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REVIEW

The Million Person Study relevance to space exploration and mars

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ABSTRACT

Understanding the health consequences of exposure to radiation received gradually over time is critically needed. The National Aeronautics and Space Administration (NASA) bases its safety standards on the acute exposures received by Japanese atomic bomb survivors. Such a brief exposure differs appreciably from the chronic radiation received during a two to three year mission to Mars. NASA also applies an individual risk-based system for radiation protection that accounts for age, sex, smoking history, and individual life styles. Because the Japanese life span study (LSS) reports women to be at 2 to 3 times greater lifetime risk of developing cancer than men, female astronauts are allowed less time in space. Another concern is the potential behavioral and cognitive impairments from galactic cosmic radiation (GCR) impinging on the nervous system that might jeopardize the mission, and, possibly, lead to dementia later in life. GCR are high-velocity heavy ions traveling through space. There are no human circumstances/analogs similar to GCR that can provide direct information on the possible effects of such high-LET exposure to brain tissue. The MPS provides a more representative group (healthy men and women) for risk estimates than the 1945 Japanese population exposed briefly to the atomic bombs. The permissible career exposure limit set by NASA for each astronaut is a 3% risk of exposure-induced death (REID) from cancer at a 95% confidence level to account for uncertainties in risk projections. Because the MPS is 10 times larger than the LSS, the 95% confidence levels will be narrower and thus allow more time in space, all things being equal. Sex-specific differences in radiation risk can be examined more fully in the MPS with over 250,000 women compared with about 32,000 women in the LSS. Noncancer outcomes such as neurological disorders also can be evaluated following low-dose rate exposures to high-LET alpha particles. Workers at several nuclear facilities had intakes of radionuclides, such as plutonium, that exposed brain tissue to alpha particles (Helium nuclei) for life. Such workers are being evaluated for mortality from dementia and other motor neuron diseases; can be evaluated for clinically diagnosed incidences of these conditions; and, though challenging, could be interviewed and ask to take cognition tests. Ischemic heart disease is also under study. The MPS, thus, provides another line of human inquiry to assist in decision-making and policy guidance for space missions beyond earth orbit.

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Introduction

I'd like to die on Mars, just not on impact – Elon Musk

Much is known about the health effects of brief high-dose exposures such as those received by patients during the treatment of benign and malignant conditions and by survivors of the atomic bombings in Japan (UNSCEAR 2008; Ozasa et al. 2012, 2018; Grant et al. 2017). However, the concerns today are related to the health consequences from prolonged low-dose exposure received over a period of years (Shore et al. 2017). The Million Person Study of Low-Dose Health Effects (MPS) was designed to precisely estimate radiation risks from chronic exposures (NCRP 2018a; Boice et al. 2019a) and to address issues of the appropriateness of the linear non-threshold dose-response model as used in radiation protection (Boice 2017a; Shore et al. 2018, 2019; NCRP 2018b). Because of the diversity of exposure circumstances within the MPS (Boice et al. 2006, 2019a; Bouville et al. 2015; Ellis et al. 2018; Leggett et al. 2018a, 2018b; Dauer et al. 2018; NCRP 2018a), the MPS has the ability to address specific issues of interest to the National Aeronautics and Space Administration (NASA), and its system of radiation protection for astronauts (NCRP 2000, 2006, 2014, 2016; NA/NRC 2012; Cucinotta et al. 2013; Cucinotta 2015; NASA 2015). The MPS populations include 170,000 medical radiation workers, 140,000 nuclear power plant workers, 130,000 industrial radiographers, 114,000 atomic veterans who participated in above-ground atmospheric weapons tests, and 360,000 workers at US Department of Energy (DOE) nuclear facilities. The large study size and broad range of doses, coupled with a very long follow-up period and consistent methodological approaches, indicates the substantial quality and statistical ability to quantify and clarify the health risks from exposures that are received gradually over time.

