THE PAST INFORMS THE FUTURE: AN OVERVIEW OF THE MILLION WORKER STUDY AND THE MALLINCKRODT CHEMICAL WORKS COHORT

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***Abstract*—The purpose of this paper is to present an overview of ongoing work on the Million Worker Study (MWS), highlighting some of the key methods and progress so far as exemplified by the study of workers at the Mallinckrodt Chemical Works (MCW). The MWS began nearly 25 y ago and continues in a stepwise fashion, evaluating one study cohort at a time. It includes workers from U.S. Department of Energy (DOE) Manhattan Project facilities, U.S. Nuclear Regulatory Commission (NRC) regulated nuclear power plants, industrial radiographers, U.S. Department of Defense (DoD) nuclear weapons test participants, and physicians and technologists working with medical radiation. The purpose is to fill the major gap in radiation protection and science: What is the risk when exposure is received gradually over time rather than briefly as for the atomic bomb survivors? Studies published or planned in 2018 include leukemia (and dosimetry) among atomic veterans, leukemia among nuclear power plant workers, mortality among workers at the MCW, and a comprehensive National Council on Radiation Protection and Measurements (NCRP) Report on dosimetry for the MWS. MCW has a singular place in history: the 40 tons (T) of uranium oxide produced at MCW were used by Enrico Fermi on 2 December 1942 to produce the first manmade sustained and controlled nuclear reaction, and the atomic age was born. Seventy-six years later, the authors followed the over 2,500 MCW workers for mortality and reconstructed dose from six sources of exposure: external gamma rays from the radioactive elements in pitchblende; medical x rays from occupationally required chest examinations; intakes of pitchblende (uranium, radium, and silica) measured by urine samples; radon breath analyses and dust surveys overseen by Robley Evans and Merril Eisenbud; occupational exposures received before and after employment at MCW; and cumulative radon concentrations and lung dose from the decay of radium in the work environment. The unique exposure reconstructions allow for multiple evaluations, including estimates of silica dust. The study results are relevant today. For example, NASA is interested that radium, deposited in the brain, releases high-LET alpha particles - the only human analogue, though limited, for high energy, high-Z particles (galactic cosmic rays) traveling through space that might affect astronauts on Mars missions. Don't discount the past; it's the prologue to the future!**

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Key words: intake, radionuclide; National Council on Radiation Protection and Measurements; radiation dose; radiation effects

INTRODUCTION

THE PURPOSE of this paper is to present an overview of ongoing work on the Million Worker Study (MWS), highlighting some of the key methods and findings and with a focus on the study of workers at the Mallinckrodt Chemical Works (MCW). The MWS will answer a major question in radiation protection (Shore et al. 2017): What is the risk when exposure is received gradually over time? MCW exemplifies how the MWS identifies study populations, traces workers for vital status, reconstructs organ-specific doses, and analyzes data. Doses have been reconstructed from six sources of radiation, and adjustment was made for individual measurements of pitchblende dust inhalation (Ellis et al. 2018; Boice et al. 2017). The only significant radiation dose–response relationship among MCW workers was for the kidney. Radiation risk estimates differed by choice of statistical model and choice of adjustment factors (Golden et al. 2017; Boice et al. 2017). These findings guide the choice of optimal approaches for dose reconstructions and statistical analyses.

THE MILLION WORKER STUDY OF LOW DOSE RADIATION HEALTH EFFECTS

The MCW study is part of the MWS. The MWS includes 360,000 U.S. Department of Energy workers (Boice et al. 2011; Boice 2012, 2017a); 150,000 nuclear utility workers (Boice 2016, 2017b); 115,000 atomic veterans who participated in above-ground atmospheric tests (Till et al. 2014; Caldwell et al. 2016; Beck et al. 2017);

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250,000 radiologists and medical workers (Bouville et al. 2015); and 130,000 industrial radiographers (Boice 2012, 2015).

The study of Japanese atomic bomb survivors is comparatively small with only 86,000 subjects (Ozasa et al. 2012) and is 12 times smaller than the MWS. The exposure was brief, on the order of a second in time, and not chronic over years as is of interest today. As well as including many more individuals, the MWS cohort includes many more subjects in both the low (<100 mGy) and high (>100 mGy) dose categories. These large numbers and the broad dose distribution equate to substantial statistical ability to detect and precisely estimate radiation risks for individual organ sites from exposures received gradually over time (Boice 2017a). One overarching goal is to integrate radiation biology with the MWS to enhance the understanding and prediction of disease risk following low-dose exposures and develop biologically-based dose response models (NCRP 2015; Preston 2015, 2017; Rühm et al 2017).

