Standardized Mortality Ratio (SMR) analyses were conducted as well as internal analyses using Cox proportional hazards models with adjustment for sex, educational attainment, and year of birth. Excess relative risks (ERR) were also estimated. The LANL population was 75% male and 81% White. At the end of vital status tracing, 60% had died, and only 89 (<1%) were lost to follow-up. The presentation included SMRs for lung cancer and leukemia other than chronic lymphocytic leukemia (CLL), as well as the associated hazard ratios (HRs) from the Cox model and ERRs. Full study results for the LANL population are available (Boice et al. 2021b). Radiation was not found to increase the risk of leukemia or lung cancer. Esophageal cancer, however, was associated with radiation; bone cancer was linked to plutonium intakes, and there was a suggested radiation association for Parkinson's disease. Ischemic heart disease (IHD) and cerebrovascular disease were not associated with radiation dose. More precise evaluations are planned with pooled analysis of workers with similar exposures such as at Rocky Flats (Boice et al. 2019a).

8. *MPS Cohort: Nuclear Power Plant Workers and Industrial Radiographers*, was presented by Dr. Lawrence T. Dauer (Memorial Sloan Kettering Cancer Center).

The two largest cohorts within the MPS are the nuclear power plant workers and the industrial radiography workers. More than 500,000 workers have been employed in U.S. nuclear power plants since the first commercial production of electricity in 1957 (NCRP 2018a). The consistent reporting of annual worker doses required by the U.S. NRC for their licensees provides a high-quality dosimetry database that was redesigned in 1994 to facilitate epidemiologic study (Hagemeyer et al. 2018). Because workers' annual recorded dose in the nuclear industry has decreased over the years down to on the order of 2 mSv or less on average, only the workers at nuclear power plants first employed from 1957 through 1985 are included in the MPS. Cohort members were selected from databases available from the REIRS, which is maintained by the U.S. NRC, and supplemented with data available from Landauer, Inc. The number of nuclear power plant workers under study (n=135,193) includes nearly three times the number of adults males and females over age 20 years at exposure than the study of Japanese atomic bomb survivors, and over seven times the number of adult males. Most radiation exposures were due to penetrating external gamma rays, although low-level neutron exposures were possible during some reactor work circumstances. There were no or negligible internal exposures. The results have been recently published (Boice et al. 2021c). Occupational exposure to radiation over many years increased the risk of leukemia other than CLL as seen in the nuclear power plant workers and industrial radiographers (Table 3, Table 4). Radiation associations were not found for either lung cancer or ischemic heart disease. An association with Parkinson's disease was suggested, but was not statistically significant. There was no difference in the calculated radiation risk for lung cancer between men or women who worked at a nuclear power plant, although the estimates were imprecise. Mesothelioma and asbestosis were significantly elevated (Mumma et al. 2018).

Industrial radiography is an inspection method to detect fractures and other deficiencies in metallic and other dense materials by exploiting the penetrating ability of higher energy photons to create radiographic images, typically using film, of the defects. The period of greatest external exposure for radiographers is during the time the source (e.g., x-ray, ^{192}Ir and ^{60}Co) is outside its shielded container while being transported into and from the material being radiographed but also depends on the time required to achieve a radiographic image with the appropriate contrast to reveal any defects (NCRP 2018a). For the MPS, a cohort of 123,556 workers employed as industrial radiographers in the United States as early as 1940 was selected from records within the REIRS database and Landauer dosimetry database. To date, 26,000 of the industrial radiographers are known to have worked in naval shipyards. Preliminary epidemiology results (Table 3) show a significant excess of leukemia other than CLL (NCRP 2018b). A significant dose-response for lung cancer among males but not among females was seen (Boice et al. 2019c). Mesothelioma and asbestosis were significantly increased and linked to asbestosis exposure in shipyards (Mumma et al. 2018).

9. *Importance of Radiation Epidemiology: the U.S. Department of Defense Perspective* was presented by Dr. Paul K. Blake (Defense Threat Reduction Agency).

The U.S. Department of Defense (U.S. DoD) currently employs approximately three million military (active & reserve) and civilian workers. Approximately 70,000 U.S. DoD workers (2%) are annually monitored for ionizing radiation exposure (Blake and Komp 2014). U.S. DoD workers and their dependents can potentially be exposed to ionizing radiation for medical purposes and during nuclear war scenarios or operations other than war. The U.S. military was an early adopter of ionizing radiation for diagnostic purposes. Less than three years after Roentgen's discovery of the X-ray, both the U.S. Army and U.S. Navy were employing X-ray machines in the war with Spain (1898). However, U.S. DoD's existing occupational radiation exposure records programs arose during the Manhattan Project in World War II. These programs expanded with the U.S. development of nuclear weapons and nuclear power applications. The U.S. DoD radiation monitoring infrastructure includes three nationally accredited external personal radiation dosimetry programs (Army, Navy, and Air Force), a variety of internal personal monitoring programs, various environmental and food radiological analysis laboratories, and five radiation dose repositories with records on over 2 million individuals [Atomic Veterans (1945-1992), Army/National Guard, Navy/Marines, Air Force, and Operation Tomodachi Registry (OTR)] (Blake 2014). The OTR is unique in that it includes dependents, in addition to military and civilian adults (Marro 2014). U.S. DoD dose repositories also include Coast Guard and Merchant Marine exposures and non-US DoD visitor exposures. There have been numerous radiation epidemiology studies of these workers (Mueller et al. 2020). Most of these studies have been performed by external entities, including the ongoing MPS, which includes 114,270 male veterans who participated in seven U.S. atmospheric nuclear test series, and the first test at TRINITY (Boice et al. 2020). In summary, radiation epidemiology studies are important to U.S. DoD in (1) understanding the impact of ionizing radiation exposures on the health and safety of the U.S. DoD-affiliated population, (2) addressing the credibility of U.S. DoD's radiation safety programs, and (3) providing a technical basis for associated radiogenic disease compensation programs.

10. *MPS Cohort: Nuclear Weapons Test Participants* was presented by Dr. Emily A. Caffrey (Radian Scientific, Inc.) and Dr. John E. Till (Risk Assessment Corporation).

The nuclear weapons test participants form an important component of the MPS. These 114,270 military veterans are part of a larger group of approximately 235,000 individuals who took part in one or more atmospheric nuclear weapons tests at the Nevada Test Site (NTS) or the Pacific Proving Grounds (PPG) between 1945 and 1962 (Caldwell et al. 2016; Boice et al. 2020). The dosimetry for this cohort is of high quality (CV of ~ 0.5) due to the detailed historical records available to researchers, information provided about exposure rate fields, location of ships and units, and the availability of film badge dosimeter readings for about 20% of the participants (Till et al. 2014, 2018a). The mean estimated external dose for red bone marrow was 6 mGy (maximum of 108 mGy) based on a case-cohort study. Two-thirds of the sampled cohort received doses less than 5 mGy (Boice et al. 2020). The 65-year follow-up case-cohort epidemiological study concluded there was no evidence for increasing trends with radiation dose for leukemia (excluding CLL), myelodysplastic syndrome, multiple myeloma, ischemic heart disease (IHD), or cancers of the lung, prostate, breast, and brain (Boice et al. 2020). This presentation briefly reviewed the dosimetry and epidemiological results, with a focus on the radiological and non-radiological contributions of this component of the MPS. Insights into future low dose research gleaned from the nuclear weapons test participants cohort were discussed, along with ideas on how to combine radioepidemiological studies to expand our practical knowledge of low dose radiation effects for the purposes of radiation protection.

A collaborative study comparing biological dosimetry, dose reconstruction, and film badge readings was conducted among 12 veterans who had received doses in excess of 200 mGy and 12 matched control participants with no evidence of exposure (Simon et al. 2019). The range of doses for the full cohort used for this biodosimetry study are found in Beck et al. (2017). The correlation between the three dosimetry methods was remarkable, especially considering it had been more than 60 years since the exposures to fallout from nuclear weapons tests had occurred. This radiobiology evaluation lends credibility to the estimated doses for the entire cohort. Further, reliable dose estimates were derived from the chromosome aberration-based retrospective biodosimetry technique used that might be applicable in other long-term dose reconstruction circumstances (McKenna et al. 2019). An inverse relationship between telomere length and dose estimates was unexpected but also might be pursued in other exposed populations.

The atomic veterans are a key component of the Million Person Study because they comprise a large, low dose cohort with high-quality dosimetry. There was no evidence that the low doses of radiation received by the veterans increased their risk of cancer or IHD, although statistical variation was such that slight excesses could not be excluded with 95% confidence. Incidence rates of mesothelioma and prostate cancer were elevated, but these were not related to radiation exposure (Till et al. 2018b; Boice et al. 2020). For the first time, many veterans are getting answers about what their radiation dose level means and its implications for their health. The MPS will build on this work, focusing on low doses in the range of 0-100 mGy above background, to continue to work towards shining a light on the effects of low doses of radiation.

11. *Importance of Radiation Epidemiology: a NASA Perspective* was presented by Dr. Steve R. Blattnig (NASA Langley Research Center).

Radiation is one of the primary risk factors to human health that provides an obstacle to the safe exploration of space (NASA 2021). Radiation in space is of a different composition than most exposures on earth, consisting of high energy charged particles and resulting particle fragments from collisions with materials in spacecraft and the human body. Exposures can also be relatively high, with a mission to Mars estimated to be of the order of 300-450 mGy (870-1200 mSv) (Simonsen et al. 2020). Beyond low earth orbit, space radiation consists of continuous exposure to galactic cosmic rays (GCR) and sporadic eruptions from the sun that produce solar particle events. The health risks of primary concern are cancer, cardiovascular disease, and central nervous system diseases (NCRP 2014, 2020b). NASA's strategy to mitigate these effects currently consists of the development of permissible exposure limits that effectively limit the time individuals spend in space, as well as shielding from solar particle events (NCRP 2014). Because shielding from GCR is of limited effectiveness (Slaba et al. 2016, 2017), the Human Research Program is currently investigating the potential for biomedical countermeasures (NASA 2021; Werneth et al. 2020, 2021). A common theme of this risk mitigation strategy is a need to understand and quantify these health risks to counter them cost-effectively. Radiation epidemiology provides a primary basis to understand and quantify the response in humans and is integrated with animal and other experimental data to develop risk models for specific disease endpoints. Currently, the MPS is investigating lung cancer risks (Boice et al. 2019c) among women and men, and the risks of cognition dysfunction and dementia following intakes of radionuclides specifically for NASA (Boice 2017, 2019; NCRP 2019). However, all results that improve the understanding of radiation risks in humans can provide benefit to NASA's risk mitigation approach.

12. *Lung Cancer Risk among Men and Women* was presented by Dr. Ashley P. Golden (Oak Ridge Associated Universities).