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Because of the relatively high cumulative doses possible during a mission to Mars and return, cosmic radiation is arguably the limiting factor in going to Mars (Shay et al. 2011; Zeitlin et al. 2013) in addition to the many stresses that flight crews would have to deal with that affect behavioral health, performance and cognition, e.g. sleep and circadian rhythm disturbances, CO_2 build-up, microgravity, isolation and confinement, mission duration, workload and psychosocial adaptation, including team coordination, cooperation, and communication (NCRP 2014, 2016; NASA 2015). Astronauts on a Mars mission would receive approximately 200 mGy from the exposure to high-energy protons but perhaps more importantly, a comparable dose from the heavy ions of high atomic number and high energy (HZE particles) traveling at high speed. The NASA-defined effective dose (Cucinotta et al. 2013, 2013; NA/NRC 2012; Zeitlin et al. 2013; Norbury et al. 2016; Simonsen and Zeitlin 2017) would be about 900–1200 mSv received at a rate of about 1 mSv d^{-1} which would be similar to receiving a whole-body CT examination every 7 or 8 days. Overviews are available describing the many aspects of the MPS that are relevant to NASA, space exploration and, perhaps someday, even colonization (Davies and Schulze-Makuch 2011; Boice 2014a, 2014b, 2015a, 2015b, 2016, 2017b; Bouville et al. 2015; Boice et al. 2018a; NCRP 2018a; see also Davies and Schulze-Makuch 2011) and will be summarized here.

NASA is unique in applying an individual risk-based system for radiation protection that considers an individual's lifetime radiation risk of cancer mortality that accounts for the astronaut's age, sex, smoking history, and other risk factors as known (NA/NRC 2012; Cucinotta et al. 2013; NCRP 2014; NASA 2015). This is in contrast to the system of dose limits for occupational exposures used by terrestrial-based organizations which is based on age-averaged, sex-averaged risk estimates, subjective tissue-weighting factors and other considerations for computing effective dose and demonstrating compliance for regulatory purposes (ICRP 2007). NASA sets a permissible career exposure limit of a 3% lifetime Risk of Exposure-Induced Death (REID) from cancer at a 95% confidence level to account for uncertainties in risk projection assumptions (NCRP 2006; NA/NRC 2012; Cucinotta et al. 2013; NASA 2015). Once these limits are exceeded, allowable time in space is reduced. Current estimates are based on the Japanese atomic bomb survivor life span study (LSS) of acute exposures among 86,000 survivors, and about 54,000 adults (Ozasa et al. 2012). There is some evidence from epidemiologic studies that prolonged exposures over a period of years may result in a lower estimate of radiation-related cancer risk than seen following the acute exposure received by Japanese bomb survivors (Shore et al. 2017). The MPS will reduce the statistical uncertainty in the LSS risk estimates, narrow the 95% confidence (credibility) interval, and thus allow more time in space for flight crew even if the lifetime risk estimates turn out to be similar to those from the atomic bomb survivor study.

Because of the sex-specific differences in radiation-induced cancer, female flight crew have reduced allowable time in space due to their higher risk of radiation-induced cancer based on the Japanese LSS (NCRP 2014). This difference is not only because the much higher female radiation-risk of breast and ovarian cancer than the male radiation-risk of testicular and prostate cancer, but is related in large part to a comparatively high risk of lung cancer, about 2–3 times higher, in women that observed for men. The MPS has nearly 250,000 women which will provide a very strong evaluation of any risk differences by sex for all cancers including lung cancer in particular. The ongoing study of 170,000 medical radiation workers is designed to address sex-specific differences in risk focusing on lung cancer dosimetry and lung cancer risks (Yoder et al. 2018; Boice et al. 2019b).

One major difference between the study of Japanese atomic bomb survivors exposed in 1945 and occupationally exposed workers is the dose rate, i.e. the time over which the exposures were delivered (Shore et al. 2017). The Japanese LSS can only address brief exposures that occurred in a very short period of time, whereas worker exposures occurred over many years if not decades. The second major difference is that healthy American workers are more representative of today's workers, the public, and flight crews than the 1945 population of Japanese atomic bomb survivors.

