Evidence Report:

Risk of Cardiovascular Disease and Other Degenerative Tissue Effects from Radiation Exposure

**Human Research Program
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I. RISK OF CARDIOVASCULAR DISEASE AND OTHER DEGENERATIVE TISSUE EFFECTS FROM RADIATION EXPOSURE

Degenerative tissue (non-cancer or non-central nervous system [CNS]) effects, such as cardiovascular disease, cataracts, and digestive and respiratory diseases, are documented following exposures to terrestrial sources of ionizing radiation (e.g., gamma rays and x-rays). In particular, cardiovascular pathologies such as atherosclerosis are of major concern following gamma ray exposure. This provides evidence for possible degenerative tissue effects following exposures to ionizing radiation in the form of galactic cosmic rays (GCR) or solar particle events (SPEs) expected during long-duration spaceflight. However, the existence of low dose thresholds and dose-rate and radiation quality effects, as well as mechanisms and major risk pathways, are not well-characterized. Degenerative disease risks are difficult to assess because multiple factors, including radiation, are believed to play a role in the etiology of the diseases. Data specific to the space radiation environment must be compiled to quantify the magnitude of this risk to decrease the uncertainty in current permissible exposure limits (PELs) and to determine if additional protection strategies are required.

II. EXECUTIVE SUMMARY

Occupational radiation exposure from the space environment may result in non-cancer or non-CNS degenerative tissue diseases, such as cardiovascular disease, cataracts, and respiratory or digestive diseases. However, the magnitude of influence and mechanisms of action of radiation leading to these diseases are not well characterized. Radiation and synergistic effects of radiation cause DNA damage, persistent oxidative stress, chronic inflammation, and accelerated tissue aging and degeneration, which may lead to acute or chronic disease of susceptible organ tissues. In particular, cardiovascular pathologies such as atherosclerosis are of major concern following gamma-ray exposure. This provides evidence for possible degenerative tissue effects following exposures to ionizing radiation in the form of the GCR or SPEs expected during long-duration spaceflight. However, the existence of low dose thresholds and dose-rate and radiation quality effects, as well as mechanisms and major risk pathways, are not well-characterized. Degenerative disease risks are difficult to assess because multiple factors, including radiation, are believed to play a role in the etiology of the diseases. As additional evidence is pointing to lower, space-relevant thresholds for these degenerative effects, particularly for cardiovascular disease, additional research with cell and animal studies is required to quantify the magnitude of this risk, understand mechanisms, and determine if additional protection strategies are required.

The NASA PELs for cataract and cardiovascular risks are based on existing human epidemiology data. Although animal and clinical astronaut data show a significant increase in cataracts following exposure and a reassessment of atomic bomb (A-bomb) data suggests an increase in cardiovascular disease from radiation exposure, additional research is required to fully understand and quantify these adverse outcomes at lower doses (<0.5 Gy) to facilitate risk prediction. This risk has considerable uncertainty associated with it, and no acceptable model

for projecting degenerative tissue risk is currently available. In particular, risk factors such as obesity, alcohol, and tobacco use can act as confounding factors that contribute to the large uncertainties. The PELs could be violated under certain scenarios, including following a large SPE or long-term GCR exposure. Specifically, for a Mars mission, the accumulated dose is sufficiently high that epidemiology data and preliminary risk estimates suggest a significant risk for cardiovascular disease.

Ongoing research in this area is intended to provide the evidence base for accurate risk quantification to determine criticality for extended duration missions. Data specific to the space radiation environment must be compiled to quantify the magnitude of this risk to decrease the uncertainty in current PELs and to determine if additional protection strategies are required. New research results could lead to estimates of cumulative radiation risk from CNS and degenerative tissue diseases that, when combined with the cancer risk, may have major negative impacts on mission design, costs, schedule, and crew selection. The current report amends an earlier report (*Human Research Program Requirements Document*, HRP-47052, Rev. C, dated Jan 2009) in order to provide an update of evidence since 2009.

III.   INTRODUCTION

The environment outside of the shield-like atmosphere and magnetosphere of the Earth contains several types of radiation. Most of the particles in interplanetary space are derived from the solar wind, which produces a constant flux of low-energy particles. However, dangerous and intermittent solar particle events (SPEs) can produce large quantities of highly energetic protons and heavy ions. Galactic cosmic rays (GCR) represent an additional particle constituent of space radiation and emanate from outside our solar system. GCR is comprised of mostly highly energetic protons with a small component of high-Z, high-energy (HZE) nuclei. Researchers have predicted that an astronaut will receive a total body exposure of approximately 300-450 mGy, or 1 to 1.3 Sv, for a 3-year mission to Mars, and these numbers will increase in the event of a SPE (Guo et al. 2015; Kohler et al. 2014).

Exposure to ionizing radiation affects cells and tissues either by directly damaging cellular components or by producing highly reactive free radicals from water and other constituents of cells. Both of these mechanisms can produce sufficient damage to cause cell death, deoxyribonucleic acid (DNA) mutation, or abnormal cell function (Li et al. 2014). The extent of damage is generally believed to depend on the dose and the type of particle and to follow a linear response to radiation dose for initial induction of damage for high and moderate radiation doses, but it is extremely difficult to measure for lower doses where the shape of the dose response curve is less well-defined and may be affected by non-targeted effects that are difficult to distinguish from normal cellular oxidative stress (Li et al. 2014).

Because HZE nuclei are the components of space radiation that have the highest biological effectiveness, they are a large concern for astronaut safety. HZE nuclei produce highly ionizing tracks as they pass through matter. In addition, they leave columns of damage at the molecular level when they traverse a biological system – damage that is different in severity and complexity from the damage that is left by low-linear energy transfer (LET) radiation sources such as gamma- and X-rays (Durante and Cucinotta 2008). HZE nuclei impart damage

through the primary energetic particle and secondary delta-ray electrons as well as from fragmentation events that produce a spectrum of other energetic nuclei, protons, neutrons, and heavy fragments (Wilson et al. 1995). Therefore, a large penumbra of energy deposition extends outward from the primary particle track. The lack of epidemiological data and sparse radiobiological data on the effects of these HZE nuclei leads to a high level of uncertainty in risk estimates for long-term health effects after exposure to GCR and SPEs.

NASA has funded several previous reports from the National Academy of Sciences (NAS) and the National Council on Radiation Protection and Measurements (NCRP) that provided evidence for the radiation risks in space. The NCRP is chartered by the U.S. Congress to guide federal agencies such as NASA on the risk from radiation exposures to their workers. Reports from the NCRP and the National Research Council (NRC) on space radiation risks are the foundation for how NASA views the wide scientific body of evidence that is used for its research and operational radiation protection methods and plans. Recent reports of particular relevance to this Evidence Report include NCRP 2000, NCRP 2006, NAS/NRC 2008, NCRP 2010, and NCRP 2014. The International Commission on Radiological Protection (ICRP) has also released guidance and reviews, with ICRP 2007 and 2012 being of particular importance. Additionally, the UK Health Protection Agency recently reviewed the subject of radiation-induced circulatory risk (Health Protection Agency 2010).