There is conflicting evidence on the differences in radiation-related lung cancer risk between men and women. The lung cancer ERR estimated from Japanese atomic bomb survivors indicates that women are at nearly three times greater radiation risk than men on a relative scale (Ozasa et al. 2012; Cahoon et al. 2017). Recent results (Boice et al. 2019c) from five occupational cohorts within the MPS indicated little evidence that chronic or fractionated exposures increased the risk of lung cancer (n=403,067 men and 50,679 women), and, not surprisingly, there was no evidence that radiation risk estimates were higher among women than men. Results for an additional four MPS cohorts (Table 5, Table 6) also failed to uncover any significant differences in the lung cancer risks between men and women (Boice et al. 2021a, 2021b, 2021c, 2021d). These studies are consistent with the absence of an association between fluoroscopic chest x-rays and lung cancer reported in the Canadian TB-Fluoroscopy Cohort Study and the Massachusetts TB-Fluoroscopy Study (Howe et al. 1995; Brenner 2010). The reasons behind the conflicting evidence for lung cancer risks are not clear but might be related to different patterns of cigarette smoking among the Japanese bomb survivors, e.g., most male survivors smoked whereas most female survivors did not, and the ERR/Gy varied by number of cigarettes smoked and approached 0.00 for the heaviest smokers (Furukawa et al. 2010). Further, different population characteristics and circumstances may have influenced the radiation-related lung cancer risks: the Japanese survivors were exposed briefly in 1945 to the Hiroshima or Nagasaki atomic bombs and then lived in a war-torn country. The MPS cohorts were healthy U.S. radiation workers who were exposed chronically over many years during the course of their employment. Further, the 1945 Asian population has different characteristics than U.S. populations, and it is challenging to make comparisons, e.g., to "transfer risks" from a 1945 Asian population with different background rates for lung cancer to other populations.

NCRP Scientific Committee SC 1-27 is preparing a Commentary on the "Evaluation of Sex-Specific Differences in Lung Cancer Radiation Risks and Recommendations for Use in Transfer and Projection Models" which incorporates detailed evaluations of MPS cohort study results (NCRP 2021a). Since protection standards for astronauts currently are based on individual lifetime risk projections, any sex-specific difference in lung cancer risks limits the time women can spend in space (NASA 2021; NASEM 2021b).

13. *Cognition and Dementia Following Intakes of Radionuclides* was presented by Dr. John D. Boice Jr. (NCRP and Vanderbilt University School of Medicine) and Michael Mumma (International Epidemiology Institute and Vanderbilt University School of Medicine).

The American author and screenwriter, Ray Bradbury, once noted, “It’s not going to do any good to land on Mars if we’re stupid.” (NPR 2012). Relatively high cumulative doses to brain tissue from Galactic Cosmic Rays (GCR) are possible during a mission to Mars (Boice 2019; NCRP 2019; Simonsen et al. 2020). Galactic cosmic rays are a whole range of ions, including high-velocity ions (HZE particles) traveling near the speed of light through space. Animal studies have revealed early and late neurological disorders from relatively brief exposures to these high-velocity heavy ions (NCRP 2014; NCRP 2020b). These studies have raised concern about possible effects on astronauts that might impair performance so that the mission would not be completed or, conceivably, there might be a risk of Alzheimer’s or dementia years after the voyage is over.

There are no human circumstances on earth that can approximate GCR exposures to brain tissue. In fact, there is little to no evidence in human studies that low-LET radiation (at doses below those used in radiotherapy) is associated with dementia or Alzheimer’s disease. However, a recent study of Russian Mayak workers has suggested a link with Parkinson’s disease following low-LET radiation (Azizova et al. 2020) which has increased interest in this area (Pasqual et al. 2021). Further, analyses within the MPS cohorts of populations exposed to low-LET radiation are consistent with the Mayak study (Table 7, Table 8). As a possible, though imperfect, analogue to the high-LET portion of the GCR exposure, radium dial painters (Martinez et al. 2021; NCRP 2021c) and U.S. DOE workers with intakes of alpha-particle emitting radionuclides are being evaluated for dementia, Alzheimer’s disease, Parkinson’s disease, motor neuron disease and for cognitive impairment (Boice 2017, 2019). The internally deposited alpha emitters in radiation workers (Leggett et al. 2018) comprise a possible human analogue for high-LET GCR exposure to brain tissue in space. All MPS cohorts now include Parkinson's disease as an outcome for dose-response evaluation and somewhat surprising the majority have been positive to date (Table 7). These epidemiologic studies are intended to provide another line of evidence to consider when making judgments for radiation protection guidance for flight crews on missions in space.

Interestingly, cigarette smoking is consistently seen to decrease the risk of Parkinson's disease (Mappin-Kasirer et al. 2020; Bloem et al. 2021). Preliminary results in MPS studies of atomic veterans, industrial radiographers, and nuclear power plant workers confirmed indirectly such negative associations. Surrogates of high smoking prevalence were taken as being an enlisted man for veterans and having only a high school education or less for workers. These persons had significantly low SMRs of dying from Parkinson's disease. In contrast, they had significantly high SMRs of dying from lung cancer. After linkage with the Medicare and Medicaid Services files described below (CMS 2021), we will have more detailed information on individual tobacco use to confirm these provocative associations.

Studies have begun of alpha particle (He nuclei) exposure to brain tissue and mortality from dementia, Alzheimer's, Parkinson's and motor neuron disease, as well as cognitive impairment that will be incorporating quantitative scores from neuropsychological testing available from Medicare and Medicaid Services (CMS) files and nursing home files. The cohorts of U.S. DOE workers being evaluated (Phase 1) include workers at Los Alamos National Laboratory, Mallinckrodt Chemical Works, Mound, Rocketdyne, Rocky Flats, Tennessee Eastman Corporation (TEC), Fernald, Middlesex, Portsmouth Gaseous Diffusion Plant, Paducah Gaseous Diffusion Plant, Oak Ridge National Laboratories (X-10, K-25, Y-12), Savannah River Site and Hanford. Of special note is the possibility that several thousand workers with plutonium burdens could be interviewed and administered the same or similar battery of cognition tests (COGNITION) taken by astronauts on the International Space Station today (Phase 2) (NCRP 2021b).

The strengths of this investigation are that the exposure is to humans, and not rodents; the exposure is from high-LET radiation at a low dose rate (over years and not minutes or weeks as in most of the animal experiments); the human exposure is to a mixed field of high-LET radiation and low-LET radiation (similar to exposures in space); the energy deposition is similar for a wide range of particle types and energies (cf, Brenner 1990; Zaider 1996; Hofmann et al. 2020); and human outcomes of interest can be directly evaluated, i.e., the occurrence of dementia and Alzheimer's disease as well as quantitative measures of cognitive impairment.

Low-energy alpha particles are a significant portion of the GCR exposure experienced inside a space vehicle on a long voyage. Much of the high-LET portion of radiation space exposure is actually from low-energy alpha particles and protons (NCRP 2014). While there are similarities between high-LET alpha-particle exposure to brain tissue and high-LET GCR exposure, there are also dissimilarities, e.g., GCR and alpha particles emitted from radionuclides may share the same LET values, but their track structures and energies are distinct. A critical component of this array of studies of high-LET exposure to brain tissue is the accurate assessment of individual worker doses. The next presentations by Caleigh Samuels (ORNL) and Sergei Tolmachev (USTUR) cover the comprehensive approaches being employed for dose reconstruction.

14. *Brain Dose Estimates for Alpha Emitters at MPS Sites* was presented by Dr. Caleigh Samuels (Oak Ridge National Laboratory).

The MPS cohorts studied so far include tens of thousands of workers with elevated intakes of alpha particle emitters, primarily ^{238}Pu, ^{239}Pu, ^{241}Am, ^{226}Ra, ^{210}Po, and U isotopes. Some subsets of these alpha emitters generally dominate reconstructed doses to MPS cohorts from internal emitters and, for some sites, from all internal and external sources. In the course of the MPS, the brain has emerged as a tissue of concern due to potential cognitive effects from internal emitters, particularly alpha emitters (see presentation 13). To this point, the biokinetic models applied in MPS dose reconstructions, which are generally the latest models of the International Commission on Radiological Protection (ICRP), do not explicitly address the brain. Instead, the brain is treated as a mass fraction of a pool of tissues called *Other* that represent the remainder of the body after the removal of tissues explicitly identified in the biokinetic model. We investigated the feasibility of revising the biokinetic models for radionuclides of concern to include the brain as an explicitly identified pool with parameter values derived from element-specific biokinetic data (Leggett et al. 2018; NCRP 2021b).

Case studies were performed for 17 radionuclides [^{52}Mn, ^{53}Mn, ^{54}Mn, ^{134}Cs, ^{194}Hg (vapor), ^{203}Hg (vapor), ^{207}Bi, ^{209}Pb, ^{210}Pb, ^{210}Po, ^{224}Ra, ^{226}Ra, ^{230}U, ^{234}U, ^{237}Pu, ^{239}Pu, ^{241}Am]. In addition to radionuclides frequently encountered in the MPS, the case studies include radioisotopes of elements for which brain kinetics have been examined in some detail (e.g., Mn, Hg, Pb). Injection dose coefficients (50-y equivalent doses to the brain following injection into blood of an adult) were calculated for each radionuclide using each of two versions of the ICRP's current systemic biokinetic model for that element for workers (ICRP 2016, 2017, 2019, 2021): the original version and a modified version differing only in the treatment of the brain. If the ICRP model contained an explicit brain region, the modified version of that model removed the brain compartment(s) representing the brain and included the brain as part of *Other*. If the ICRP model did not have an explicit brain pool but instead included the brain in *Other*, the modified version included an explicit brain region with kinetics based on best available brain-specific data (Leggett et al. 2018; NCRP 2021b). The comparison of dose coefficients for a given radionuclide was expressed as a ratio A:B, where A and B are the injection dose coefficients based on the versions of the model with and without an explicit brain region, respectively. The derived ratio A:B was <0.2 in two cases (^{224}Ra, ^{241}Am), in the range 0.5–2.0 in 12 cases (^{52}Mn, ^{54}Mn, ^{134}Cs, ^{203}Hg-vapor, ^{207}Bi, ^{209}Pb, ^{210}Po, ^{226}Ra, ^{230}U, ^{234}U, ^{237}Pu, ^{239}Pu), and in the range 3–5 in three cases (^{53}Mn, ^{194}Hg-vapor, ^{210}Pb). Thus, cases were found in the use of an explicit brain model that: (1) had little effect on the estimated dose to the brain, (2) resulted in a much lower dose estimate for brain or (3) resulted in a much higher dose to the brain (Leggett et al. 2018; NCRP 2021b). An interesting finding from these case studies and a broader review of the literature was that the brain usually has a much lower rate of uptake of elements per gram of tissue but a longer residence time than do most other studied soft tissues. Thus, an initially low uptake of a radionuclide by the brain should not be interpreted as indicating that the dose to the brain is substantially lower than that to most other tissues.

15. *Radionuclide Concentrations in Brain Segments: Autopsy Series* was presented by Dr. Sergei Y. Tolmachev (Washington State University), Dana Wegge (University of Missouri), Dr. John Brockman (University of Missouri)

The United States Transuranium and Uranium Registries (USTUR) is a federal-grant-funded human tissue research program providing long-term study of actinide biokinetics in former nuclear workers with internal depositions of these elements. The USTUR conducts autopsies and performs radiochemical analyses of voluntarily donated tissue samples (Kathren and Tolmachev 2019; Tolmachev et al. 2019). The National Human Radiobiology Tissue Repository (NHRTR) holds all tissues donated to the USTUR, along with specimens acquired from the U.S. Radium Worker Studies (Rowland 1994; Martinez et al. 2021). The USTUR/NHRTR is a unique resource for retrospective analyses and distribution studies of plutonium, uranium, and americium, as well as radium and beryllium in the human body and in specific tissues and organs. This presentation provided preliminary results of plutonium (^{239}Pu), uranium (^{238}U), beryllium (^{9}Be), and radium (^{226}Ra) analyses in brain tissues from occupationally exposed individuals. Distributions of these elements among different segments of the brain and the impact of this distribution on brain dosimetry were discussed. This study was conducted in close collaboration with the MPS (Leggett et al. 2018; NCRP 2021b) and the University of Missouri Research Reactor.