Animal experiences following brief exposure to high-velocity heavy ions (HZE particles) simulating GCR exposures in space indicate detrimental early and late effects of space irradiation on behavior and cognitive performance (NCRP 2016). 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 (Cherry et al. 2012; Cucinotta et al. 2014; Limoli 2015; NCRP 2016). There is no analog of human studies or circumstances that can approximate these heavy-ion (HZE) exposures to brain tissue. If fact, there is no evidence in human studies that low-LET radiation is associated with dementia or Alzheimer's disease (Yamada et al. 2009). However, worker cohorts at several DOE facilities (e.g. Mound, Rocketdyne, Mallinckrodt, Middlesex, Los Alamos National Laboratory, Rocky Flats, and Hanford) had intakes of radionuclides such as polonium, plutonium, radium, uranium, and americium which provide alpha particle dose to the soft tissue within the brain and not from depositions in bone (Leggett et al. 2018a; Boice et al. 2018b).

Although mortality is a weak indicator of behavioral issues, large numbers of deaths due to dementia, Alzheimer's disease, Parkinson's disease, and motor neuron disease are being evaluated with regard to brain tissue dose from high-LET alpha particles coupled with low-LET gamma radiation (Boice et al. 2014; Boice 2017b). More to the point, however, ongoing studies of workers at nuclear facilities with high intakes of radionuclides could incorporate cognition tests similar to those astronauts take. Clinically based diagnoses of dementia, Alzheimer's and other motor neuron conditions, including behavioral and cognition impairment, also could be evaluated within Medicare or other nursing record files (Rector et al. 2004; CMS 2018a, 2018b).

The study of workers with intakes or radionuclides that expose brain tissue to alpha particles has the following strengths: (1) humans and not rodents are being studied; (2) the exposure occurs over many years (the radionuclides have very long half-lives and continually expose brain tissue for years after intake) and not over minutes or weeks as in the rodent experiments; (3) the radionuclides emit alpha particles (He nuclei) which constitute about 14% of the GCR flux (though of lower energy); (4) the working environment would include many years of concomitant exposure to gamma rays (low-LET radiation) which would contribute about 90% or more to the brain dose which can be compared with the 85% contribution of protons (low-LET radiation) to the GCR flux (Zeitlin et al. 2013; Norbury et al. 2016) and (5) standardized tests of cognitive function (Basner et al. 2015; CMS 2018b) are available or could be administered, and dose-response analyses made, i.e. the test scores could be contrasted with alpha-particle brain dose as estimated from extensive urinary excretion data on individual workers. The alpha-particle dose would be computed from intake up until the time of diagnosis and/or of testings. The weakness of this study is that HZE particles are not being evaluated. While HZE particles are of high energy and would interact with neural tissue differently than deposited radionuclides emitting alpha particles, the approximately uniform distribution of alpha particle dose to brain tissue might be a similarity.

A previous analysis of heart mortality among Apollo astronauts claimed an elevated rate of heart disease (Delp et al. 2016), but was severely limited (Cucinotta et al. 2016) and not borne out with subsequent study using a more valid methodology (Elgart et al. 2018). However, it remains uncertain whether low doses (<500 mGy) cause ischemic heart disease (IHD) (NCRP 2018a; Shore et al. 2019) and whether cumulative exposures to chronic low-dose low-LET or high-LET galactic cosmic rays should be considered a detriment of space travel (Cucinotta et al. 2015; NASA 2015). The size of the MPS will allow comprehensive evaluations of non-malignant conditions such as IHD, including both low-LET and high-LET exposures (Boice 2017b; Golden et al. 2018, 2019; NCRP 2018a).

Overview of relevant MPS cohorts

> People will visit Mars, they will settle mars, and we should because it's cool – Jeff Bezo

The various cohorts within the MPS are of such diverse nature that they can contribute to research efforts that are relevant to the NASA radiation protection program (Table 1). The combination of all cohorts will provide the most precise estimates of radiation risk following low-dose-rate exposures over years yet possible. This precision will provide guidance as to the relevancy of the continued use of the Japanese LSS study of acute exposures for use in model projections that are used to set individual guidance limits. The large number of women in the MPS, nearly a quarter of a million, will provide evidence as to any difference of sex-specific radiation risks, particularly for lung cancer, following chronic exposures. The major cohorts within the MPS to evaluate sex-specific differences include the medical radiation workers, nuclear power plant workers, industrial radiographers, as well as the workers at Mound, Los Alamos National Laboratory, Rocky Flats, Hanford and other facilities. The DOE workers with intakes of radionuclides, such as plutonium, will provide estimates of radiation dose from high-LET particles to various organs such as the lung, brain and heart which can be used in the evaluation of organ-specific conditions, e.g. lung cancer, as well as the possibility of looking at any association with dementia and Alzheimer's disease and, conceivably, cognitive behavioral impairments.