A.   Description of Degenerative Risks of Concern to NASA

The effects of protracted exposure to low dose rates (< 20 mGy/h) of protons, HZE particles, and neutrons of the relevant energies for doses up to ≈ 0.5 to 1 Gy (corresponding to exposures estimated for design reference missions in deep space) on degenerative conditions of the circulatory and other organ systems are of concern. Current Mars design reference mission exposure estimates vary between 0.25 and 0.5 Gy from GCR, with shielded SPE exposures on the order of 0.15 to 0.5 Gy to internal body organs within a typically shielded spacecraft. Approximate relative dose (Gy) contributions to total organ exposure from GCR include protons delivering ~50-60% of the dose, alphas delivering approximately 10-20%, heavies of 3<Z<9 contributing ~5-10%, heavies of Z > 10 contributing ~5-10%, and secondary radiation (e.g., neutrons, pions, and muons) contributing on the order of 10% of the total dose. The major degenerative conditions of concern that could potentially result from space radiation exposure are as follows:

- Degenerative changes in the circulatory system, including cardiovascular diseases (ischemic heart disease (IHD), atherosclerosis), cardiomyopathy, and cerebrovascular and peripheral arterial diseases, leading to stroke
- Cataract formation
- Other diseases related to accelerated aging effects, including premature senescence and fibrosis
- Immune and endocrine system dysfunction
- Other possible degenerative diseases of concern may include respiratory or digestive diseases; however, a clear base of evidence has yet to be established for space-relevant exposures.

Note that risks to the central nervous system (CNS) may also involve degenerative conditions, but they are treated as a stand-alone risk category by NASA and are described in the Evidence Report titled "Risk of Acute and Late Central Nervous System Effects from Radiation Exposure" found at http://humanresearchroadmap.nasa.gov/Evidence/reports/CNS.pdf (Nelson et al. 2015).

B.   Current NASA Permissible Exposure Limits

Permissible exposure limits (PELs) for short-term and career exposures to space radiation have been approved by the NASA Chief Health and Medical Officer, who also sets the requirements and standards for mission design and crew selection. Tables 1 and 2, which are taken directly from NASA-STD-3001, Volume 1, rev. A (NASA 2014), list the current short- and long-term PELs for non-cancer effects (Table 1; in mGy-Equivalents or mGy) and relevant relative biological effectiveness (RBE) values (Table 2). The lifetime limits for cataracts and heart disease are imposed to limit or prevent risks of degenerative tissue diseases. The current PELs are based on recommendations from NCRP 2000, which defines a threshold as an exposure below which clinically significant effects do not occur. However, the ICRP recently redefined their notion of a threshold dose as the dose required to cause a 1% incidence of an observable effect (ICRP 2007 and 2012). In particular, ICRP 2012 included newer evidence and noted a lower threshold for both cataractogenesis and cardiovascular effects from ground-based radiation exposure, with the previous threshold of 2 Gy lowered down to 0.5 Gy. NCRP's latest update to their PEL recommendations in commentary 23 (NCRP 2014) states: "A research program that provides additional scientific and technical data may lead to the need for further definition of acceptable levels of radiation risk, for example to take into account additional health effects and the difference in mission scenarios, resulting in more restrictive mission limits. At this time, NCRP does not recommend any specific radiation protection limit for exploratory missions." Because NASA has established short-term dose limits to prevent clinically significant deterministic health effects, including performance degradation in flight, these dose limits and accumulated evidence will be reviewed by NCRP in the next five years to establish whether there are sharp thresholds or there may still be some risk at lower doses. This deterministic approach, which uses an estimate of threshold doses for cardiovascular and cataract risk, is quite distinct from that for cancer risk limits, in which a probabilistic assessment of the risk is made using a projection model. Given the trend of increasingly lower threshold doses, it is likely that a similar stochastic approach will be needed in the future for degenerative risks.

Table 1. **Dose Limits for Short-Term or Career Non-Cancer Effects (in mGy-Eq. or mGy)** (NASA STD 3001 Rev A).
Note: RBEs for specific risks are distinct as described below.

Organ	30-day limit	1-year limit	Career
Lens*	1,000 mGy-Eq	2,000 mGy-Eq	4,000 mGy-Eq
Skin	1,500 mGy-Eq	3,000 mGy-Eq	6,000 mGy-Eq

BFO	250 mGy-Eq	500 mGy-Eq	Not applicable
Heart**	250 mGy-Eq	500 mGy-Eq	1,000 mGy-Eq
CNS***	500 mGy	1,000 mGy	1,500 mGy
CNS*** (Z ≥ 10)	–	100 mGy	250 mGy

*Lens limits are intended to prevent early (<5 yr) severe cataracts, e.g., from a solar particle event. An additional cataract risk exists at lower doses from cosmic rays for sub-clinical cataracts, which may progress to severe types after a long latency (>5 yr) and are not preventable by existing mitigation measures; however, they are deemed an acceptable risk to the program.
**Circulatory system doses calculated as the average over heart muscle and adjacent arteries.
***CNS limits should be calculated at the hippocampus.

Table 2—RBE for Non-Cancer Effects[a] of the Lens, Skin, BFO, and Circulatory Systems (NCRP 2000).

Radiation Type	Recommended RBE[b]	Range
1 to 5 MeV neutrons	6.0	(4-8)
5 to 50 MeV neutrons	3.5	(2-5)
Heavy ions	2.5[c]	(1-4)
Proton > 2 MeV	1.5	-

[a] RBE values for late deterministic effects are higher than those for early effects in some tissues and are influenced by the doses used to determine the RBE.
[b] There are insufficient data on which to base RBE values for early or late effects by neutrons of energies <1 MeV or greater than about 25 MeV.
[c] There are few data on the tissue effects of ions with a Z>18, but the RBE values for iron ions (Z=26) are comparable to those for argon (Z=18). One possible exception is cataract of the lens of the eye because high RBE values for cataracts in mice have been reported.

IV.   EVIDENCE

A. Ground-based Evidence

1. Cataracts

1a. Cataract studies with low-LET radiation

The development of ocular cataracts, which is a degenerative opacification of the crystalline lens, is a well-recognized late effect of exposure to ionizing radiation. Comprehensive reviews of the evidence for radiation-induced cataracts include NCRP 2006 and 2014, as well as ICRP 2012. The first reports of radiation-induced cataracts appeared early in the 20th century, shortly after the first X-ray machines were developed (Rollins 1903). It is now clear that radiation-induced cataracts exhibit relationships between radiation dose and disease severity, as well as between dose and latency. Evidence for this link comes, most notably, from survivors of radiotherapy who received high doses (>5 Gy) of ionizing radiation using X rays, gamma-rays, and proton beams for ocular tumors (Ferrufino-Ponce and Henderson 2006; Blakely et al. 1994; Gragoudas et al. 1995) and from individuals who received whole-body therapeutic radiation (Belkacemi et al. 1996; Dunn et al. 1993; Frisk et al. 2000).

Evidence of radiation exposure leading to cataract formation (moderate- to low-dose gamma-ray exposures) comes from epidemiological data from A-bomb survivors followed in the Life Span Study (LSS) conducted by the Radiation Effects Research Foundation (RERF). This is a longitudinal study of Japanese survivors of the bombings of both Hiroshima and Nagasaki, which remains one of the most valuable and informative epidemiological studies for evaluating long-term health effects of radiation exposure (Preston et al. 2003).

Among the A-bomb survivors, the frequency and severity of cataracts are dose-dependent. Severity refers to the size and loss of visual acuity due to the cataract or the presence of conditions requiring lens implants to prevent blindness. Symptoms appeared as soon as several months after exposure for severe cases and several years after exposure for less-severe cases. The frequency of cataracts was related to the proximity of the subject to the hypocenter of the atomic bomb. A possible threshold dose was originally estimated to be in the range of 0.6 to 1.5 Gy (Junk et al. 1998; Otake and Schull 1982 and 1991), but a non-threshold dose model has been proposed in more recent reports (Neriishi et al. 2007). In a prospective study that followed the development of radiation-induced cataracts in workers who were exposed to radiation during the efforts to clean up after the Chernobyl nuclear power plant disaster, it was found that posterior subcapsular or cortical cataracts were present in 25% of the examined individuals. The investigators estimated that the dose effect threshold for cataract formation following radiation exposure is less than 1 Gy (Worgul et al. 2007).