Using alpha-spectrometry, ^{239}Pu activity concentrations were measured in the cerebellum and the right cerebrum lobe of six occupationally-exposed male individuals. In cerebrum lobe samples, ^{239}Pu concentration was about two times higher than the average for other brain segments, suggesting non-uniform plutonium distribution between brain segments. The distribution of uranium, beryllium, and radium was studied in the brain of a female occupationally-exposed to ^{226}Ra. The concentrations of ^{238}U,

^{9}Be, and ^{226}Ra were measured with inductively coupled plasma mass-spectrometry (Thomas 2013) in the corpus callosum, the white and grey matter of the cerebrum lobes, the cerebellum, and brainstem segments of the brain. Preliminary results indicated that the highest ^{238}U concentration was measured in the cerebrum grey matter, while in other brain segments it was about 25% lower. High ^{9}Be concentrations were measured in the corpus callosum and, analogously with uranium, in the grey matter of the cerebrum lobe. In three other segments, beryllium concentrations were approximately 50% lower. In contrast to uranium and beryllium, radium accumulated preferentially in the white matter of the cerebral lobes. The ^{226}Ra concentration in the white matter was about four times higher than the average of all other brain segments. Acknowledging the limited number of cases studied, preliminary results suggest that plutonium, radium, beryllium, and, to a lesser extent, uranium are non-uniformly distributed in the human brain. This finding might have a direct impact on biokinetic modeling of internally-deposited radionuclides in the brain as well as on the assessment of radiation doses to the brain. Current systemic biokinetic models, recommended by the ICRP, assume a uniform distribution in the brain for any specific element.

16. *A Million More Dreams* was presented by Dr. John D. Boice Jr. (NCRP and Vanderbilt University School of Medicine), Dr. Lawrence T. Dauer (Memorial Sloan Kettering Cancer Center), and Dr. Derek W. Jokisch (Francis Marion University and Oak Ridge National Laboratory)

The vision for the MPS includes a long-term follow-up of all exposure cohorts and an expansion of efforts in radiation biology. Currently, over 800,000 workers and veterans within 25 of the over 30 individual MPS cohorts have been followed for mortality, and in the next 2-3 years all will be. At regular 5 to 10 year intervals, there will be a new follow-up to update the mortality experience of the MPS and to conduct new dose-response evaluations.

The power of the MPS is in combining the similar datasets to make strong inferences about health effects from chronic, low-dose exposures (Zhang et al. 2014; Boice et al. 2019a, 2019c; Boice and Dauer 2021). NCRP SC1-27 has developed a methodology used to combine four available MPS cohorts for lifetime radiation risk projections for lung cancer (NCRP 2021a). The use of ensemble models to combine various diverse data sets within the MPS is being discussed (Simonsen and Slaba 2020). The MPS data will be harmonized as far as feasible while still taking account of differences in important variables in different cohorts, such as socioeconomic status. Combined studies will include workers with an intake of radionuclides (e.g., plutonium and uranium), and workers exposed primarily to gamma- and x-rays (nuclear power plant workers, industrial radiographers, medical radiation workers, atomic veterans). The evaluation of radiation-related ischemic heart disease is an important ongoing activity within the MPS (Table 9, Table 10). The dose-response analyses will be organ-specific as the combining of all tumors together has limited biological meaning although it is important for radiation protection. Ways to combine organ-specific dose response relationships will be developed and enhanced. The MPS is a dynamic and evolving program of radiation studies. New inclusions this year are the study of nearly 113,000 U.S. Navy nuclear submariners starting with service on the Nautilus in 1954, the updated study of 3,276 radium dial painters, and the possible study of 97,000 nuclear shipyard workers. A large study of over 50,000 workers with measured values of cumulative neutron dose is being considered. While challenging, workers with measured bioassay samples of tritium could be considered (Little and Wakeford 2008). A new study of nearly 14,000 women who worked during WWII (1943-47) at the Tennessee Eastman Corporation (TEC) uranium processing plant is noteworthy in that the cohort has never been studied, lung doses from intakes of uranium are up to 1,000 mGy (Boice et al. 2021d), and the women are recognized by the public as “the girls of the atomic city” (Kiernan 2013). This follow-up is in conjunction with an update of 18,000 men who worked at TEC during the same calendar years, which will facilitate sex-specific comparisons in lung cancer risk (Polednak and Frome 1981).

Also underway is a study revisiting a cohort of 3,276 radium dial painters (Rowland 1994; Fry 1998; Martinez et al. 2021). The last published follow-up was in 1980, and nearly 60% of the dial painters were alive at that time (Stebbings et al. 1984). In addition to updating the status of cohort members, the radiation dosimetry will be updated and enhanced. Updated biokinetic modeling will be applied and will be sex-specific and also specific to age throughout life. The biokinetics of radium progeny will be modeled independently and will include a sophisticated treatment of radon produced *in vivo* by the decay of radium. The latest nuclear decay and energy absorption data published by ICRP will be used to compute absorbed dose rates and annualized absorbed doses to targets of interest including the skeleton, red bone marrow, breast, brain, and lungs. A novel biological study of radium dial painter blood and tissue is provided below as an example of what might be possible in MPS future investigations.

DNA Methylation, Neurodegenerative Disorders, Epigenetic Age Acceleration. A novel biological study is being considered to evaluate whether DNA methylation studies of radium dial painter blood can reveal associations with epigenetic age acceleration possibly associated with lower cognitive ability and brain vascular lesions. A key question to evaluate is whether such studies might predict radiation-related cognitive decline. Blood samples and smears are available from the radium dial painters and have been used previously to estimate radiation doses from alpha particles (Goans et al. 2019). DNA methylation studies and molecular signatures of aging have been linked in some studies as predictors of cognitive decline (Hillary et al. 2019; Nabais et al. 2021). Molecular signals of aging also have been associated with lifespan shortening, toxic exposures, and unfavorable health behaviors. Contrasts have been made between epigenetic age and chronological age. Persons with high-LET exposure to internal alpha emitters as well as low-LET external radiation may demonstrate epigenetic age acceleration (EAA) as estimated from genome-wide methylation evaluation of blood-derived DNA. These DNA methylation evaluations have found associations with lower cognitive ability and brain vascular lesions and appear to be predictors of mortality associated with different measures of brain health (Hillary et al. 2019; Nabais et al. 2021; Qin et al. 2021).

A National Center for Radiation Epidemiology and Biology (NCREB) is envisioned to provide continued support and guidance for addressing national needs. Currently, there is an infrastructure within the MPS collaborative teams that could be considered a *de facto* National Center for Radiation Epidemiology, but a radiation biology component will require a reinvigorated focus, expanded collaborators and substantial resources. We are encouraged by support from many agencies and the U.S. Congress (US GAO 2017). In FY20, for the third year in a row, the Senate Appropriations Bill included a line item to support "the Epidemiologic Study of One Million U.S. Radiation Workers and Veterans…" (Boice et al. 2019b). Further, it is encouraging that the U.S. Congress has recently requested the National Academies to prepare a report entitled *Developing a Long-Term Strategy for Low-Dose Radiation Research in the United States* (NASEM 2021a).

The MPS will expand its role in training radiation scientists in epidemiology, statistics and dosimetry and will continue to offer opportunities for collaborative research as well as master and doctoral degrees. In addition to substantially improving knowledge of the potential health effects from low-level radiation exposures received gradually over time, the MPS will be able to make strong inferences regarding the adequacy and appropriateness of the LNT model as used in radiation protection.

The MPS builds upon 25 years of dreams, some sleepless nights, but no nightmares.

17. *Virtual Symposium Wrap Up* was presented by Brian Quinn (MSKCC and Greater New York Chapter of the Health Physics Society).

This MPS virtual symposium, presentations, scientific discussions and preliminary results represented a tremendous collaboration of many different people and groups toward successful initial completion and ongoing follow-up and refinement of this important program of studies. The symposium was an opportunity not only to recognize the extraordinary individual and combined efforts but also to celebrate the results to date while envisioning the exciting work to come. It is always encouraging to see scientific progress while a diverse group of scientific experts openly acknowledges limitations to current knowledge, and then they recognize the opportunity to address them in a meaningful way. Meetings such as these are important in part to spread the word about these projects to a diverse group of radiation scientists and protection professionals, but also to encourage and engage other individuals to be thinking about the big questions and gaps in knowledge that surround the ubiquitous radiation world we live in.

QUESTIONS AND ANSWERS

Symposium attendees and panelists were encouraged to provide written questions to speakers throughout the presentations for a fruitful dialogue and discussion on related topics. Several responses were provided by the panelists during the symposium. The submitted questions were combined and compiled below by category along with answers/responses.

Department of Defense radiation studies

Has the USS Ronald Reagan study been published?

Yes. In response to the Consolidated Appropriations Act, 2014, U.S. DoD published a final report for the Congressional Defense Committees concerning personnel radiation exposures while serving on the United States Ship (USS) RONALD REAGAN (CVN 76) during Operation Tomodachi in 2011 (US DOD 2014). The report is available to the public (see https://www.health.mil/Reference-Center/Reports/2014/06/19/Radiation-Exposure-Report)

Has the *in utero* group study been published?

Yes, see the report by Conlin et al. (2013) entitled "Outcomes among pregnant women included in the Operation Tomodachi Registry."

Space radiation exposures

What are examples of radiation countermeasures being considered for extended space missions?

For the unlikely yet still possible occurrence of acute radiation syndrome from an extremely large solar particle event there are FDA-approved-countermeasures that were developed for terrestrial applications that can be used (Carnell 2020). For late effects such as cancer, cardiovascular diseases and neurodegenerative diseases there aren't any biomedical countermeasures that have been established to be effective (Werneth et al. 2021). However, aspirin is currently being investigated because of its apparent effectiveness in reducing background risk of gastrointestinal as well as other cancers (Werneth et al. 2020; Zhang et al. 2021).

How accurate have we become at calculating and measuring radiation doses from the various forms of space radiation which vary in type, linear energy transfer, and energy over fairly wide ranges?

While some gaps remain in the understanding of the physics, we can predict the exposures from GCR quite accurately (Norbury et al. 2019) with the major remaining uncertainties in the biological response (Simonsen et al. 2020). The capability of predicting solar particle events is still largely lacking but calculating exposures after the fact is quite feasible (Mertens and Slaba 2019). Measurement capability has also improved significantly over the last decade to measure dose equivalent and even the energy deposition spectra quite well (Kroupa et al. 2015; Stoffel et al. 2016)

Is NASA flying dosimeters on the Mars rover missions in anticipation of manned expeditions?

Yes, the Radiation Assessment Detector flown on the Curiosity rover has measurements in transit to Mars (Zeitlin et al. 2013) as well as on the surface (Zeitlin et al. 2019).