Anticipated contributions

> You can see a lot just by observing – Yogi Berra

The MPS is so large, so complete, with such comprehensive dosimetry and long follow-up that it will make critically important contributions regarding the level of risk when radiation is received over a period of years and not briefly (GAO 2017; Davis et al. 2019) (Table 1). Gradual exposures to low doses at low-dose rates are the type of exposures experienced by workers, the public, and flight crew. For NASA and the decisions that will have to be made with regard to radiation protection for astronauts on long missions beyond Earth orbit, the MPS will provide precise estimates of cancer risk following prolonged exposure that can be incorporated into lifetime risk projections; the MPS will provide precise estimates of sex-specific radiation risks for lung and other cancers that can also be incorporated into NASA lifetime risk models for radiation guidance for individual astronauts; the MPS will provide risk estimates following chronic exposure to brain tissue from high-LET radiation that might be relevant, in certain ways, as a human analog to GCR experienced in space. There is interest in integrating the MPS epidemiology with biologically based models to improve risk estimates at low doses (Preston 2015; Rühm et al. 2017). Finally, the MPS will contribute knowledge regarding the risks of non-malignant diseases such as ischemic heart disease and central nervous system disorders and whether such conditions might be relevant to adding to models of detriment following radiation exposures received at low doses and at low-dose rates.

Better risk estimates for cancer following prolonged exposure

> There's nothing I would like more than to watch a manned Mars landing – Andy Weir

The MPS is so large that the estimates of radiation risk following prolonged or chronic exposures over a period of years will be very precise (Table 1). NASA uses an individual risk-based system for radiation protection based on the lifetime risk estimates considering the radiation risk and the astronaut's characteristics such as age, sex, smoking history,

Table 1. Relevance of the Million Person Study (MPS) research to NASA's missions in space.

Issue for NASA	MPS relevant research
Dose rate	
Radiation Protection Guidance is based primarily on the acute (brief) exposures received by Japanese atomic bomb survivors in 1945.	MPS workers accumulated radiation exposures over a period of years and thus at a dose rate more similar to what astronauts would receive during a 2–3 year mission to Mars.
Representativeness	
The Japanese survivors lived in a war-torn country and faced malnutrition, infections, and deprivations after the War.	The MPS consists of healthy male and female workers and thus more similar to healthy astronauts.
Time in space	
Radiation Protection Guidance is based on the 95% upper confidence level about a 3% increased lifetime risk of cancer death from the Japanese LSS.	The MPS is 10 times larger than the Japanese LSS. Statistical variability will be reduced, 95% confidence levels narrowed, and more time in space allowed, all things being equal.
Time in space for women	
The Japanese life span study (LSS) finds women to be at 2–3 times greater lifetime risk of dying from cancer than men, particularly for lung cancer, and thus women are allowed less time in space than men.	The Japanese data include ∼32,000 adult women and ∼21,000 adult men. The MPS has 250,000 adult women; and a cohort of 170,000 medical radiation workers (1/2 females) is designed to address differences in sex-specific lung cancer risks.
High-let effects on brain and other tissues	
Galactic Cosmic Radiation (GCR) consists of heavy ions traveling through space at high energy. Animal studies at high-dose rate (about a minute) indicate a decrease in cognitive abilities and even development of Alzheimer's disease.	There are no human analogues or circumstances similar to GCR exposures in space. MPS workers at DOE facilities comes close: intakes of radionuclides, e.g. plutonium, continually exposed brain tissue to alpha particles (Helium nuclei) for life. Human brain tissue exposed to low-dose-rate high-LET radiation is being evaluated with large numbers and long follow-up. All organs can be similarly evaluated.
Dementia, Alzheimer's other CNS	
Modified mouse strains indicate an early-onset of Alzheimer's disease after heavy ion exposures.	The MPS will evaluate deaths from dementia, Alzheimer's, Parkinson's and other motor neuron diseases following brain exposure to alpha particles from plutonium, polonium, radium, uranium, and americium.
Cognition	
Animal studies of high-dose rate exposures to energetic heavy ions (GCRs) find a decrease in measures of cognitive function. The concern is whether a similar decline might affect astronauts to such an extent that the mission would be in jeopardy.	Thousands of workers with alpha particle exposures to brain tissue could be evaluated for the occurrence of dementia and cognitive impairment, including neuropsychological test scores, via Medicare records. Further, though challenging, large numbers of workers could be asked to take cognition tests similar to those taken by astronauts.
Ischemic heart disease (IHD)	
It is uncertain whether low doses (<500 mGy) cause ISH and whether cumulative exposures to chronic low-dose low-LET or high-LET galactic cosmic rays should be considered a detriment of space travel.	The MPS has substantial statistical power to evaluate the risk of ischemic heart disease (IHD) related to radiation doses below 300–500 mGy.
Uncommon cancer sites	
Uncommon or infrequent cancer sites within the Japanese LSS cannot be evaluated because of small numbers.	The MPS is so large, that all cancer sites (by sex) can be evaluated and incorporated explicitly into lifetime risk projection models.