As noted by Blakely et al. (2007a and 2010), published data on radiation-induced human cataracts are limited in predicting the risk from chronic exposure to low doses of protons or low fluences of heavy ions, such as those encountered in space, because of the possible qualitative differences in effects. However, studies on proton exposures in cancer patients suggest an RBE near one for protons except near the Bragg peak, where the LET is significantly higher (ICRP 2012). Studies of cataracts in astronauts provide important insights as described below (Cucinotta et al. 2001; Jones et al. 2007; Chylack et al. 2009 and 2011).

1b. Cataract Studies with Protons, Neutrons, and HZE Nuclei

Although the largest body of information on radiation-induced cataractogenesis comes from studies using low-LET radiation sources, substantial data also describe the induction of cataracts in a variety of animal species by different types of particle radiation sources that are similar to those that are encountered in space, including protons and high-LET particle radiation. The U.S. Air Force (USAF)/NASA Proton Bioeffects Project was an effort to identify delayed or late effects of X rays, electrons, and protons of differing energies on the long-term health of a colony of Rhesus monkeys. A subpopulation of the primates that were studied in the USAF/NASA project was monitored for about 30 years for late effects, including cancer, cataracts, and shortening of life. Analyses of these primates for signs of cataractogenesis began 20 years after exposure, and significant opacifications of the eye lens were seen in these monkeys 20 to 24 years after exposure to 55-MeV protons at 1.25 Gy and higher levels. The results that were obtained from these experiments suggest that the dose-response relationship for induction of cataracts by protons is similar to that seen with low-LET radiation (Lett et al. 1991; Cox et al. 1992). These findings are supported by other studies on cataract formation in animal models using high-energy proton beams (Niemer-Tucker et al. 1999; Fedorenko 1995). In many studies of heavy ions, cataractogenesis that was induced by individual high-LET

components of the space radiation spectrum was analyzed. The conclusions derived from these studies are that a trend exists for a decrease in the latency between exposure and the appearance of cataract lesions and that this decrease in latency occurs at lower dose thresholds for heavy ions compared to low-LET x-rays and protons. Table 3 lists representative studies for different heavy ion species. Studies in animals showed an age-dependent sensitivity, with the younger animals exhibiting a lower dose threshold for cataract induction than the older animals (Cox et al. 1992).

Table 3. References for Cataractogenesis Studies Conducted with High-LET Radiation

High-LET Component	Selected References
Neutrons	Ainsworth 1986; Riley et al. 1991; Worgul et al. 1996; Christenberry et al. 1956
Argon	Merriam et al. 1984; Lett et al. 1980; Worgul 1986; Abrosimova et al. 2000; Jose and Ainsworth 1983
Neon	Lett et al. 1980; Abrosimova et al. 2000; Jose and Ainsworth 1983
Iron	Brenner et al. 1993; Lett et al. 1991; Medvedovsky et al. 1994; Riley et al. 1991; Tao et al. 1994; Worgul 1986; Worgul 1993; Davis et al. 2010
Protons	Niemer-Tucker et al. 1999; Fedorenko 1985; Lett et al. 1991; Cox et al. 1992

2.   Cardiovascular Diseases

2a. Epidemiologic Studies

The association between high doses of radiation exposure and cardiovascular damage is well established. Patients who have undergone radiotherapy for primary cancers of the head and neck and mediastinal regions have shown an increased risk of heart and vascular damage and long-term development of radiation-induced heart disease. These data are well-detailed in several reports (NCRP 2006 and 2014; ICRP 2012; Health Protection Agency 2010).

Like the evidence described for cataractogenesis, the major driving evidence that proves a link between ionizing radiation exposure and the development of degenerative heart and vasculature changes comes from prospective studies that follow the long-term, radiotherapy-related effects in cancer survivors. These patients received relatively high therapeutic doses (~5–50 Gy) of low-LET thoracic radiation in the course of therapy for cancers of the head, neck, and mediastinal regions, such as Hodgkin's lymphoma and breast cancer (Prosnitz et al. 2005; Darby et al. 2005; Carver et al. 2007; Swerdlow et al. 2007; Mulrooney 2009; Darby et al. 2013). There is a dose-dependent increase in the development of a wide variety of cardiovascular diseases, including acute and chronic pericarditis, coronary artery disease, cardiomyopathy, valvular disease, and conduction abnormalities, in these individuals. The study of Darby et al. (2013) reported the relationship of the risk of ischemic heart disease after breast cancer radiotherapy to radiation dose to the heart and to other cardiac risk factors. Figure 1 shows the

linear dose-dependent relationship between exposure and excess relative risk (ERR) based on their findings, with the risk increasing 7.4% for every gray of exposure at these high doses.
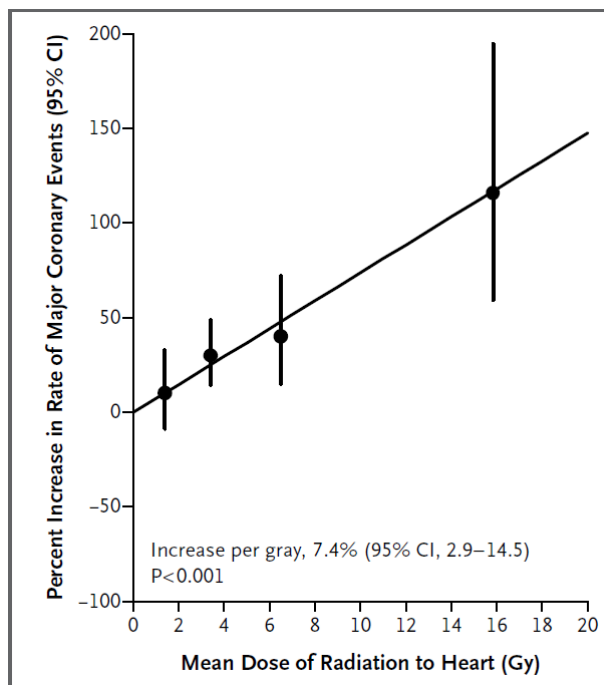

Figure 1 - Rate of Major Coronary Events According to the Mean Radiation Dose to the Heart Compared with the Estimated Rate with No Radiation Exposure to the Heart (Darby et al. 2013).

Within 5 years after radiotherapy, the frequency of major coronary events starts to increase in a linear manner with no apparent threshold and continues for at least 20 years after radiation exposure. Women with cardiac risk factors at the time of radiotherapy have greater absolute increases in risk from radiotherapy than those without (Darby et al. 2013). These high doses (>5 Gy exposures) are associated with damage to the structures of the heart and to the coronary, carotid, and other large arteries, including marked diffuse fibrotic damage, especially of the pericardium and myocardium, pericardial adhesions, microvascular damage, and stenosis of the valves (Little 2013). Mechanisms of damage involve cell killing or inactivation of large numbers of cells which cause functional impairment.

At moderate doses of radiation exposure, between 0.5 and 5 Gy, other evidence that supports a link between the occurrence of cardiovascular disease and radiation exposure is derived from prospective studies of A-bomb survivors who received moderate doses of radiation (0–2 Gy), as well as from occupationally exposed workers who received continuous low-dose exposure (Shimizu et al. 2010; McGale and Darby 2008; Darby et al. 2005; Yamada et al. 2004; Preston et al. 2003; Hayashi et al. 2003). In A-bomb survivors who are enrolled in the Life Span Study (LSS), the development of health effects has been extensively studied through continuous longitudinal health assessments. The average doses that were received by the A-bomb survivors (Preston et al. 2003) are similar to the effective doses for an International Space Station (ISS) mission (50-100 mSv for 6-month stays) and somewhat lower than the

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effective dose that is expected for a Mars mission (1 to 1.3 Sv). A significant dose-response relationship exists for hypertension, stroke, and heart attack in survivors who were exposed at less than 40 years of age; their ERR is estimated to be 14% per Sv. However, the existence of a threshold dose cannot be excluded for risks that are associated with doses that are less than 0.25 Sv (Table 4). At these moderate doses, mechanisms of action are thought to involve atherosclerosis, potentially through inflammation, oxidative stress, endothelial dysfunction, and cellular senescence (Health Protection Agency 2010).