Cohorts of American workers and veterans exposed to radiation have been assembled since the 1940s by U.S. government agencies for the purposes of occupational monitoring, epidemiologic research, licensee requirements [by the U.S. Nuclear Regulatory Commission (NRC) and individual state authorities] and compensation. It was critical that the essential ingredients for high-quality epidemiologic research were available: well-defined populations with personal identifiers (e.g., name, date of birth and social security number) for vital status determination; occupational records (e.g., dates of employment, job titles); radiation records on doses received over time; comparable measures of outcome (i.e., cause of death) based on state and national mortality records; and bioassay data (e.g., urine samples) as needed to determine any intakes of radioactive material. Women comprise about 25% of the study population. High quality exposure assessment is the key to good epidemiology and is a priority focus within the MWS (Boice et al. 2006; Bouville et al. 2015; Till et al. 2014, 2017; Beck et al. 2017; NCRP 2017).

MALLINCKRODT CHEMICAL WORKS

"The story of the supply of uranium is by itself a thrilling one, and the production of enough pure metallic uranium to do our task in time was a technological and industrial miracle." —Arthur Holly Compton

In addition to discovering the "Compton effect," Arthur Compton was an influential scientist during World War II, overseeing both Enrico Fermi and Robert Oppenheimer during the Manhattan Project. In 1942, he knew that ether, a dangerous and explosive solvent, would be required to refine large amounts of uranium ore needed to produce uranium metal and uranium oxide. He met with his friend Edward Mallinckrodt, Jr., the president of MCW, and persuaded him to take on the refining because of the national need and the company's success in safely using ether in an industrial setting. Mallinckrodt agreed with a handshake, and the uranium processing began in July 1942. On 2 December 1942, 40 tons (T) of uranium oxide produced at MCW in St. Louis were used at the University of Chicago by Enrico Fermi to produce the first manmade sustained and controlled nuclear reaction (USACE 1996). The atomic age was born, and the world was irrevocably changed.

MCW workers were first exposed to occupational radiation in 1942, and many decades later, the 2,514 workers were followed for mortality and reconstructed dose from six sources of radiation exposure: (1) external gamma rays from the radioactive elements in pitchblende; (2) medical x rays from occupationally required chest examinations; (3) intakes of pitchblende (uranium, radium and silica) measured by urine samples; (4) radon breath analyses for radium depositions and dust surveys overseen by Robley Evans and Merril Eisenbud; (5) occupational exposures received before and after employment at MCW; and (6) assessment of radon and its progeny present in the work areas during the early days of production.

External exposures of the 2,514 white male workers employed at MCW between 1942 and 1966 (the period when uranium was processed at MCW) were evaluated previously through 1993 (Dupree-Ellis et al. 2000). The current study updated the follow-up by 19 years, through 2012, and vital status was obtained for 99.2% of the workers who were all employed 50 to 70 y ago. Organ dose reconstruction was one of the most comprehensive of any radiation epidemiologic study, conducted with the inclusion of external gamma rays from the decay products in the pitchblende and uranium ore being processed; the internal intakes of uranium and radium based on 39,451 urine bioassays and 2,341 radon breath results; 31,297 occupational medical x rays required during employment; and 210 records of radiation exposure received at facilities both before and after employment at Mallinckrodt (Ellis et al. 2018). The concentration of radon and its progeny were high in the working environment and have been examined for lung dose (Dupree et al. 1995; ORAUT 2010). In the 1940s, radon breath and other analyses were reported by Robley Evans [Professor at Massachusetts Institute of Technology and a future president of the Health Physics Society (HPS)] to Merril Eisenbud (Chief of the Radiation Health and Safety Branch, Atomic Energy Commission, and a future president of HPS) (Eisenbud 1975; Harley et al. 1951). Further, the contributions of uranium dust and silica exposures to risk could be addressed because measurements of uranium dust were made during most of the years of processing uranium (Blatz and Eisenbud 1950; Harris 1958; Dupree et al. 1995; ORAUT 2010). The mean external dose was ~50 mSv (maximum 1 Sv; percent workers >100 mSv, 13%). The mean dose to kidney from occupational chest x-rays was ~14 mGy (maximum 46 mGy). The mean dose to kidney, including both external and internal dose (RBE set as 1), was 59 mGy (maximum 1.1 Gy) (Ellis et al. 2018; Boice et al. 2017).