and more. Because there is uncertainty with regard to the radiation risk from space radiation as well as the uncertainties of converting an acute radiation risk from a 1945 Japanese population to an American cohort of astronauts, NASA sets their limitation guidance based on the 95% upper confidence (or credibility) level about the permissible career exposure limit of a 3% lifetime Risk of Exposure-Induced Death (REID) (NCRP 2014; NASA 2015). The MPS will reduce the statistical uncertainty in the risk estimates being used for lifetime cancer risk projections; will provide relevant estimates of risk based on chronic prolonged exposures which eliminate the need for making adjustments based on dose rate considerations (Shore et al. 2017); will alleviate the need to adjust for differences in underlying background cancer rates between an Asian population and a western population, thus removing this contribution to uncertainty; and will provide sex-specific radiation-risk estimates for uncommon and infrequent cancer sites not possible within the Japanese LSS because of small numbers. Reducing these measures of uncertainty, would reduce the 95% confidence (credibility) level and thus allow more time in space given current radiation protection approaches, all things being equal. That is, that the risk levels from the MPS turn out to be the same or less than those of the atomic bomb survivors which appears to be the case for radiation-induced lung cancer (Boice et al. 2019b).

Better estimates of sex-specific radiation risk for lung and other cancers

> If you don't know where you're going, you might not get there
> – Yogi Berra

Lung cancer is the largest potential cancer risk from space travel (Shay et al. 2011). This risk is not entirely from gamma radiation, but from high-energy protons from solar flares (which occur 5 to 10 times per year) and from GCR (the HZE particles such as Fe). It is unclear whether sex-specific lung cancer risks differ appreciably between women and men. Based on the Japanese LSS data (Ozasa et al. 2012; NCRP 2014; Cahoon et al. 2017), women are about 2–3 times more sensitive to radiation than men, due in part to the differences in the sensitivity of the sex organs, i.e. cancers of the female breast and ovaries are increased after radiation exposure, whereas cancers of the testis and prostate are not. But the major difference is due to a 2–3 times greater risk of lung cancer among women than men. This difference limits the time female astronauts can spend in space as well as their potential departure on long-term missions such as to Mars (Table 1). The Japanese data, however, are based on relatively small numbers, only about 32,000 adult women and about 21,000 adult men. The MPS has 250,000 adult females under study so that precise comparisons with the 750,000 adult males in the study will be possible (Boice et al. 2019b).