Table 4. Estimates of Excess Relative Risk per Sievert for Non-cancer deaths from the Life Span Study of the Atomic Bomb Survivors (Preston et al. 2003).

Cause	ERR per Sv	Deaths[a]	Estimated number of radiation-associated deaths
All non-cancer diseases (0–139, 240–279, 290–799)	0.14 (0.08; 0.2)[b]	14,459	273 (176; 375)[b]
Heart disease (390–429)	0.17 (0.08; 0.26)	4,477	101 (47; 161)
Stroke (430–438)	0.12 (0.02; 0.22)	3,954	64 (14; 118)
Respiratory disease (640–519)	0.18 (0.06; 0.32)	2,266	57 (19; 98)
Pneumonia (480–487)	0.16 (0.00; 0.32)	1,528	33 (4; 67)
Digestive disease (520–579)	0.15 (0.00; 0.32)	1,292	27 (0; 58)
Cirrhosis (571)	0.19 (–0.05; 0.5)	567	16 (–2; 37)
Infectious disease (000–139)	–0.02 (< –0.2; 0.25)	397	–1 (–14; 15)
Tuberculosis (010–018)	–0.01 (< –0.2; 0.4)	237	–0.5 (–2; 13)
Other diseases[c] (240–279; 319–389; 580–799)	0.08 (–0.04; 0.23)	2,073	24 (–12; 64)
Urinary diseases (589–629)	0.25 (–0.01; 0.6)	515	17 (–1; 39)

[a]Deaths among survivors between 1968 and 1997; [b]90% confidence interval (C.I.); [c]Excluding diseases of the blood and blood-forming organs.

For occupationally exposed workers, such as employees of nuclear power facilities, data are mixed at this range of moderate doses (0.5-5 Gy). A study of U.S. workers who were exposed to radiation at doses below 1 Sv in nuclear power plants showed a significant correlation between radiation dose and death from cardiovascular disease (Howe et al. 2004). However, similar studies (Table 5) have shown either risks that are more similar to those for the A-bomb survivors or no increased risk. Recent analyses of Mayak worker data (Azizova et al. 2010a, 2010b, and 2014) show a highly statistically significant trend in the dose-response relationship for ischemic heart disease and cerebrovascular events. They also adjusted for major lifestyle risk factors such as smoking and alcohol use. However, these studies are also unique in that they included populations with internal radiation exposures from internally deposited radionuclides such as plutonium. Further studies are warranted, as evidence suggests that a similar trend is present at doses below 0.5 Sv (Vrijheid et al. 2007). Finally, follow-up studies of the health risks in Chernobyl recovery workers also show an increased risk for cardiovascular diseases; however, the contribution of lifestyle factors to this risk estimate cannot

be eliminated at this point, and further analysis is needed (Ivanov et al. 2006; McGale and Darby 2005).

Table 5. Occupational Studies and Circulatory Disease Mortality (Hoel 2006).

Occupationally Exposed Persons			
Study	**Workers (Circulatory deaths)**	**ERR per Sv**	**Comments**
U.K. radiologists (Berrington 2001)	2,698 (514)	< 0	Time trend in cancer but not in CVD
U.S. radiologists (Matanoski 1975)	30,084	0.2	Time trend in cancer but not in CVD
U.S. radiology techs (Hauptmann 2003)	90,284 (1,070)	0.01–0.42	Time trend in both stroke and CHD
Nuclear worker study			
IARC 3 country study (Cardis 1995)	95,673 (7,885)	0.26	5% works > 0.2 Sv 2% workers > 0.4 Sv
U.S. power reactors (Howe et al. 2004)	53,698 (350)	8.3	95% C.I.: (2.3, 18.2)
Mayak workers (Bolotnikova 1994)	9,373 (749)	0.01	
Chernobyl emergency (Ivanov 2001)	65,095 (1,728	0.79	Exposures 0 to 0.35 Sv

CHD = coronary heart disease; CVD = cardiovascular disease; IARC = International Agency for Research on Cancer.

Table 6. ERR coefficients for circulatory diseases as a result of exposure to low-level radiation ≥ 5 years earlier, by disease (Little et al. 2012).

Disease	References	Fixed-effect estimate of ERR/Sv (95% CI)	Random-effect estimate of ERR/Sv (95% CI)	1-sided significance, p-value (fixed effect/ random effect)	Heterogeneity χ^2 (df)/p-value
IHD (ICD-10 I20–I25)	Azizova et al. 2010a[a], Ivanov et al. 2006, Lane et al. 2010, Laurent et al. 2010, Muirhead et al. 2009, Shimizu et al. 2010, Vrijheid et al. 2007, Yamada et al. 2004	0.10 (0.05, 0.15)	0.10 (0.04, 0.15)	< 0.001/< 0.001	7.20 (7)/0.408
Non-IHD (ICD-10 I26–I52)	Ivanov et al. 2006, Shimizu et al. 2010[b], Vrijheid et al. 2007[c]	0.12 (–0.01, 0.25)	0.08 (–0.12, 0.28)	0.031/0.222	4.65 (3)/0.199
CVA (ICD-10 I60–I69)	Azizova et al. 2010b[d], Ivanov et al. 2006, Kreuzer et al. 2006, Lane et al. 2010, Laurent et al. 2010, Muirhead et al. 2009, Shimizu et al. 2010, Vrijheid et al. 2007, Yamada et al. 2004	0.20 (0.14, 0.25)	0.21 (0.02, 0.39)	< 0.001/0.014	34.28 (8)/< 0.001
Circulatory disease apart from heart disease and CVA (ICD-10 I00–I19, I53–I59, I70–I99)	Ivanov et al. 2006[e], Shimizu et al. 2010[f], Yamada et al. 2004[g]	0.10 (0.05, 0.14)	0.19 (–0.00, 0.38)	< 0.001/0.026	66.83 (7)/< 0.001

Values are from Table 1, unless otherwise indicated.
[a]Analysis based on morbidity from IHD, with a 10-year lag. [b]Analysis based on mortality from heart failure and other heart disease. [c]Analysis based on mortality from heart failure. [d]Analysis based on morbidity from CVA, with a 10-year lag. [e]Analysis based on morbidity from hypertension, disease of arteries, arterioles and capillaries, veins, lymphatic vessels, and lymph nodes. [f]Analysis based on mortality from rheumatic heart disease and circulatory disease apart from heart disease and CVA. [g]Analysis based on morbidity from hypertension, hypertensive heart disease, and aortic aneurysm.

In a comprehensive and systematic review by Little et al. (2012), information was summarized on circulatory disease risks associated with moderate- and low-level whole-body ionizing radiation exposures with criteria of whole-body radiation exposures and a cumulative

mean dose of < 0.5 Sv or exposure at a low dose rate (< 10 mSv/day). Although mean cumulative radiation doses were ≤ 0.2 Gy in most of the examined studies, the small numbers of participants exposed to high cumulative doses (≥ 0.5 Gy) drive the observed trends in most cohorts in these higher dose groups. Table 6 summarizes ERR coefficients for circulatory diseases as a result of exposure to low-level radiation ≥ 5 years earlier, by disease. Analyses supported an association between circulatory disease mortality (excess risk of IHD) and low and moderate doses of ionizing radiation above >0.5 Gy (Little et al. 2012). Data were not statistically significant at lower doses. This may be due to statistically significant heterogeneity across exposed populations (Japanese atomic-bomb survivors compared with a Western cohort of largely European/American populations). This lack of significance may also be partly due to uncontrolled confounding factors, such as lifestyle and genetic factors, within the many studies included in the meta-analyses.