Confounding and effect measure modification in the MPS

How is smoking as a confounder for lung cancer being handled by the MPS? Is COPD being analyzed as a possible test for smoking effects?

The MPS includes over 30 individual cohort studies and the approach to addressing tobacco use as a potential confounder is addressed in various ways. In some of the cohorts, comprehensive interviews with workers had been conducted, such as at LANL, and this information is being used directly and indirectly to confirm that education was a good surrogate for tobacco use (Mahoney and Wilkinson 1987; Boice et al. 2021b). For some studies, we were able to sample workers and ask for information on smoking which was used to confirm our use of pay type (white collar/blue collar) as a surrogate measure for tobacco use (Boice et al. 2006a). In other studies, smoking histories were available on medical questionnaires administered during workers' employment and we have abstracted and continue to abstract this information from archival records (Petersen et al. 1990; Dupree et al. 1995).

A broad objective for each MPS cohort is to develop an understanding of possible differences in smoking habits by the level of radiation exposure. As is often the case in epidemiologic studies, without direct information on cigarette smoking use for individual workers, a measure of socioeconomic status (SES) based on employment job categories, salary, education, or other demographic characteristics is used and assumed as an adequate adjustment for smoking and other lifestyle habits. For our studies of atomic veterans, rank (enlisted vs officer) is used; and for other studies, job category, pay type (white collar/blue collar) or education are most often used. In some studies, SES assignments for individuals were based on area-wide educational levels obtained from census-block group residential histories (Cohen et al. 2018; Boice et al. 2021c).

Chronic obstructive pulmonary disease (COPD) and nonmalignant respiratory diseases are being evaluated as possible indicators of smoking histories. Elevated SMRs of these conditions related to cigarette smoking would suggest an increased prevalence of tobacco use compared with the general population. Internal cohort analyses would suggest the possible confounding effect of tobacco use if a dose response were revealed, i.e., for conditions not known to be related to tobacco use. Further, another statistical approach includes the joint modeling of COPD and lung cancer mortality as an indirect approach to control for unmeasured confounding of tobacco use (Richardson and Wing 2011).

Are there differences between the LSS and MPS female cohorts on smoking prevalence?

In the LSS, the majority of female adult survivors were nonsmokers. The differences in smoking prevalence vary by the MPS cohorts of female workers. In the MPS, the majority of most medical radiation workers (e.g., radiologists and interventional fluoroscopists) were also nonsmokers. For women employed during WWII, smoking prevalence might be as high as 20-25% (Mahoney and Wilkinson 1987; Dupree et al. 1995). Information on smoking histories is an important aspect of the MPS and additional efforts continue to obtain as many individual histories of tobacco use as available in archival records.

How are potential exposures to other chemicals such as asbestos, beryllium, or stable heavy metals as confounders being handled by the MPS?

Each cohort is evaluated on a case-by-case basis. Asbestos exposure has been evaluated among nuclear weapons test participants who served in the Navy (Till et al. 2018b), among workers in the nuclear power industry, and among industrial radiographers, including those who worked at naval shipyards (Mumma et al. 2018). In contrast to the challenges in identifying health effects at very low levels of radiation, the signals associated with asbestos and asbestosis are large, often greater than 5-fold. For example, among nuclear power plant workers the SMR for asbestos-related mesothelioma and pleural cancer was 5.6, whereas for leukemia, a radiation-related malignancy, the SMR was 1.06 (Boice et al. 2021c). Beryllium is an issue regarding several of the U.S. DOE facilities (US DOE 2019). U.S. DOE has a comprehensive program for beryllium evaluations which provides information on levels of potential exposures. Increases in berylliosis, though based on small numbers, have been identified in studies of LANL (Stefaniak et al. 2003; Boice et al. 2021b) and Rocky Flats workers (Viet et al 2000). Further, within the USTUR we have the opportunity for quantitative assessments of tissue levels of beryllium. Several radiation workers with high exposures to beryllium have donated their bodies to science, and development of biokinetic models of systemic distribution specific to levels of exposure to beryllium (high versus low exposure) is feasible (Tolmachev et al. 2019).

Is ethnicity (and potential for higher rates of certain cancers in some ethnic groups) being considered for cohorts in the MPS?

Yes, this is considered to the extent that we have ethnicity available within the occupational records. For example, the LANL population included statistically meaningful numbers of Hispanic workers, and separate analyses identified increased rates for certain diseases in comparison with the white population. However, there was no correlation of any of these diseases with radiation dose (Boice et al. 2021b). It is standard procedure to obtain all available information on race/ethnicity for all workers, including Asian, Black, Hispanic, Native American, and White. It will only be when the MPS cohorts are combined, however, that more precise evaluations of radiation health effects by ethnicity are possible.

Epidemiological methods

How does MPS analyze uncertainty in dosimetry or modeling (e.g., sensitivity analysis, using regression calibration or Monte Carlo maximum likelihood techniques)? What confidence intervals are reported for dose-response analyses?

While most of the current uncertainty analyses for MPS have included sensitivity analyses, more rigorous, comprehensive uncertainty analyses are yet to be conducted within the MPS. However, they are high priority and soon will be initiated. We plan to apply, to the extent feasible, the new approach published by Stram et al. (2021) for uncertainty analyses among Mayak workers where there appeared to be little if any effect for photon exposures, but a meaningful effect for the plutonium intakes. For our recent paper on LANL workers, an uncertainty analysis was conducted following the methods outlined by Gilbert and colleagues (Gilbert and Fix 1996; Gilbert et al. 1996; Gilbert 1998). However, given that there were few changes in the point estimates or confidence limits, we presented the dose-response confidence intervals from the primary analyses. We are also looking at innovative ways to apply ensemble models with regard to the uncertainties associated with particular parameter inputs (Simonsen and Slaba 2020). For sensitivity analyses, we often change the parameter values for the dosimetric models for intakes of radionuclides. Among the TEC men and women, the primary exposure came from the inhalation of uranium dust associated with the operation of calutrons. There were four key parameters in the dosimetry model, including particle size and breathing rate. Minimum and maximum realistic values for these parameters were assumed and the dose-response analyses for lung cancer were conducted to test whether there was any appreciable difference in the dose response. As each one of over 30 individual cohorts comprising the MPS provides a different scenario for exposure uncertainty, individual approaches are taken. Another example would be in the study of medical radiation workers where the wearing of a lead apron was the primary determinant of dose, followed by orientation and assumption of incident energy. Various combinations of the parameter values in the preferred model - extreme, minimum, and maximum - were considered and evaluated regarding their effect on the various dose-response relationships.

What is the statistical power for individual cohorts and for the entire pooled studies for the MPS likely to be? Can this be compared to the next largest study?

The statistical power of the MPS to reveal health effects associated with low-level radiation experienced gradually over time is exceptionally large since power depends on sample size and broad distribution of organ-specific doses. As we complete and combine various cohorts, we can either detect underlying health effects or, equally important, exclude relatively low-risk levels with 95% confidence. For example, we have recently combined three studies of low-LET radiation exposure received gradually over time and evaluated lung cancer risk. The combined nuclear power plant worker and industrial radiographer studies had been published (Boice et al. 2019c), and recently the study of medical radiation workers has been included. A study of nearly 400,000 workers indicated a radiation association that was not statistically significant (ERR per 100 mGy of 0.02; 95% CI -0.03, 0.07) which indicates that an excess relative risk above 0.07 at 100 mGy can be excluded with 95% confidence. As the additional 600,000 MPS workers are included in the combined analysis, much more precision will be achieved.

How does length of follow up on the MPS play into the significance of any sex-dependent risk estimates (e.g., for lung cancer)?

The statical power to uncover any underlying health effects greatly increases when the follow-up is long and when workers have lived to ages later in life when the background rates of lung cancer are high. While the time-dependent analyses evaluate risk among the workers as they age up to about 95 y, the power of the analysis depends on the number of workers reaching "old age". Currently, there are six MPS cohorts which include males and females for whom sex-specific lung cancer risks have been evaluated and are being incorporated into pooled and combined analyses (Boice et al. 2019c; NCRP 2021a). Comprehensive follow-up has been conducted through 2011 for all cohorts and has been or is being updated for all cohorts through 2017-2019. The percentage of workers in each U.S. DOE worker cohort who have died is usually over 50% and the lengths of follow-up are over 40 y on average. The cohorts that began after WW II have shorter follow-up times. The percentage of workers who have died and the mean duration follow-up are for LANL 60% and 45 y, TEC women 89% and 51 y, Mound workers 51% and 40 y, nuclear power plant workers 22% and 30 y, industrial radiographers 17% and 22 y, and medical radiation workers 10.5% and 25 y, respectively. Updated tracing will increase the percentage who have died as well as the mean duration of follow-up. More importantly, the follow-up occurs later in life when cancer rates increase. The medical radiation worker cohort includes more recent workers, shorter mean follow-up and fewer percentages of deaths. Because nearly 40% of the cohort was over age 65 y at last follow-up and since mortality rates increase markedly among the elderly, the new follow-up will improve the power of the analyses to reveal any differences in sex-specific lung cancer risk estimates.

While the MPS individual cohort results to date appear to show that there is little evidence for lung (and other) cancer risks from fractionated, low dose, low dose-rate exposures, will a quantitative dose threshold analysis be performed for the pooled MPS study?

Most MPS cohorts find evidence of radiation effects; for example, among nuclear power plant workers and industrial radiographers, there were clear excesses of radiation-associated leukemia Table 3, Table 4). Also, while sex-specific differences in lung cancer radiation risks are not apparent, several cohorts find significant associations such as the male medical radiation workers and the male industrial radiographers. Several cohorts reveal significant dose-response relationships for esophageal cancer, as does the Mayak study (Sokolnikov et al. 2015), suggesting the possibility of confounding by alcohol. When the pooled results are complete, hopefully in the next two years, we will be able to evaluate radiation risks in a variety of ways. First, we will be able to report the statistically significant findings and the various model fits for individual site-specific risks. Model fits include linear and quadratic fits. Second, if significant findings are not apparent, we will be able to present the level of radiation risks that could be excluded with 95% confidence. Third, we hope to be able to incorporate biologically-based models in a way to improve the estimate of risk in the low-dose domain (NCRP 2020b; Preston et al. 2020; Mi and Norman 2020). As is reported in several non-MPS studies, we would present dose-response relationships showing the lowest range of doses where a significant response is apparent. Again, if there is a relatively flat or even negative response in the low-dose domain, we will present confidence bounds indicating the lowest level of radiation risk that could be excluded with confidence.

Will the MPS also evaluate the possibility of hormetic effects of low doses of radiation? While it appears that the MPS typically uses a < 5 mSv or < 10 mSv referent group for dose-response evaluations, does this introduce a negative bias in that the possibility that low doses might have a hormetic effect on cancer incidence? Is it possible to also compare to results derived using non-radiation workers as a referent group?