In addition to the ongoing comparisons between male and female risks for lung cancer in the ongoing studies mentioned (Boice et al. 2019b), the definitive comparison will be with the ongoing study of 170,000 medical radiation workers of which 65,000 are men and 65,000 are women. The dose distribution is broad and organ doses are being comprehensively being determined (Yoder et al. 2018). These data may influence the current models used by NASA to project lifetime estimates of cancer risk and thus modify the amount of time that astronauts are allowed in space taking into account the most accurate and relevant estimates of sex-specific risks. Further, several of the studies will provide information on high-LET exposures to the lung and other organs from the intake of radionuclides for men and women which also should contribute to the understanding of any sex-specific differences.

A new study will be of 21,000 female workers who worked from 1943 to 1947 at the Tennessee Eastman Corporation in Oak Ridge, TN. These women had never been studied and are mentioned in the novel *The Girls of the Atomic City* (Kiernan 2013). They worked in the facility that eventually became known as Y-12 and many operated the 1052 calutrons, i.e. mass spectrometers that used electromagnetic fields to separate uranium-235 from natural uranium for the World War II effort (specifically for the 'Little Boy' weapon dropped on Hiroshima).

Risk estimates following chronic exposure to brain tissue from high-LET radiation

> It's not going to do any good to land on Mars if we're stupid – Ray Bradbury

High-LET particles in space pose a great mystery since it is unknown what human health effects might result from these exotic high energy and high atomic number (Z) ions (HZE particles). The challenging questions concern their biological effectiveness to cause cancer, non-cancers, and cognitive impairment and behavior changes. Rodent experimental models have raised these important issues but are not entirely satisfactory. The MPS attempts to address some of these issues in studies of humans with brain exposure to helium nuclei (alpha particles) as another line of evidence supporting or not some of the experimental results.

The radiation exposures in space are reasonably well-characterized but are extremely complex and vary over time (Cucinotta et al. 2013; NA/NRC 2012; Zeitlin et al. 2013; Borak et al. 2014; Norbury et al. 2016; Simonsen and Zeitlin 2017; NCRP 2018a). The flux of galactic cosmic rays (GCRs) 'consists of about 85% protons… and about 14% helium ions. The remainder of the flux consists of heavier ions referred to as "HZE particles" [high (H) atomic number (Z) and high energy (E)]' (Zeitlin et al. 2013). Further, the absorbed dose depends not only on the changing space radiation environment, but also on mission time, shielding characteristics of the space capsule and of structures on Mars, and any radionuclide power sources brought on board. Depending on the assumptions made regarding exposure scenarios for a 30 month roundtrip journey to Mars, including a 6 month stay on the surface, the absorbed dose from all sources of exposure might range from 250 to 400 mGy or about 1–1.2 Sv (NASA 'effective dose' or 'dose equivalent') (NA/NRC 2012; Cucinotta et al. 2013; Zeitlin et al. 2013; Norbury et al. 2016).

The exposure scenarios and assumptions made include: solar particle events (SPEs)—mainly high-energy protons ($Z = 1$, 130–180 mGy); GCRs: He ($Z = 2$, 45–70 mGy); $Z =$ 3–9 particles (20–40 mGy); $Z > 10$ particles (30–40 mGy), and neutrons and other particles (20–30 mGy); the thickness of the space capsule; secondary radiation, e.g. neutrons and pions, from proton and GCR fragments after impacts with the space capsule; shielding characteristics of structures on the surface of Mars; any nuclear isotope power sources transported with the astronauts; and the 'quality factors' selected for the menagerie of space radiations (the fluence of low and high Z particles from atomic numbers 1–28 and their energy spectra) to multiply times the absorbed does to obtain a dose equivalent measure in mSv [i.e. a NASA defined 'effective dose' that applies weighting factors that are not the ICRP tissue weighting factors (ICRP 2007)], and the extent of solar activities during the 30 month journey and sojourn (Cucinotta et al. 2013; Zeitlin et al. 2013; NASA 2015). The experimental simulations of the radiation environments in outer space and on Mars is to say the least exceedingly challenging (Norbury et al. 2016).