Currently, a large-scale effort known as the Million Worker Study is underway to evaluate late health effects associated with low dose, low dose-rate ionizing radiation exposure. This epidemiology study of US radiation workers and veterans will primarily focus on cancer mortality but will also address causes of death due to cardiovascular and cerebrovascular disease and should provide important information related to dose-rate effects that is not currently available from the A-bomb survivor studies where the exposure was acute (Bouville et al. 2015).

At these low doses <0.5 Gy, the mechanisms of action may involve non-targeted effects, monocyte killing, and kidney dysfunction. In a 2003 analysis of 992 patients treated for testicular cancer, those who received mediastinal radiotherapy showed a significant increase in their risk for a cardiac event (Huddart et al. 2003). More notably, patients who received intradiaphragmatic radiotherapy (irradiation below the diaphragm, excluding the heart) still had higher risk compared to controls. With a low estimated heart dose of 0.75 Gy, the authors suggested radiation nephropathy, leading to hypertension, may be a partial cause for their elevated risk of CVD. More recent studies of the survivors of the A-bombs of World War II in Japan suggest that the increased risk of circulatory disease from acute exposures to gamma-rays at low to moderate doses (up to 3 Gy) is related to renal dysfunction, with concomitant changes in blood pressure and inflammation (Adams et al. 2012; Sera 2013). Adams et al. (2012) reported that a quadratic dose response model best fits their data, which is consistent with the finding of Shimizu et al. (2010) and the observations of Little et al. (2008), who reported that inflammation was not increased after low-dose radiation exposure (<0.5 Gy). Work by Lenarcyzk et al. (2013) in rats showed comparable levels of cholesterol (total, HDL, LDL, and triglycerides) compared to sham-irradiated controls when the kidneys were shielded during irradiation (10 Gy gamma). Additional research is currently being conducted to investigate this role of the kidney in radiation-induced CVD at lower, space-relevant doses (Baker et al. 2015).

Consideration should also be given to cataract monitoring as a potential window on other degenerative effects caused by space radiation exposure. Hu et al. (2001) put forth a "common soil hypothesis" that there may be common pathways between the development of cataracts and CVD, suggesting that oxidative damage from a more generalized aging process may responsible for both. This has been reiterated in several other studies linking cataracts with increased risk of CVD (Kessel et al. 2006; Klein et al. 2006; Nemet et al. 2010). In a recent review by Wong et al. in 2014, even kidney disease was linked with ocular disease through the

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common soil hypothesis with the suggestion that shared vascular risk factors and pathogenic mechanisms act as a basis for both. Given the well-documented effects of radiation on increased oxidative stress and noting that cataract formation is a measurable, direct disease endpoint resulting from space radiation exposure in humans, monitoring of cataracts in astronauts may have benefit in providing information on radiation quality, progression and latency. Cataracts may represent a very useful biomarker for radiation-induced cardiovascular effects.

In summary, these observations are supportive of a threshold dose for circulatory disease risk from radiation of approximately 0.5 Gy of acutely delivered gamma-rays. However, it is not known how the threshold might be modified for other radiation qualities, dose-rate effects, or individual sensitivity. For healthy workers who refrain from tobacco use and have a normal body mass index (BMI) and moderate alcohol use, a higher threshold dose would be predicted based on theoretical considerations. In contrast, the epidemiological meta-studies of Little et al. (2013) and Schollnberger et al. (2012) are consistent with an increased risk below a 0.5 Gy threshold. Additionally, the Health Protection Agency 2010 report identified several other possible mechanisms, such as mitochondrial dysfunction and DNA damage, through which radiation exposure may cause circulatory damage, leaving the existence of a threshold an open question.

2B. Experimental Data from Animal and Cellular Studies and Mechanisms of Damage

Systematic studies on the progression of radiation-induced heart diseases were first conducted in rabbits (Fajardo and Stewart 1970) and rats (Yeung and Hopewell 1985; Lauk et al. 1985) with high doses of X-rays in the range of 10 to 20 Gy. Similar studies were conducted using heavy ions during the course of the JANUS program at Argonne National Laboratory, in which ultrastructural studies of the mouse heart and vasculature were performed after the animals had been irradiated with neutrons. The results of the studies were compared with results from irradiating mice with low-LET radiation and showed vessel morphological changes, including marked fragmentation of vascular smooth muscle layers and an increase in deposition of extracellular matrix in vessel walls, similar to the changes observed in animals of advanced age (Yang et al. 1976 and 1978; Stearner et al. 1979). Changes in the coronary arteries and aorta at 18 months post-exposure were greater in animals receiving fractionated neutron exposures compared to the single-exposure group. Opposite results were observed for the gamma-ray-exposed animals, with single dose exposures being more effective than fractionated exposures. RBEs for neutron effects increased with decreasing dose or dose fractionation, with RBE values exceeding 100 with protracted exposures (Yang et al. 1978). Similar results were found in early studies with low doses of Ne and Ar ions (Yang and Ainsworth 1982). Studies on the atherogenic changes that are associated with irradiation were conducted in dogs to compare the effects of fractionated doses of fast neutrons (15 MeV avg.) with those of low-LET photons. The RBE of neutrons was estimated at 4 to 5 from these studies (Bradley et al. 1981).

More recently, studies aimed at defining the mechanisms by which radiation induces heart diseases were conducted using atherosclerosis-prone animal models. Increased oxidative stress (from the formation of reactive oxygen species [ROS]) and promotion of inflammation have been implicated as possible mechanisms by which radiation promotes atherogenesis. For example,

accelerated formation of aortic lesions occurred in a dose-dependent manner in x-ray-irradiated C57BL/6 mice fed a high-fat diet (Figure 2), while smaller lesions were observed in their irradiated transgenic littermates that over-expressed CuZn-superoxide dismutase, which is expected to decrease chronic oxidative stress and lead to a decreased susceptibility to degeneration (Tribble et al. 1999). The lowest dose in these studies was 2 Gy. Impairment in nitric oxide signal transduction may also contribute to degenerative vascular changes (Soloviev et al. 2003). In another study (Stewart et al. 2006), radiation was shown to accelerate the formation of macrophage-rich inflammatory atherosclerotic lesions in atherosclerosis-prone mice lacking the gene for apolipoprotein E (*apoE$^{-/-}$*). These mice were given a single high dose of gamma-rays (14 Gy) to the neck, supporting the notion that radiation promotes degenerative heart diseases though an inflammatory mechanism.