We often use a <5 mSv or <10 mSv category as a "referent group" to make categorical comparisons, i.e., visual graphics for the reader to accompany the model dose-response fits, usually linear but also quadratic, as opposed to just presenting model fits, i.e., the regression model lines. Our analyses do not have a specific referent or a specific category for risks among the non- or low-exposed. Many readers appreciate having some point of reference, although arbitrary. What happens, though, is that we can change the appearance of the point estimates and confidence intervals just by changing the referent group and the categories. However, the plot of the dose response, whether it's a linear or quadratic model, always remains the same because it is not dependent on our chosen referent level for graphical comparison. The most valid analyses are comparing radiation workers to radiation workers over various levels of dose category. What is often seen in occupational studies is that the non-radiation workers (those who are not badged) are often appreciably different from the radiation workers in terms of SES and associated demographic and lifestyle factors which are not measured and thus we are not able to control.

We found this to be a concern in our study of Rocketdyne and Mound workers (Boice et al. 2006a, 2014). The non-radiation workers were evaluated and presented but we did not use them in the internal dose response categories because their patterns of mortality were so completely different compared with those of the very low-dose radiation workers. So, we continue to choose our comparisons to be “like to like”, radiation worker to radiation worker. Also, when we evaluate various cut-off points for dose response to identify if possible the lowest dose range for which a radiation effect (positive or negative) may be apparent, if there was evidence for adaptive response given the fractionated and often daily exposure to low doses, we would be able to pick that up and analyses to do so certainly will be conducted.

What is the potential overlap of the MPS Medical Worker cohort with the National Cancer Institute United States Radiologic Technologists (USRT) study?

The MPS medical radiation worker cohort (Boice et al. 2021a) is quite different from the U.S. Radiologic Technologists (USRT) study (Simon et al. 2006) in design, calendar years of selection, male/female percentages, and completeness of recorded monitoring data.

(1) The USRT study includes only radiologic technologists, whereas the U.S. medical radiation worker study includes not only technologists, but also radiologists, interventional fluoroscopists, radiation oncologists, and nuclear medicine physicians. Also included were nuclear pharmacists, medical and radiation physicists, nurses, veterinarians, chiropractors, dentists and allied healthcare support workers monitored for radiation in similar environments. (2) The selections of the cohorts were very different. The USRT cohort was selected from the computerized files of the American Association of Radiological Technologists (ARRT) and covered the years 1926-1980 (Boice et al. 1992). The U.S. medical radiation worker study was selected from the computerized Landauer® dosimetry database and covered the years 1965-1994. Thus, 65% of the workers in the MPS medical worker study were first monitored after 1980, i.e., the last year for USRT inclusion, and could not be in the USRT study. (3) The USRT cohort included only

questionnaire respondents who were alive in 1980; thus, anyone dying before 1980 was excluded. The U.S. medical worker study was not too dissimilar in this regard but did exclude anyone who died before 1977. (4) The initial linkage of the USRT study roster against the Landauer® dosimetry database found matches for only 19% of the cohort (Boice et al. 1992). The U.S. medical radiation worker cohort selection is based entirely on long-duration of measurement coverage within the Landauer® dosimetry database. The mean duration of monitored personal dosimetry records was 27 y with few gaps in coverage from first to last monitoring. (5) The USRT study includes approximately 25% males in contrast with 51% within the U.S. medical worker study. Specifically, the USRT study consists of 106,068 radiologic technologists, including 80,180 women and 25, 888 men (Velazquez-Kronen et al. 2020). The MPS medical worker study consists of 109,019 workers, including 53,801 women and 55,218 men. So, while there likely is some overlap between the two studies, the design, calendar years of selection, male/female percentages, and completeness of recorded monitoring data coverage within the Landauer® dosimetry database indicate that any overlap is small.

What MPS cohorts have the potential for radiation dose from internal emitters? Will there be enough data in the pooled results for meaningful comparisons between external and internal exposures on epidemiologic outcomes?

One of the unique strengths of the MPS is the number of cohorts with detailed information on internal emitters so that organ-specific estimates of radiation dose can be made. These cohorts include the U.S. DOE workers at LANL, Rocky Flats, Hanford, Savannah River, Linde, Middlesex, Mallinckrodt, Mound, TEC, Y-12, Fernald, gaseous diffusion plants (K-25, Portsmouth and Paducah) (Boice et al. 2019a), workers at Rocketdyne (Boice et al. 2006a, 2006b, 2011), and the radium dial painters (Martinez et al. 2021). Also, there will be sufficient information to contrast radiation effects from the intakes of radionuclides with external exposures. This is one of the important goals of the pooled analyses for which meaningful comparisons between external and internal exposures are possible. And it is not only the large numbers of workers with intakes of radionuclides that are being evaluated that is noteworthy, but also the comprehensive, and time-consuming dose reconstructions to obtain individual organ-specific estimates of dose from the intakes of radionuclides, in large part alpha particle emitters. Comparisons are being made now within the individual cohorts, but study sizes are not large enough to be definitive. Such comparisons, for example, have been done for the workers at Rocketdyne, Mound, and Los Alamos National Laboratory. The wealth of data for future comparisons and combined analyses will include the workers at Hanford, Rocky Flats, Savannah River, Mallinckrodt, Linde and gaseous diffusion plants where meaningful organ doses from the intakes of radionuclides and from external gamma radiation can be contrasted. In more basic analyses, risk estimates from cohorts with only low-LET exposures, such as industrial radiographers, nuclear power plant workers, medical radiation workers, and nuclear submariners can be contrasted with estimates from cohorts with primarily high-LET doses such as the TEC cohort and the radium dial painters. Although methodically challenging, there are substantial numbers of workers with neutron exposures that will be evaluated, since there are no human populations that have been able to evaluate possible effectiveness of neutrons in causing cancers or place upper bounds on possible equivalent dose estimates . Finally, quite a number of the workers had intakes of tritium and possible health effects will be evaluated, although this is challenging because of the higher concomitant doses from gamma and other radiation (Boice et al. 2019a). The complexity of these comparisons is that gamma radiation often dominates the organ-specific doses, and few studies include workers with only high-LET exposures, only neutron exposures, or only tritium exposures. The TEC study, however, is mainly high-LET exposure to the lung from uranium dust as external exposures were minimal. Overall, we are optimistic that meaningful comparisons can be made when the large numbers of workers with intakes of radionuclides are pooled, organ-specific doses are estimated based on the latest biokinetic models, and contrasts are made with low-LET exposures.

Are flight crews classified as radiation workers and could they be included in MPS?

NCRP has recognized that the cockpit and cabin crews of commercial aviation are occupational groups that may receive the highest average annual effective doses of all occupationally exposed workers (NCRP 2018c). These commercial airline crews and the pilots of cargo and corporate aircraft, however, are not normally monitored. Nonetheless, effective doses are estimated based on calculations of solar and GCR exposures for various flight routes and altitudes (NCRP 2018c). Because this exposure to naturally occurring sources of radiation results from occupational activities, the ICRP judged that these workers should be considered occupationally- exposed and managed as such. CDC and OSHA also recognize flight crews as occupational-exposed workers (Waters et al. 2000; FAA/OSHA 2000; Grajewski et al. 2011; CDC 2017; OSHA 2021). NCRP has not taken an official position at this time. NRC generally does not regulate naturally occurring sources of radiation, and it is left to individual states (Agreement States) to do so. NASA provides radiation safety standards for astronauts that currently differ from terrestrially-based standards for workers (NCRP 2014; NASEM 2021b). Commercial flight crews are currently being comprehensively studied by NIOSH (Yong et al. 2014). Conceivably, such studies could be included in the MPS, or pooled in the future, and would certainly add value given the unique exposures received at high altitudes. Because such workers are already being studied, there is no need to initiate new efforts within the MPS.

Is there an MPS cohort for criticality accident-exposed individuals?

No. Any worker who received >250 mSv in a given calendar year is excluded because such an exposure would not be consistent with the overall goal to evaluate low-level and low-dose rate exposure over time (Boice et al. 2019a). Nonetheless, the MPS can identify the excluded workers with both high-dose rate exposures and those who were exposed during criticality accidents and survived. Thanks for the question; it is an interesting idea for the future.

Is there an MPS cohort group for uranium miners (either U.S. or international)?

No. MPS does not currently include uranium miners or populations exposed to indoor radon. Our primary focus has been following workers and veterans exposed to low-level radiation at low-dose rates so that improved estimates of health consequences can be made with increased validity and precision for today's populations who are exposed in occupational, medical, and environmental circumstances. There are notable comprehensive studies of underground miners in Germany and Europe (Richardson et al. 2021) that have extended the compilation of underground miner cohorts that was done some 20 years ago at the National Cancer Institute and comprehensively evaluated in the BEIR VI report (NRC 1999).

How does the current global COVID-19 pandemic affect the epidemiological study? Does it skew health effects data or change the characteristics of the cohorts to unhealthy?

COVID-19 will not affect the MPS epidemiological studies currently being conducted. All our investigations provide the cause of death mortality information through or before Dec 31, 2018, i.e., before the start of the pandemic. It is of note that NCRP, NCI and NIAID recently held a workshop to evaluate the rationale behind using low-dose radiotherapy (0.3–1.5 Gy) as a treatment for severe COVID-19 respiratory disease (Prasanna et al. 2020). Without refuting or endorsing low-dose radiotherapy, general guidance to clinicians and researchers was provided. Others, however, come down a bit stronger and find little justification and potential long-term risk from such radiation treatments (Kirsch et al. 2020).

In addition to utilizing the Centers for Medicare and Medicaid Services (CMS) data to investigate neurocognitive effects, are there more general plans to use that data to analyze other non-malignant effects (e.g., cardiovascular effects, metabolic syndromes, etc.)?

Yes. When we link all MPS study participants to CMS data, we will obtain all medical diagnosis and procedure codes associated with Medicare and Medicaid claims (CMS 2018). Having this information will allow us to investigate not only the CNS conditions of import but also cancer incidence, less fatal cancers, and a broad range of other nonmalignant diseases and medical conditions including depression, cataracts, cardiovascular and cerebrovascular disease, and renal failure. The CNS evaluations include cognitive function scores within the Minimum Data Set of Nursing Home admissions (CMS 2021a). A unique aspect of the nationwide CMS data is the possibility to obtain smoking information among all workers (CMS 2021b). After the initial evaluations are completed the opportunities for evaluated radiation-disease associations among the 600,000 workers and veterans for whom CMS linkage is possible are limited only by the imagination of the investigators.

How diverse (age, race, gender, economic status, etc.) is the MPS? Is it currently a population representative of the workforce or of the United States overall? Will any results need to be adjusted to be representative of the U.S.?

The MPS is diverse and includes healthy workers and veterans of all races, SES levels, geographic residence, years of birth (calendar years) and sex, but not ages. The MPS comprises adults and a few pre-teens or teenagers (11 to 21 y) but no children (ages 0 to 10 y). Over 250,000 adult women are being studied, including the “girls of the atomic city”, and there are about 1,000 pre-teen or teenage radium dial painters. The SES levels cover all walks of life: blue collar and white collar, enlisted men and officers, elementary school education and advanced Ph.D. degrees (think Los Alamos and Oppenheimer). Most previous occupational studies have focused on White males, but the MPS is much more diverse. While we are unaware of any studies showing racial differences in effects of ionizing radiation, even though differences in the background rates for disease can be substantial, potential differences in radiation response will be evaluated especially for Blacks where nuclear workers appear notably healthier than the U.S. population average (Wartenberg et al. 2001). Hispanics at LANL have been studied independently: increased mortality rates were seen for diabetes and certain cancers but there was no difference in radiation response (Boice et al. 2021b). Workers who are Asian or Native American are identified but the numbers are not large enough to date for independent analyses. Exposed workers spanned nearly a century, from the radium dial painters in the 1920s to medical workers in the 2010s. Age (young, middle age, elderly), sex, and race (White, Black), SES (education; white-collar, blue-collar) specific cancer and noncancer risks will be evaluated once the million individual workers in the over 30 MPS cohorts are combined. For some of the future analyses, which could involve upwards of a billion data variables per individual (when including the CMS and Nursing Home linkages), cluster computing (perhaps with the use of supercomputers) would likely be of inestimable value.