There were no significant radiation dose-response relationships except for kidney cancer and for nonmalignant kidney diseases including nephritis (Boice et al. 2017; Ellis et al. 2018). Cumulative silica dust estimates were correlated with the uranium dust measures (Ellis et al. 2018; Boice et al. 2017). Silica is a possible kidney carcinogen and has been linked to increased rates of nonmalignant kidney disease (Steenland et al. 2001; Liu et al 2017). Uranium is a heavy metal toxin, but the evidence as a human carcinogen is limited (IARC 2012). Over 50 y of follow-up of workers processing uranium have failed to reveal clear and consistent evidence of an excess of chronic renal failure or any cancer that could be attributed to uranium intake (IOM 2000). Kidney damage of clinical importance has not been observed in workers exposed to high levels of uranium compounds (Kathren and Burklin 2008; IOM 2000) or in veterans exposed to depleted uranium from embedded shrapnel (McDiarmid et al. 2007). Further, the types of kidney cancers in excess among MCW workers were of the kidney corpus, which has not been convincingly linked to radiation exposure (UNSCEAR 2008). Finally, silica and/or the non-radiogenic (chemical) properties of uranium may have played an important role in damaging the kidneys. Further analyses within the MWS are ongoing to address these issues.

ANALYSIS APPROACH

The choice of statistical model and software package mattered when computing risk estimates, such as the excess relative risk for specific cancers following radiation exposure (Boice et al. 2017). Oak Ridge Associated Universities (ORAU) and Vanderbilt University are evaluating different statistical approaches and software packages used in the analysis of radiation epidemiology data, including Cox proportional hazard models and Poisson piece-wise regression, both grouped and ungrouped. Radiation risk estimates were then compared as produced from software packages such as SAS, R and Epicure (Boice et al. 2017; Golden et al. 2017). The influence of specific covariates, such as duration of employment and socio-economic status, is also being evaluated. Preliminary results suggest that the choice of analytic approach and the selected covariates can determine whether the results are statistically significant or not (Boice et al. 2017). Choose wisely and properly, and when in doubt and different approaches produce divergent results, present all results, analytic designs, and underlying assumptions.

EXPOSURES 75 Y AGO ARE RELEVANT TODAY—FOR EXAMPLE, MISSION MARS

In evaluating possible health risks to astronauts from space radiation during a 3-y mission to Mars, the National Aeronautics and Space Administraiton (NASA) is interested in assessing the radiation-related cancer risk (NA/NRC 2012; NCRP 2014; Boice 2016). In addition, there is concern over the potential behavioral and cognitive impairments from space radiation on the central nervous system, as well as the possibility that dementia and other motor neuron diseases might develop later in life (NCRP 2016). Galactic cosmic rays (GCR), the high-velocity heavy ions (e.g., ^{56}Fe) whizzing through space after a supernova explodes, are of special interest (NCRP 2006, 2014, 2016; National Academies/National Research Council, 2012). Early and late neurological disorders from brief exposures to these heavy ions are seen in mice studies (Underwood 2015). There are no human exposures/analogues similar to GCR in space. However, workers at MCW and Middlesex, a smaller NJ facility that stored the pitchblende processed at MCW, had intakes of radium that resulted in high-LET dose to brain tissue from alpha particles (Ellis et al. 2018). Radium in brain tissue has been detected in workers (Hursh and Lovaas 1963). Radionuclides that emit alpha particles have been detected in the brains of persons after intakes of polonium (Nathwani et al. 2016), americium (McInroy et al. 1985), plutonium (McInroy et al. 1991) and uranium (Avtandilashvili et al. 2015). Brain dose from alpha particles has been or is being estimated for workers at Mound (Boice et al. 2014), Rocketdyne (Boice et al. 2011), Los Alamos National Laboratory (Wiggs et al. 1994) and Rocky Flats (Brown et al. 2004). These cohorts and others that are part of the MWS will be combined to examine deaths due to dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease. The helium nuclei (alpha particles) are of much lower energy than GCR and the distribution of dose within brain tissue differs, but the exposures are to humans and the dose rate is low. The human brain exposed for years to alpha particles may be relevant to a Mars mission in contrast with the mouse brain exposed to heavy ions for a few minutes (Cherry et al. 2012).

CONCLUDING COMMENTS

Don't discount the past; it's the prologue to the future. Mallinckrodt Chemical Works and other comparable cohorts exemplify what can be learned from the past that is relevant to questions today, such as any effects of alpha particle dose on brain tissue that lead to increases in death due to dementia (of importance to NASA and the quest for traveling to MARS). The MWS is also relevant to issues of environmental contamination from hydraulic fracturing and the associated radioactive sludge, estimating risk following computed tomography medical examination, compensating workers for past exposures and disease development, dealing with terrorist attacks with dirty bombs or improvised nuclear devices, managing risks from high-level waste repositories, assessing risks for aircrew flying higher and longer with cosmic ray exposures increasing, and the ever increasing use of medical radiation. It is a credit to the Atomic Energy Commission (and what is now the U.S. Department of Energy) for having industrial hygiene programs in the 1940s for worker protection and the foresight to archive the comprehensive records that could be used for research applicable to problems faced today and will be faced tomorrow. The past can address questions for the future that haven't yet been asked. It's our challenge to learn from the legacies of the past and apply the findings to present and future needs of the nation!

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