Exposure with high doses of ^{56}Fe ions showed a similar pattern of accelerated lesion development in this mouse model (Yu et al. 2011), which is associated with early impairment of normal vascular reactivity (Yu et al. 2011; White et al. 2014). At doses less than 0.5 Gy, the response of this model is more complex. Mitchell et al. (2011) analyzed aortic lesion frequency, size, and severity as a function of gamma-ray dose, dose rate, and disease state. This study revealed nonlinear responses with a complex combination of protective and detrimental effects depending on dose rate and disease stage, with maximum effects occurring between 25 and 50 mGy (Mitchell et al. 2011).
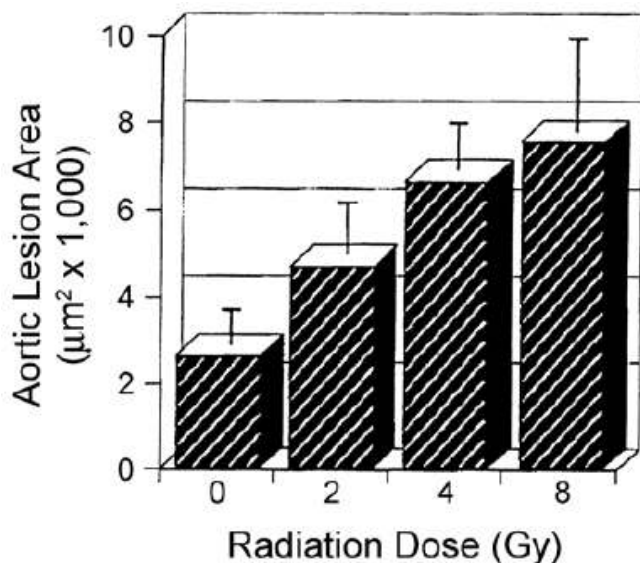

Figure 2. Dose-dependent effects of ionizing radiation on aortic lesion formation in fat-fed mice (repeated-measures analysis of variance: P = 0.02) (Tribble et al. 1999).

Using wildtype animals, Soucy et al. showed chronic vascular dysfunction due to radiation-induced xanthine oxidase-dependent ROS production and nitrosoredox imbalance in rats after 1 Gy ^{56}Fe particle irradiation, a particularly damaging component of the GCR spectrum (Soucy et al. 2011). At doses as low as 0.1 Gy of ^{28}Si ions, changes in apoptosis and markers of chronic inflammation were observed in heart tissue of mice up to 6 months following exposure

(Tungai et al. 2013). Similarly, Sasi et al. (2015) irradiated C57Bl/6NTac mice or bone-marrow- (BM-) derived endothelial progenitor cells (EPCs) with 0.9 Gy of protons or 0.15 Gy of ^{56}Fe ions and showed early (5-24h) and delayed (28 days) apoptosis in the mice and non-targeted effects in the cells. In the same mouse model irradiated with 0.5 Gy of protons or 0.15 Gy of ^{56}Fe ions, cardiac fibrosis and hypertrophy still observed at late time points (up to 10 months). However, functional markers of cardiac physiology were not impaired compared with controls at those time points (Yan et al. 2014).

In summary, substantial evidence from human epidemiology data and animal studies suggests that low-LET radiation strongly impacts the development of degenerative heart and cardiovascular diseases at doses above 0.5 Gy, which may be related to the overall acceleration of age-related processes. It is still an open question as to whether there is a risk below 0.5 Gy and how dose rate and radiation quality modify the overall radiation response. Human epidemiology data are subject to large errors due to inconsistencies in organ dose evaluations and, more importantly, in the understanding of the role of life-style factors. Circulatory disease risks may be impacted by factors such as smoking status, obesity and nutrition, alcohol consumption, and stress to a much larger extent than cancer risks. Human epidemiology analysis often lacks corrections for these confounders. These considerations will be vitally important for astronauts because of their longevity and because definitive evidence for a healthy worker effect is present (Cucinotta et al. 2013a). Additionally, data on these same effects of irradiation with protons or heavy ions are clearly lacking, and the few studies with HZE particles to date have used doses higher than those present in space and often used animals pre-disposed to heart disease that were fed a high-fat diet not reflective of the status and diet of astronauts. The Center for Space Radiation Research (CSRR), awarded in 2014 by the National Space Biomedical Research Institute (NSBRI), is a 3-year research consortium centralized at the University of Arkansas for Medical Sciences that was funded to generate research to fill some of these noted knowledge gaps. They will be utilizing cell and animal models (mice, rats, and rabbits) with protons, HZE, and gamma-ray controls to further characterize this risk of radiation-induced cardiovascular disease.

3. Digestive and Respiratory Diseases

Evidence for the development of late complications to the respiratory and digestive system are largely derived from the LSS study of the Japanese A-bomb survivors. An early RERF publication reported a significant increasing trend with dose in mortality from digestive diseases for the period 1950-1985, with liver cirrhosis being the major digestive disease (Shimizu et al. 1992). Several follow-up surveys that included non-cancer deaths have confirmed the early findings of digestive disease risks in the A-bomb survivors (Shimizu et al. 1999; Preston et al. 2003). Figure 3 shows results from Preston et al. (2003) for the ERR for death vs. dose for several diseases, including digestive and respiratory diseases.

An additional follow-up study of the A-bomb survivors for the period 1998-2003 was published in 2012 (Ozasa et al. 2012). As of 2003, 3394 A-bomb victims died of digestive diseases, with an ERR of 0.11 (-0.01, 0.2)/Gy (Ozasa et al. 2012). When the non-cancer disease mortality is divided between the early period (1950-1965) and late period (1966-2003), ERR showed marginal differences between the periods, as shown in the dose-response relationship in Figure 4. For digestive disease deaths in the late period alone, the ERR was found to be 0.20

(0.05, 0.38), suggesting a possible late development of the diseases; however, in the analysis, liver cirrhosis, a major digestive disease, did not show any increase with radiation exposure.
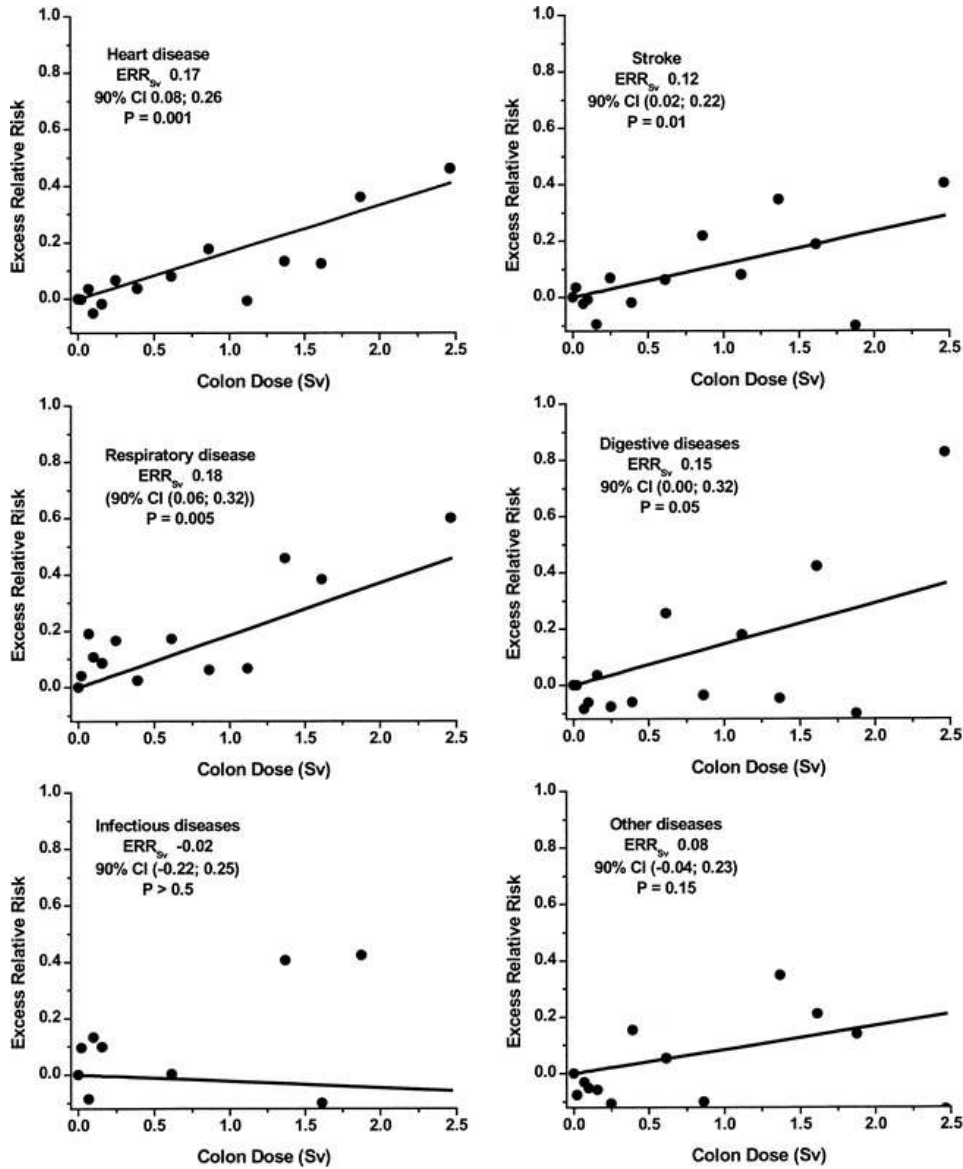