The MPS can provide evidence of high-LET health effects associated with continuous, low-dose-rate exposures to human brains following intakes of alpha-particle-emitting radionuclides. Ingested or inhaled intakes of radionuclides that decay by emitting alpha particles can deposit in the brain and expose brain tissue for many years (Leggett et al. 2018a; Boice et al. 2018b). Such exposure is more uniform across brain tissue and differs from alpha particle exposure that might occur from bone-seeking radionuclides that deposit in the cranium. Currently, an NCRP committee with colleagues at the Oak Ridge National Laboratory are developing biokinetic models for estimating brain dose directly following the intake of radionuclides and not by using the current indirect approach that considers dose to all soft tissue and apportions the dose to brain based on weight or other considerations (Leggett et al. 2018a).

Postmortem radiochemical analyses of tissues have shown that intakes of radium deposit in the brain and result in alpha particle exposure to brain tissue (Schlenker et al. 1982). Similarly, radiochemical analyses have detected brain depositions for radionuclides such as plutonium (James et al. 2003, 2007), americium (McInroy et al. 1985, 1991), uranium (Avtandilashvili et al. 2015; Kathren and Tolmachev 2015), and polonium (Nathwani et al. 2016). Thorium has been detected in brain tissue of a patient injected with Thorotrast, a colloidal radiographic contrast medium containing thorium dioxide (McInroy et al. 1992). The generosity of radiation workers and patients made this remarkable research possible by donating their bodies for scientific research to the United States Transuranium and Uranium Registries (USTUR) (Filipy and Russell 2003; Tolmachev et al. 2011; Tolmachev and McComish 2016; USTUR 2018). In addition to postmortem radiochemical analysis of tissues, location of radionuclide deposition within the brain is to be examined by synchrotron-based X-ray fluorescent microscopy using the Advanced Photon Source at Argonne National Laboratory (Paunesku et al. 2012; Chen et al. 2015).

Limitations to these evaluations include the different dose distributions within the brain and the energy depositions from alpha particle emitters compared with that of high-energy particles and heavy ions (HZE particles) experienced in space (Cucinotta et al. 2013; Zeitlin et al. 2013; Norbury et al. 2016; Boice 2017b). Nonetheless, there is no other human analog/circumstance that provides information on possible health risks from high-LET radiation to brain tissue, recognizing the limitations (Boice et al. 2018a). The mouse models provide valuable insights into effects of space radiation on the brain, but they too have sizeable uncertainties. The mouse, for one, has considerable limitations as a laboratory model for the human brain. Further, the dose delivery in experimental studies is brief and of the order of minutes to possibly weeks compared with the years it will take for a mission to Mars. In addition, while the space environment is relatively well-characterized as described above, the experimental simulations of space radiations are far from perfect, i.e. per above, ideally the rodent should be exposed to high energy low-LET protons, high energy alpha particles, a menagerie of HZE particles (from atomic number 3–28), neutrons, pions, other fragmented particles from shielding GCR shielding impacts, and so on. It's an impossible task, so a wide-range of brilliant experiments with, hopefully, equally brilliant assumptions, are brought to bear to provide optimum answers to health effects in mice that are relevant to health effects in women and men (Cucinotta et al. 2013; Norbury et al. 2016).

The current research within the MPS (Table 1) will add to the collection of evidence, albeit with large uncertainties, that are needed to inform radiation protection guidance against the possible health effects of galactic cosmic radiation on brain function (NCRP 2016).