While the MPS is currently for United States workers, are there any plans or possibilities for extending to other international radiation worker cohorts?

There are no current plans for extending the MPS to include other international radiation worker cohorts. One of the largest international cohorts, the INWORKS study (Thierry-Chef et al. 2015), already includes 5 U.S. cohorts of which 3 (ORNL, SRS and Hanford) overlap with the MPS. Idaho National Laboratory (INL) and Portsmouth Naval Shipyard are included in INWORKS but not in the MPS. The previous 15-Country study (Cardis et al. 2007) included 4 U.S. cohorts: ORNL, Hanford, a cohort of nuclear power plant workers, and INL. Only INL is not included in the MPS. The 3-Country study (Cardis et al. 1995) included 3 MPS cohorts: Hanford, Rocky Flats and ORNL. Once we have completed our first evaluation and pooling of all the more than 30 cohorts, any unique opportunity for collaboration and comparisons with our international colleagues, including the Canadian and UK worker studies, would be encouraged.

How much do animal models play into the MPS research at moderate dose-rate effects?

Animal models are essential for assigning dose weighting factors (DWF) for alpha-particle emitters, tritium, and thermal and fast neutrons. Animal models can also provide guidance as to the shape of dose-response functions that might be considered for organ-specific evaluations, e.g., linear, quadratic, threshold, over a broad range of doses. Biologically-based models including animal and cellular models will play an important future role for the application of the MPS research. NCRP has completed a recent report addressing the integration of radiation biology and epidemiology (NCRP 2020b, Preston et al. 2020). The committee concluded that populations such as the MPS will provide important epidemiologic data for which biologically-based models can be applied to enhance and improve the estimation of radiation risks in the low-dose domain. Biologically-based models are not limited only to carcinogenesis, e.g., adverse outcome pathways for space radiation-induced neurological diseases, e.g., Alzheimer's, are being evaluated (Mi and Norman 2020). Animal experiments play a critical role in assessing space-radiation induced cognitive impairment (Britten et al. 2021).

What is the current speculation about the basis for the difference in relative risk for lung cancer in women compared to the atomic bomb survivor study? Is it all *healthy worker effect* or has that been controlled for? Is it dose rate?

The cohort populations in the MPS are quite different from the LSS population of Japanese atomic bomb survivors. Perhaps the most important difference that might partially explain the absence of a sex-specific difference in the MPS cohorts is that the exposure in Japan was brief, perhaps on the order of a second, whereas the exposure in the MPS cohorts was gradual over time and over a period of years (Boice et al. 2019a). Animal studies have provided evidence that for low-LET radiation the risk at cumulative dose comparisons is lower for prolonged exposures (Dauer et al. 2010). Another difference is the general health of the exposed populations and environmental conditions. The Japanese survivors were exposed in 1945 and had to live in a war-torn country under conditions of deprivation, infections, and malnutrition (Boice et al. 2019a). The MPS cohorts started as very healthy men and women working in the United States. The sex-specific comparisons in Japan are made between women who had a low prevalence of smoking in contrast to the men who had a very high prevalence. For the comparisons in the MPS, some of the female cohorts were in large part nonsmokers and this is particularly apparent among the medical radiation workers which included radiologists and fluoroscopists, and other physicians and health-conscious individuals. Perhaps the strongest evidence for an absence of sex-specific differences in lung cancer risk is among the population of TEC workers. Here, approximately 30,000 workers, 58% men and 42% women, were evaluated and over 90% have died. The estimated lung doses for the inhalation of uranium reached 0.5 Gy (DWF=1) and the weighted dose (DWF=20) up to 10 Gy. Information at the time of employment on tobacco use was obtained from questionnaires and is being used in the adjustment process. There is probably a combination of factors influencing the differences in the findings from the Japanese survivor study and the MPS. These include: dose rate, race (and the underlying differences in background rates of cancer between Japanese and Americans), unmeasured effects of deprivation, uncontrolled effects of cigarette smoking (there is a peculiar ERR response in the LSS by numbers of cigarettes smoked per day, i.e., no radiation risk among the heaviest smokers), and a Japanese cohort exposed during one period of time during a few seconds in August 1945. Further, it is important to note that it is not only the occupational cohorts within the MPS that fail to reveal differences in lung cancer rates between women and men, but also results from the pooling of over 20 comprehensive international studies of indoor radon, including nonsmokers (Darby et al. 2006; Cheng et al. 2021), and from studies of tuberculosis patients in two countries where the total lung doses from repeated chest fluoroscopies reached exceptionally high levels (i.e., up to 4 Gy) (Howe 1995; Brenner 2010; Boice et al. 2019c).

When evaluating risk differences between males and females for lung cancer, were there any differences in the risk of breast cancer?

Yes. We will conduct sex-specific internal dose-response comparisons for breast and other cancers among the MPS cohorts, similar to what is being done for lung cancer. However, one of the challenges for breast cancer comparisons is that male breast cancer is rare; thus, the power of detecting a radiation association or any sex-specific differences may only be possible from the combination of the MPS cohorts. Another issue may be the relatively low doses to the breast in comparison with the higher doses to the lung, especially for workers who had inhaled radionuclides. The TEC workers, for example, had a substantial lung dose related to the inhalation of uranium dust but the dose from the minimal external exposures was negligible to the breast. Table 11 shows the SMRs and numbers of breast cancers for males and females in 8 MPS cohorts consisting of over 545,000 workers. While the number of male workers is very large, the number of male breast cancers is small, only 49, in contrast to 1,038 breast cancers among females. When compared with the general population, the total SMRs for males and females are

0.91, showing that both males and females show a healthy worker effect that indicates a 9% lower chance of dying from breast cancer.

Are there any plans to compare individuals working at boiling water reactors to those working at pressurized water reactors? Are there differences in exposure versus megawatt of the unit?

These are interesting questions. We had not thought about comparing individuals who worked at boiling water reactors with those working at pressurized water reactors per se as we would not anticipate any difference in regard to the effectiveness of radiation to cause a health effect. It is interesting, though, to consider tabulating the cumulative exposure levels for workers per MW. The NRC publishes detailed information on the annual doses by reactor characteristics, but not by cumulative doses.

Dosimetry for the MPS cohorts

What tissue weighting factor is being used for tritium for MPS cohort studies (e.g., LANL, etc.)?

In our evaluations, the computed dose from intakes of tritium is assumed to be a whole-body dose and not tied to a specific tissue weighting factor, so the weighting factor would be 1. For the analysis, we assume different dose weighting factors from 1 to 3 (NCRP 2018d).

What dosimetry conversion factors are used in the MPS (ICRP Report 74 or ICRP Report 116)?

As noted in NCRP Report 178 (NCRP 2018a), dose coefficients relating personal dose equivalent to organ dose for photons are derived primarily from ICRP Report 116 (ICRP 2010) and for neutrons are derived from tables C1-C30 of ICRP Report 116 (ICRP 2010) and Table A.42 of ICRP Report 74 (ICRP 1996).

How are minimum detectable levels (MDL) for dosimetry being handled by the MPS?

Both NCRP Report 178 (NCRP 2018a) (for all cohorts) and NCRP Commentary 30 (NCRP 2020a) provide specific guidance for handling issues associated with MDL practices over time. An example on how this is done in practice is found in the study of medical radiation workers (Boice et al. 2021a). Adjustments for “missed dose” were done by increasing each annual dose to a minimum value of 0.4 mSv and adding 0.2 mSv for annual doses that were between 0.4 and 1.0 mSv. Such adjustments for doses below the MDL of the recording dosimeter did not influence the dose responses reported in this study.

How are occupational doses over several different cohorts during the working life of an individual handled by the MPS and what cohort are you assigned to?

When creating a worker's dose history, we use occupational doses from several data sources, including dosimetry records from the facility in which the worker was employed, the U.S. DOE REMS database, the NRC REIRS database, dose records from a private dosimetry company (Landauer), and military service (DTRA, Army, Navy and Air Force) dose records. A manuscript we published in May 2006 entitled "A comprehensive dose reconstruction methodology for former Rocketdyne/atomics international radiation workers" (Boice et al. 2006b) provides an overview on how we use multiple radiation databases to reconstruct a worker’s full career dose history. Workers employed at multiple U.S. DOE facilities would be included in each facility-specific cohort, combining the doses they received at other facilities in their full dose profile. Some workers had been employed at as many as five different facilities. When the cohorts are eventually combined, a worker will be counted only once.

How does the Landauer database overlap with REIRS? Are there any indications of the incompleteness of individual dose records in REIRS and can the Landauer database be used to fill in any dosimetry data gaps?

In our manuscript on nuclear power plant workers, we indicate the overlap between the REIRS dataset and the Landauer dataset (Boice et al. 2021c). For the 135,193 nuclear power plant workers in the study cohort, 16.6% were in both datasets, 82.6% in REIRS only, and 0.8% in Landauer only. One of the benefits of the Landauer database is that there is the ability to provide information for workers that may not be included in REIRS or were included but with incomplete coverage (mainly for the very early workers for which voluntary retrospective reports to REIRS were not as complete as for workers in later years) (Hagemeyer et al. 2018).

What are the dose ranges observed in the MPS cohorts to date?

Table 6 provides information on absorbed dose to the lung for nine MPS cohorts completed to date. Information is presented on nearly 550,000 workers with individual dosimetry determinations. The mean doses to lung range from a low of 6.4 mGy among the atomic veterans to highs of 477 and 508 weighted-mGy among TEC and Mallinckrodt workers, respectively. The maximum doses to lung range from 970 mGy among the atomic veterans to highs of 16-18 weighted-Gy among TEC, Mallinckrodt and LANL workers. These absorbed dose distributions differ from the personal dose equivalent distributions reported in NCRP Report 178 (2018a), as expected. Years of effort were needed to convert the badge and personal dosimetry reading into organ doses accounting for energies and orientation, for incorporating organ doses from the intakes of radionuclides, and for adding career doses for individual workers who were employed at multiple facilities. The dose ranges for red bone marrow, brain, and heart are presented in Tables 4, 8, and 10.

The dose distribution of MPS workers and veterans contains more high dose persons, i.e., > 50 mSv, than the Japanese study of atomic bomb survivors, i.e., ~180,000 adults compared with 25,035 children and adults (Boice et al. 2019a). The dosimetry for the LSS also continues to be revised with significant organ-dose modifications possible once the question of higher neutron dose and gamma dose to organs closer to the body surface than the colon is resolved (Cordova and Cullings 2019). Further a new set of hybrid phantoms has been developed based on the Japanese 1945 population with improved anatomical and age definitions than the stylized phantoms currently used (Griffin et al. 2019). The hybrid phantoms apparently result in different doses than DS02 and impact the organ-specific radiation risk estimates. The importance of dosimetry is again reenforced as the cornerstone for accurate and valid epidemiologic research.