Figure 3. Dose-response functions for non-cancer deaths from the LLS study of A-bomb survivors (From Preston et al. 2003).
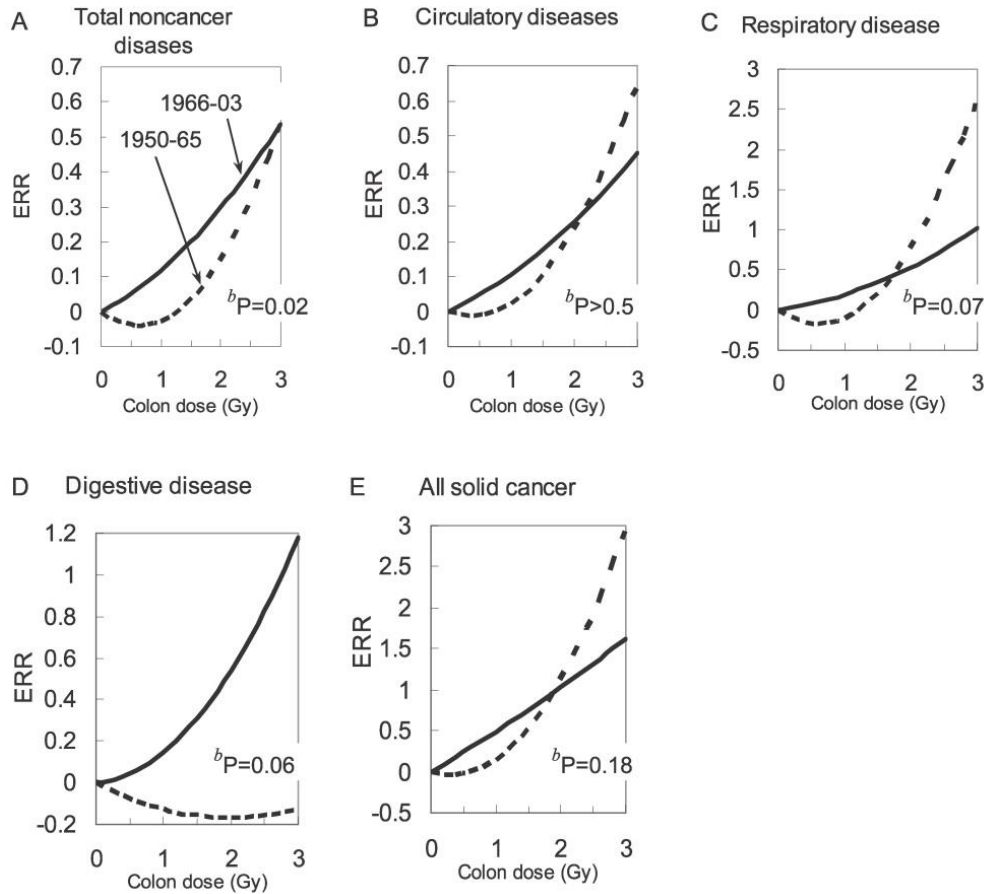
Figure 4. Comparison of dose-response curves for the early period (dashed line) and late period (solid line) for non-cancer diseases (From Ozasa et al. 2012).

For the respiratory system, there is a clear association between high, therapeutic doses of radiation and development of lung diseases, including acute pneumonitis and chronic fibrosis (Choi et al. 2004). At the lower dose levels relevant to space travel, data from the A-bomb survivors again provide most of the evidence for respiratory diseases due to exposure to external, acute low-LET radiation. Respiratory diseases observed in this cohort include chronic obstructive pulmonary disease (COPD), pneumonia/influenza, and asthma. According to the latest published results from the LSS study for the period 1950-2003, the ERR per Gy for respiratory diseases was 0.21 (0.10, 0.33), with pneumonia being the major cause of death (Ozasa et al. 2012). However, in a more detailed examination of the LSS data that included additional adjustments for indications of cardiovascular disease and/or cancer, the only respiratory complication that remained significant was an excess risk for pneumonia/influenza (Pham et al. 2013).

There is no evidence for the association of charged particle exposure with digestive diseases and very little evidence for the development of respiratory diseases at the doses and dose rates that are relevant to space travel. A recent study investigated the late effects of gamma-rays, protons, ^{56}Fe, and ^{28}Si ions on the lungs of mice approximately 2 years post-exposure and revealed histopathological abnormalities and changes in markers of oxidative stress in the lung tissue of mice at doses as low as 0.1 Gy ^{56}Fe and 0.1 Gy ^{28}Si ions. However,

these alterations were associated with changes in functional parameters, as approximated by systemic oxygenation levels, only at higher doses that are not space-relevant (Christofolodou et al. 2015).

In summary, acute exposure to gamma-rays may increase the risk of non-cancer mortality from digestive and respiratory diseases. However, available epidemiological evidence is limited and confounded by the impact of other lifestyle stressors and misdiagnoses, making the level of these risks unclear. Additionally, because the association between low dose radiation exposure and digestive and respiratory diseases is only evident in isolated groups, caution in the interpretation of these findings is warranted (Little et al. 2013).

4. Evidence for Other Age-Related Effects Caused by Radiation

Many of the cellular and physiological changes in organ systems that are associated with the normal aging process are shown to be accelerated by radiation exposure. These include changes in immune and endocrine function, fibrosis, and cellular senescence. Examples of studies showing radiation effects on markers of aging include the following (NCRP 2006):

- Studies of structural changes in specific organs
- General life span longevity studies that are performed in animal models
- Analyses of biochemical and molecular markers of cellular aging, including oxidative damage, inflammation, and cellular senescence

The possibility of radiation-induced accelerated aging was noted very early on in follow-up studies of the A-bomb survivors (Anderson et al. 1974), and it is now clearly established that the survivors are at an increased risk of developing age-related conditions, most notably, diseases of the circulatory system, cataracts, altered immune system function, and changes in inflammatory marker status (Kusunoki et al. 2010 and 2012). Although exposure to HZE particles occurs at low fluences during space travel, accumulated molecular changes resulting from long-term exposure have been found that are similar to those seen in aged animals (Manda et al. 2008; Poulose et al. 2011).