High-level cognitive performance is critically important during space missions, which can involve environmental, physiological and psychological stressors (Basner et al. 2015; Moore et al. 2017). Radiation exposure to GCRs is a possible stressor that may affect brain function (Cucinotta et al. 2014; NCRP 2016). Interestingly, a recent experimental study hints at possible sex-based differences in cosmic ray-induced cognitive decline (Krukowski et al. 2018; Wenz 2018). NASA has supported the development of tests that assess multiple domains of neurocognitive functions: Cognition Test Battery and WinSCAT (Moore et al. 2017) which have been administered to astronauts. Investigators within the MPS are considering the value of evaluating cognition among workers who have had continuous brain tissue exposure to alpha particles for up to 40 years after the intake of plutonium or other radionuclides. Some workers today come back to national laboratories voluntarily and provide urine samples, suggesting a willingness to participate in health research. Over 1000 workers could be identified with known radiation doses to brain who might be contacted and asked to complete a modified cognitive test/s similar to ones taken by astronauts on the International Space Station or elsewhere. A cognition test could be administered at home over the internet and take <30 min. In addition, for workers who had reached the age of 65 years in or after 1996, Medicare and other nursing home records might be searched for any diagnoses of cognitive decline, dementia, Alzheimer's disease or other motor neuron conditions as well as for any quantitative scores from neuropsychological testing (Rector et al. 2004; CMS 2018a, 2018b). Then the diagnoses (and/or cognitive scores) could be correlated with estimated alpha-particle dose to brain tissue, providing another line of evidence for the possibility that high-LET radiation might lead to cognitive and behavioral changes (Table 1).

Risk estimates for ischemic heart disease for prolonged exposures

Love hurts, love scars, love wounds, and mars – Roy Orbison

There appears to be little convincing or consistent evidence that low doses of ionizing radiation below about 0.5 Gy cause cardiovascular disease, particularly ischemic heart disease (NCRP 2018b; Shore et al. 2019). Nonetheless, there is concern whether cumulative exposures to chronic low-dose radiation and to high-LET galactic cosmic rays might be a detriment of space travel (Cucinotta et al. 2015; NASA 2015). The MPS has substantial statistical power to evaluate any risk of ischemic heart disease (IHD) related to radiation doses below 300–500 mGy. Further, radionuclides intakes among DOE workers also contribute to dose to all soft tissue, including the heart, and can be evaluated. Ongoing evaluations, including dose reconstructions, would contribute to understanding the possibility of IHD risks following low-LET radiation and high-LET radiation to heart tissue. Thus far, MPS studies have examined the risk of IHD following exposures to nuclear weapons test participants (Boice 2017b), nuclear power plant workers (NCRP 2018b; Golden et al. 2018), industrial radiographers (NCRP 2018b) and workers at the Mound (Boice et al. 2014), Rocketdyne (Boice et al. 2011), and Mallinckrodt (Golden et al. 2019) facilities. Combining these and ongoing studies, and refining the radiation dose estimates to heart tissue, will make a substantial contribution to knowledge on the possible risk of IHD following prolonged exposures to ionizing radiation accumulating to relatively high levels (Table 1).

Summary

The future belongs to those who believe in the beauty of their dreams – Eleanor Roosevelt

The Million Person Study will address scientific and public health issues on radiation health effects. Important research gaps will be filled to benefit scientific understanding, regulatory agencies, radiation protection organizations, and society (GAO 2017; Boice et al. 2019a). The scientific information will benefit decision makers and policy setters whose responsibility is to provide protection guidance. NASA has the challenging mission of going beyond Earth orbit and potentially to Mars. Informed judgments have to be made today amid a recognized sea of uncertainties (Cucinotta et al. 2013, 2015b; Scoles 2017; Chancellor et al. 2018). Radiation is a limiting factor for long-term missions so that as much knowledge as can be obtained now will provide guidance for the protection of flight crews (Shay et al. 2011; NASA 2015). Ways to reduce the level of uncertainties are a hallmark of the MPS. The MPS of healthy men and women exposed to radiation over years are more representative of astronauts and their exposure circumstances than is the Japanese atomic bomb survivor study of acute exposures in 1945. The large size of the MPS will provide more precise estimates of lifetime cancer risk that would reduce statistical variation and thus allow more time in space, all things being equal. Differences in sex-specific lung cancer risks from chronic radiation exposures is being evaluated that would affect female astronauts and their time in space. Whether high-LET radiation to the brain affects the late development of Alzheimer's disease is being evaluated; ways to evaluate cognition, behavior and cognitive impairment are being developed. As the United States continues to have unbounded vision and imagination to travel to other planets, it is critical that the best science available be used in the judgments to be made today on the protection of space travelers. If we can perceive it, we can achieve it. But the achievement can be based only on a strong scientific foundation (Table 1).

It's kind of fun to do the impossible – Walt Disney

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