Radiation and cognitive effects

When reviewing the CMS data, are any particular confounding variables being factored into the analysis?

Ongoing research will incorporate CMS data based on traditional Medicare claims and Minimum Data Set (MDS) nursing home assessments (CMS 2018, 2021a). These linkages will provide information on Alzheimer's disease and related dementias (ADRD) as well as cognitive function scores (Thomas et al. 2017; Nikpay et al. 2021). All U.S. radiation workers and veterans who were alive anytime from 1999 through 2020 and eligible for Medicare and/or Medicaid benefits, e.g., aged 65 years or over, will have linkages requested for CMS claims and prescription drug data. Approximately 600,000 MPS cohort members will be submitted for linkage. The pivotal comparisons will be between estimated radiation dose to the brain from high-LET alpha particles, in the presence of dose from low-LET photons, and the incidence of ADRD, with particular emphasis on cognitive function scores that are available within the CMS MDS. An important evaluation will be the odds of specialized geriatric care as an evaluation of cohort members likely to avail themselves of such facilities and receive care. Additionally, to account for or evaluate the determinants of ADRD and associated cognition scores, analyses will be conducted based on age, sex, race, marital status; income to the extent possibly available; education; and residence (urban vs. rural). The history of any long-term nursing home stays since 2001 will also be evaluated based on nursing home assessments. Studies conducted at Vanderbilt University have revealed that persons with ADRD compared with persons without such diagnoses are more likely to have visited a geriatric specialist, to be older, female, less likely to be currently married, have a low household income, have only a high school or less education, and a history of residence in a nursing home. No differences were identified by race or rural residency (Nikpay et al. 2021).

Is there evidence on the latency period for dementia development after radiation exposure? How do we know that it would develop within 2-3 years which is necessary to reach Mars?

NASA divides potential nervous system effects into two different categories: acute inflight and late degenerative (NASA 2021). The latter category would encompass typical diseases like Alzheimer’s. As discussed in section 13, current radiation epidemiology isn’t able to establish the existence of an effect or a potential latency. However, conventional forms of dementia seem unlikely to progress rapidly enough to be an inflight risk. Short latency cognitive impairment has been suggested mainly by animal experiments (Cekanaviciute et al. 2018). However, impairment has, at least in some cases, also been shown to occur after durations of a substantial portion of the lifespan of the animal (Rabin et al. 2014). In summary, the existence of cognitive impairments from space radiation-like exposures has not been established in humans, extrapolations of latencies from short-lived animal models are questionable, and the link between potential inflight effects and late degenerative ones is largely unknown; the MPS will provide the first data in humans from relevant high LET exposures that may be able to help address these questions.

How similar, microdosimetrically, is radiation track distribution and energy from alpha particles to that from galactic cosmic radiation?

The track structure of an alpha particle is significantly less complex than for a full GCR exposure. However, in a realistic scenario for the human body inside a vehicle, low-energy alpha particles and protons make up a substantial portion of the exposure (Slaba et al. 2016, see in particular figure 10) so in that sense, these exposures aren't any less relevant than any other laboratory experiment that uses a single beam. Zaider (1996) compares the energy deposition spectra of alpha emitters with higher energy heavy ion beams that have been commonly used in experiments. The difference in the track structure is that the low energy alpha particles will have comparatively very short ranges with narrower track widths that have more concentrated energy deposition. Additionally, on a more macroscopic scale, GCR exposures are relatively homogenous throughout the brain and other internal organs (Slaba et al. 2016) but it's still an open question how uniformly internal emitters are distributed throughout the brain (see section 15).

Could the non-uniform distribution of certain radionuclides in the brain be related to inhomogeneous blood flow to these areas?

It seems likely that nonuniform blood flow to different regions of the brain (Bentourkia et al. 2000) is an important contributing factor to the nonuniform distributions of some radionuclides in

> the brain. However, we do not have any compelling evidence for this. Perhaps a more important contributing factor to the distribution of radionuclides in the brain is the distribution of essential elements in the brain, as radioisotopes of those essential elements and chemically similar elements may follow the mode of entry of the essential elements and distribute in the same way as the essential elements.

Has USTUR used alpha autoradiography and neutron-induced radiography of thin brain sections to study distribution of alpha emitters and specifically plutonium in brain tissue?

> We did not use these techniques. However, in collaboration with Northwestern University and Advanced Photon Source facility at Argonne National Laboratory we applied synchrotron-based x-ray fluorescence microscopy (Chen et al. 2015) to study plutonium distribution using 5 µm-thickness paraffin-embedded sections of the brainstem, cortex, hippocampus, thalamus, and cerebellum. Unfortunately, we were not able to detect plutonium due to the insufficient limit of the detection. We are planning to apply a recently developed, and available in-house, ionizing-radiation quantum imaging detector (iQID) to image brain sections. The iQID is a digital alternative of conventional autoradiography (Miller et al. 2015) and was successfully used at the USTUR to study ^{241}Am distribution in bones (Tabatadze et al. 2019).

General information requests related to the MPS

Where can one find the link to the Centers for Disease Control and Prevention (CDC) Radiation Epidemiology for Public Health Decision Making set of training videos?

> See https://www.cdc.gov/nceh/radiation/emergencies/radiation-epidemiology.htm, which provides an overview of important considerations of radiation epidemiology, describes what distinguishes a well-designed or reliable study from an unreliable or a flawed study, explores how the results of epidemiologic studies may be misused or misrepresented, and discusses the impact of such studies on creating public policy and evidence-based health practices.

Please provide the website details for the Comprehensive Epidemiologic Data Repository (CEDR) managed by the U.S. Department of Energy Oak Ridge Institute for Science and Education (ORISE)?

https://oriseapps.orau.gov/cedr/

CONCLUSIONS

The First International Virtual Symposium on the MPS provided a sweeping overview of nearly 25 years of epidemiologic and dosimetric research. The dynamic nature of the program of investigations is evident. Not only were new results for the seven components which the MPS comprises presented in one forum, for the first time, but a broad landscape for the future was painted. We live in a world of low-level radiation exposure from medical, occupational, environmental, dietary, and lifestyle factors experienced over a lifetime. The MPS compilation of radiation-exposed populations, from the radium dial painters of the 1920s to the Girls of the Atomic City in the 1940s to medical radiation workers in the 2000s, form the basis for new insights and risk assessments of relevance today and tomorrow. The scientific results will inform policy and decision-makers responsible for the safety of society without unduly restricting the substantial benefits from the use of radiation. It is envisioned that sound scientific data will help in the communication and understanding of the real and not the perceived risks following gradual low-level radiation exposures received over time.

The symposium participants would like to thank those who attended the virtual format and provided such excellent questions that we, with due diligence, attempted to respond to in an informative way. The questions provided us with new ideas for future work as well as clarifying and expanding upon issues raised during the presentations. The partnering of radiation protection organizations and societies with government agencies, universities, and private enterprises has made for an exciting and synergistic forum for ideas and future opportunities. Stay tuned! A future symposium may very well be sponsored by the National Center for Radiation Epidemiology and Biology.

Disclosure statement

Most of the data used to reconstruct doses for the medical radiation worker cohort arose from measurements made by Landauer, Inc. and its predecessors over a period in excess of 50 years. Dr. R. Craig Yoder, a former long-term employee of Landauer, Inc and now retired, was chair of the NCRP Scientific Committee that recently completed Commentary 30 on dosimetry guidance for medical workers (NCRP 2020). He contributed to the assembling, evaluation and interpretation of the recorded doses used in the analyses as well as assuring the historical accuracy of both technical and administrative data, His participation does not reflect any endorsement of the commercial offerings of Landauer by the NCRP, and he received no compensation from Landauer with regard to any aspect of the research reported herein. Further, he attests that his former associations had no influence on the scientific accuracy, or any other aspect of the work reported here. The other authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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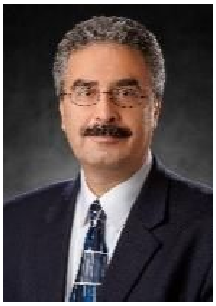

Armin Ansari is the Radiological Assessment Team Lead at the Centers for Disease Control and Prevention (CDC) serving as subject matter expert in CDC’s radiation emergency preparedness and response activities since 2002. He is a fellow and past president of the Health Physics Society and an adjunct associate professor of nuclear and radiological engineering at Georgia Institute of Technology. He serves on the National Council on Radiation Protection and Measurements (NCRP), provides consultancy to the

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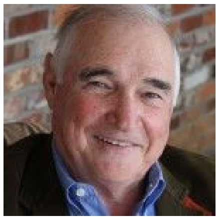
Michael T. Mumma is the Director of Information Technology at the International Epidemiology Institute and the International Epidemiology Field Station for Vanderbilt University Medical Center. He has over 20 years of experience in data analysis and conducting epidemiologic investigations. He has published on methodological topics, including geocoding and comprehensive radiation exposure assessment, and is currently developing methods to determining socioeconomic status based on residential history.

Caleigh Samuels is an assistant staff scientist in the Center for Radiation Protection Knowledge at Oak Ridge National Laboratory. She received her BS in physics from Radford University, her MS in medical physics from Georgia Institute of Technology in 2018 and is currently working towards her PhD in nuclear engineering. Her research focuses on developing and enhancing biokinetic models used in radiation protection and dose reconstruction and application of advanced Monte Carlo techniques in dosimetric modeling.



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R. Craig Yoder directed the technical activities and programs at Landauer, Inc. from 1983 through his retirement in 2015. In this capacity he influenced the technologies and measurement protocols used by the Company as it delivered dosimetry services around the world. He currently is using his historical knowledge to advise the MPS epidemiologists regarding the methods to translate personal monitoring information into mean absorbed doses to various organs. He is a Council member of the National Council on Radiation Protection.

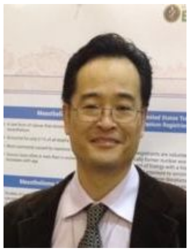

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Table 1. Million Person Study cohorts and source of populations (NCRP 2018a; Boice et al. 2019a)

Cohort (source of cohort)	Reference	Number of workers [a]
Manhattan Project and nuclear facilities (DOE)	Ellis et al. (2018)	260,000
Atomic veterans (DOD)	Boice et al. (2020)	113,806
Nuclear power plant workers (NRC)	Boice et al. (2021c)	135,193
Industrial radiographers (NRC)	NCRP (2018a), Mumma et al. (2019)	123,510
Medical radiation workers (Landauer, Inc.)	Boice et al. (2021a)	>109,019
Nuclear submariners and other navy (US Navy)	Boice et al. (2019a)	>200,000
Radium dial workers (DOE)	Martinez et al. (2021)	3,276

[a] Numbers in the Tables may differ slightly as they relate to different analyses

Table 2. Absorbed dose to lung among the medical radiation workers by occupational category (Boice et al. 2021a).

Occupational category	Number of workers	Absorbed dose to lung (mGy)			
		Mean	Median	Min	Max
General radiology	48,837	11.6	9.1	4.5	312.5
Interventional radiology	44,498	3.0	2.1	0.3	65.2
Nuclear medicine and radiation oncology	9,597	50.8	39.0	7.5	1106
Other	6,087	38.6	20.9	7.5	1271
Total	109,019	13.0	6.8	0.3	1271

Table 3. Leukemia (excluding CLL) risk among MPS cohorts

Cohort	Reference	Number of workers	ERR at 100 mGy (95% CI)
Nuclear power plant	Boice et al. (2021c)	135,193	0.15 (0.00, 0.31)
Industrial radiographers	NCRP (2018b)	123,556	0.17 (-0.02, 0.35)
Medical radiation workers	Boice et al. (2021a)	109,019	0.10 (-0.34, 0.54)
Atomic veterans	Bice et al. (2020)	114,270	-0.37 (-1.08, 0.33)
Mound [a]	Boice et al. (2014)	4,954	0.04 (-0.37, 0.71)
Mallinckrodt	Golden et al. (2019)	2,514	-0.14 (-0. 60, 0.33)
Rocketdyne [a]	Boice et al. (2011)	5,801	0.06 (-0.50, 1.13)
Los Alamos National Lab	Boice et al. (2021d)	26,328	-0.43 (-1.11, 0.24)

[a] Taken as the Hazards Ratio minus 1 at 100 mSv

ERR denotes Excess Relative Rate

Table 4. Absorbed dose to red bone marrow among MPS cohorts [a]

MPS cohort	Reference	Number of workers	Dose to red marrow (mGy)		
			Mean	Median	Max
Nuclear power plant	Boice et al. (2021c)	135,193	37.9	19.7	952.6
Industrial radiographers	Boice et al. (2019c)	123,510	12.7	0.8	1267
Medical radiation workers	Boice et al. (2021a)	109,019	12.9	6.9	1187
Atomic veterans	Boice et al. (2020)	113,806	6.2	2.3	953.1
Mound [b]	Boice et al. (2014)	4,954	26.1 [b]	2.9	640.8
Mallinckrodt [b]	Golden et al. (2019)	2,514	35.9 [b]	13.0	1219
Rocketdyne [c]	Boice et al. (2006b, 2011)	5,801	13.5 [c]	na	1000
Los Alamos National Laboratory [b]	Boice et al. (2021b)	26,328	12.4 [b]	0.8	834.9
Tennessee Eastman Corporation	Boice et al. (2021d)	26,650	na	na	na

[a] Red bone marrow doses represent the latest study compilations and may differ slightly from published values.

[b] Dose weighting factor of 1 applied for plutonium, polonium and uranium dose.

[c] Personal dose equivalent in mSv

na denotes not available

Table 5. Lung cancer risk among MPS cohorts (Boice et al. 2019c)

Cohort	Reference	Number of workers	ERR at 100 mGy [a] (95% CI)
Nuclear power plant (NPP)	Boice et al. (2021c)	135,193	-0.04 (-0.11, 0.02)
Industrial radiographers (IR)	Boice et al. (2019c)	123,556	0.13 (0.02, 0.23)
Medical radiation workers (MW)	Boice et al. (2021a)	109,019	0.15 (0.02, 0.27)
NPP + IR + MW		367,722[b]	0.02 (-0.03, 0.07)
Atomic veterans	Boice et al. (2020)	114,270	0.04 (-0.11, 0.19)
Mound	Boice et al. (2014)	4,954	0.00 (-0.03, 0.04)
Mallinckrodt	Golden et al. (2019)	2,514	-0.06 (-0.18, 0.06) [c]
Rocketdyne	Boice et al. (2011)	5,801	-0.02 (-0.18, 0.17) [c]
Los Alamos National Lab	Boice et al. (2021b)	26,328	0.01 (-0.02, 0.03)
Tennessee Eastman Corp	Boice et al. (2021d)	26,650	0.00 (-0.01, 0.01)

[a] Doses are at 100 weighted-mGy for Mallinckrodt, Los Alamos National Laboratory, and Tennessee Eastman Corporation where a dose weighting factor of 20 was used for uranium and plutonium dose

[b] 46 workers were in two cohorts and are counted only once in this pooled analysis.

[c] Taken as the Hazards Ratio minus 1 at 100 mSv, a dose weighting factor was not applied

ERR denotes Excess Relative Rate

Table 6. Absorbed dose to lung among MPS cohorts [a]

MPS cohort	Reference	Number of workers	Dose to lung (mGy) Mean	Median	Max
Nuclear power plant	Boice et al. (2021c)	135,193	43.2	22.4	1,085
Industrial radiographers	Boice et al. (2019c)	123,556	10.9	0.3	1,435
Medical radiation workers	Boice et al. (2021a)	109,019	13.0	6.8	1,272
Atomic veterans	Boice et al. (2020)	113,806	6.2	2.3	972
Mound [b]	Boice et al. (2014)	4,954	98.7	10.2	17,478
Mallinckrodt [c]	Golden et al. (2019)	2,514	511 [c]	179	8,327
Rocketdyne [d]	Boice et al. (2006b, 2011)	5,801	19.0[d]	na	3,560
Los Alamos National Laboratory [c]	Boice et al. (2021b)	26,328	28.6[c]	0.9	16,811
Tennessee Eastman Corporation [c]	Boice et al. (2021d)	26,650	477 [c]	125.6	18,538

[a] Lung doses represent the latest study compilations and may differ slightly from published values. The atomic veteran doses, for example, are the ones used in the lagged analysis.

[b] Dose weighting factor of 1 applied for plutonium and polonium dose. Using a DWF of 20 results in a mean lung dose of 1.54 weighted-Gy.

[c] Dose weighting factor of 20 applied for plutonium and uranium.

[d] mSv presented, not mGy and dose weighting factor for uranium was 1

na denotes not available

Table 7. Parkinson’s disease risk among MPS cohorts

Cohort	Reference	Number of workers	ERR at 100 mGy (95% CI)
Nuclear power plant	Boice et al. (2021c)	135,193	0.24 (-0.02, 0.50)
Industrial radiographers		123,556	0.24 (-0.02, 0.50)
Medical radiation workers	Boice et al. (2021a)	109,019	0.17 (-0.20, 0.54)
Mound	Boice et al. (2014)	4,954	0.23 (-0.01,0.54)[a]
Mallinckrodt	Golden et al. (2019)	2,514	-0.06 (-0.18, 0.06)
Los Alamos National Lab	Boice et al. (2021d)	26,328	0.16 (-0.07, 0.40)

[a] Combined dementia, Alzheimer's, Parkinson's and motor neuron disease

ERR denotes Excess Relative Rate

Table 8. Absorbed dose to brain among MPS cohorts [a]

MPS cohort	Reference	Number of workers	Dose to brain (mGy)		
			Mean	Median	Max
Nuclear power plant	Boice et al. (2021c)	135,193	33.2	17.2	833.6
Industrial radiographers	Boice et al. (2019c)	123,510	10.3	0.7	1025
Medical radiation workers	Boice et al. (2021a)	109,019	18.9	9.8	1077
Atomic veterans	Boice et al. (2020)	113,806	6.8	2.5	1058
Mound [b]	Boice et al. (2014)	4,954	26.1[b]	na	937
Mallinckrodt [c]	Golden et al. (2019)	2,514	38.8[c]	16.2	1151
Rocketdyne [b]	Boice et al. (2006b, 2011)	5,801	13.5 [b]	na	1000
Los Alamos National Laboratory [c]	Boice et al. (2021b)	26,328	11.7[c]	0.8	764.3
Tennessee Eastman Corporation	Boice et al. (2021d)	26,650	na	na	na

[a] Brain doses represent the latest study compilations and may differ slightly from published values.

[b] Personal dose equivalent, mSv

[c] Dose weighting factor of 1 applied for plutonium and uranium.

na denotes not available

Table 9. Ischemic heart disease risk among MPS cohorts

Cohort	Reference	Number of deaths	ERR at 100 mGy (95% CI)
Nuclear power plant	Boice et al. (2021c)	5,410	-0.01 (-0.06, 0.04)
Industrial radiographers	NCRP (2018b)	4,458	0.00 (-0.01, 0.01)
Medical radiation workers	Boice et al. (2021a)	1,655	-0.10 (-0.27, 0.06)
Atomic veterans	Boice et al. (2020)	13,806	-0.01 (-0.12, 0.11)
Mound	NCRP (2018b)	221	-0.14 (-0.43, 0.14)
Mallinckrodt	Golden et al. (2019)	521	0.13 (-0.01, 0.28)
Los Alamos National Lab	Boice et al. (2021d)	3,043	-0.06 (-0.16, 0.04)

ERR denotes Excess Relative Rate

Table 10. Absorbed dose to heart among MPS cohorts [a]

MPS cohort	Reference	Number of workers	Dose to heart (mGy)		
			Mean	Median	Max
Nuclear power plant	Boice et al. (2021c)	135,193	43.9	22.8	1105
Industrial radiographers	Boice et al. (2019c)	123,510	15.0	1.0	1504
Medical radiation workers	Boice et al. (2021a)	109,019	14.6	8.0	1272
Atomic veterans	Boice et al. (2020)	113,806	6.1	2.2	953
Mound [b]	Boice et al. (2014)	4,954	24.0	2.4	630
Mallinckrodt [c]	Golden et al. (2019)	2,514	49.3 [c]	24.3	1345
Rocketdyne [d]	Boice et al. (2006b, 2011)	5,801	13.5 [d]	na	1000
Los Alamos National Laboratory [c]	Boice et al. (2021b)	26,328	13.5 [c]	0.9	897
Tennessee Eastman Corporation	Boice et al. (2021d)	26,650	na	na	na

[a] Heart doses represent the latest study compilations and may differ slightly from published values.

[b] Dose weighting factor of 1 applied for plutonium and polonium dose

[c] Dose weighting factor of 20 applied for plutonium and uranium

[d] Personal dose equivalent in mSv

na denotes not available

Table 11. Standardized mortality ratios (SMRs) and number of breast cancers for males and females in 8 MPS cohorts (consisting of 545,771workers and veterans) by quality of exposure

MWS cohort	Number of Workers	Male SMR (number of breast cancers)	Female SMR (number of breast cancers)
High-linear energy transfer (LET)[a] exposures			
Mound (Boice et al. 2014)	4,954	0 (0)	1.00 (41)
LANL (Boice et al. 2021d)	26,328	0.59 (3)	1.11 (192)
TEC (Boice et al. 2021d)	26,650	0.31 (1)	0.92 (414)
Rocketdyne (Boice et al. 2011)	5,801	0 (0)	0.96 (8)
Low-linear energy transfer (LET)[b] exposures			
Nuclear power plant (Boice et al. 2021c)	135,193	0.35 (4)	1.15 (37)
Industrial radiographers	123,556	0.91 (7)	0.94 (35)
Medical workers (Boice et al. 2021a)	109,019	1.04 (5)	0.79 (311)
Atomic veterans (Boice et al. 2020)	114,270	1.17 (29)	na
Total	545,771	0.91 (49)	0.91 (1,038)

[a] High-LET exposures consist primarily of internal intakes of radionuclides and neutrons

[b] Low-LET exposures consist primarily of external photon exposures, mainly gamma rays but also x-rays.

na denotes not applicable