4a. Mechanistic candidates and biological processes of radiation-related aging

Possible aging mechanisms include oxidative stress (e.g., free radicals produced in intracellular and extracellular water), somatic DNA mutations, shortened telomeres, decline in endocrine and immune function, increased inflammation and fibrosis, and stem cell exhaustion. Radiation exposure is associated with enhanced oxidative stress and oxidative damage to DNA, proteins, and lipids, which may promote chronic inflammation, cellular senescence, premature aging, and development of age-related diseases (Li et al. 2014). Radiation-induced oxidative stress also disrupts intracellular signaling and cell-to-cell communication, leading to accelerated age-dependent decline (Trosko et al. 2005).

4b. Premature Cellular Senescence

Radiation exposure is associated with increased cellular senescence of two types: replicative senescence, mediated through DNA damage and telomere dysfunction (Shay and Wright 2005; Toussaint et al. 2000), and stress-induced premature senescence (SIPS). SIPS can result from sub-lethal exposure to a variety of stressors including ionizing radiation and oxidative stress, and does not involve telomere dysfunction. Both types of senescent cells exhibit p53-dependent cell cycle arrest and share features such as a flattened and enlarged morphology, an increase in acidic betagalactosidase activity, and chromatin condensation Funayama and Ishikawa 2007; Caino et al. 2009), as well as secretion of proinflammatory mediators and other bioactive compounds as part of the SASPs (senescence associated secretory phenotype) which consists of a wide variety of inflammatory mediators and growth factors such as IL-6, IL-8, IL-1, Gro-α, HGF, MCPs and MMPs (Ren et al. 2009). Other hallmarks of senescent cells, such as DNA-SCARs (DNA-SCARS: distinct nuclear structures that sustain damage-induced senescence growth arrest) and analysis of pathways controlling this process are being characterized (Rodier et al. 2011; Salminen et al. 2012).

4c. Defective Stem Cell Function and Aging

Stem cells in all tissues are of fundamental importance because they support tissue homeostasis, which is the ability to maintain normal tissue function and involves formation and replacement of tissue-committed cells from adult tissue resident stem cells. A decline in the number or functional capability of stem cells will impair the ability of the body to form and replace committed cells, with potentially deleterious costs for tissue maintenance. Studies that were conducted using low-LET irradiation in mouse models have shown a decline in the total number of cells and an increase in the number of cells with the senescent phenotype in bone marrow stem cells after radiotherapy and chemotherapy. These changes may contribute to the long-term deficits in bone marrow function that occur after these treatments (Wang et al. 2006).

4d. Effects of High LET Radiation on Aging

Radiation-induced aging is well documented with high doses of low-LET radiation, while low doses of low-LET radiation have been shown to stimulate cells to gain adaptive responses resulting in resistance to aging, defined as "radiation hormesis," with the implying mechanisms of strengthened cytoprotective and restorative functions (Mattson 2008, Maynard 2011). Nevertheless, high-LET radiation produces more clustered lesions and genomic instability than low-LET radiation and endogenous sources of ROS (Li et al. 2014). High-LET radiation also has an enhanced ability to damage the telomeres that are at one end of each chromosome and are believed to be involved in the aging process (Durante et al. 2006). Since telomeres are extremely sensitive to ROS, cells exposed to high-LET radiation are more prone to senescence. Some investigators report very high levels of telomere deletion in the progeny of human lymphocytes after irradiation with low doses of iron nuclei (Durante et al. 2006). Bailey (2007) is studying changes to telomeres as a function of radiation quality. Possible quantitative

differences between low- and high-LET radiation-induced damage cause telomere shortening or premature senescence and are thus a concern for space radiation risk assessment.

5. Radiation Effects on Endocrine Function

The endocrine system controls hormone production, secretion, metabolism, and levels in circulating blood. Age-related changes in the endocrine system occur in older people and result in a decreased capability of the system to respond to the internal environment. The hypothalamus is responsible for releasing hormones that stimulate the pituitary gland. During aging, individuals suffer impaired secretion of some hypothalamic hormones and direct radiation effects on the thyroid and pituitary glands, as well as subtle effects on the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis. The pituitary gland, thyroid, and gonads have been found to be sensitive to radiation (Niazi 2011; Nishi 2011). Radiation-induced atrophy of the endocrine glands has been reported, occurring a few weeks after radiation exposure (Nishi 2011). In the follow-up study of the nuclear accident in Chernobyl, childhood autoimmune thyroid disease was extensively observed (Eheman 2003). Residents in Chernobyl and nearby areas were found to have lower sympathetic activity, adrenal cortical activity, and blood cortisol levels. Accelerated sexual development in females has been reported, and the concentration of gonadotropic hormones in blood was increased (Leonova 2001). In addition, hyperparathyroidism was reported in the A-bomb survivors (Fujiwara et al. 1992; Preston et al. 2002). A-bomb radiation exposure perturbed the processes involved in T-cell homeostasis, which may result in the acceleration of immunological aging (Kusunoki 2008).

Besides A-bomb radiation exposure, various endocrine systems have been affected by radiation therapy (ICRP 2012) as well, e.g., adenomas, which are hyperplasias in the parathyroid gland, are observed in patients who are treated with low-LET radiation at doses that are below 1 Gy (Tezelman et al. 1995; Tissel et al. 1985) and in the A-bomb survivors (Fujiwara et al. 1992; Preston et al. 2002). Various endocrine systems effects have been encountered from radiation therapy (ICRP 2012); however, most of the data are derived from high exposures, which are of questionable relevance for space radiation.

6. Musculoskeletal System

ICRP 2012 reports that "radiation effects observed in bone and skeletal muscle are predominantly late effects that appear months to years after radiation exposure. While mature bone is relatively radioresistant, growing bone is more radiosensitive, and measurable growth delay can be expected after relatively low doses of radiation. Hence, while musculoskeletal radiation effects are a minor issue in most adult patients with cancer, they remain a major problem in childhood cancer survivors." There are currently no human data at space-relevant doses showing a long-term radiation-induced effect on the musculoskeletal system (NCRP 2006, ICRP 2012). Although some animal and cell work investigating the effects of HZE radiation on muscle (Bandstra et al. 2009; Shtifman et al. 2013) and bone (Willey et al. 2008; Alwood et al. 2010) has been reported, they all demonstrate transient or short-term effects. Overall, the evidence at lower doses is not sufficient to determine the existence of excess risk for musculoskeletal diseases.

7. Endometriosis

An additional effect of irradiation that was revealed by the proton bioeffects studies that were conducted in Rhesus monkeys was a significant increase in the risk of developing endometriosis, which is an abnormal growth of the uterine lining. This disease occurred in about 25% of all of the unirradiated female primates and in more than 50% of the irradiated primates. Although it is not normally life-threatening in humans, this condition proved fatal in several of the animals before proper treatment plans were put into effect. Endometriosis was evident even when relatively low-energy protons (32 MeV; penetrating to a depth of about 1 cm) and low dose exposures (0.2 to 1.13 Gy) were used (Yochmowitz et al. 1985; Fanton and Golden, 1991). As very few humans have been exposed to high-LET radiation, other health effects may arise that have not been documented to date for terrestrial forms of radiation at low to moderate doses (<2 Gy).

B. Spaceflight Evidence

The NAS Space Science Board first reviewed space flight issues in 1967 (NAS/NRC 1967) and revisited these issues in 1970 (NAS/NRC 1970). These reviews led to the establishment of dose limits that were used at NASA until 1989. Extensive reviews of human and experimental radiobiology data for space risks were also provided to NASA in 1989, 2000, and 2006 via NCRP reports (NCRP 1989, 2000, and 2006). The 1989 and 2000 NCRP Reports led to updates of the NASA dose limits. The issues of cataracts and degenerative tissue effects are discussed in many of these reports. Reviews on other degenerative risks have been given more priority in the more recent of the reports. The more recent reviews suggest that threshold doses may be lower than previously estimated or do not occur, especially for high-LET radiation. A major question also remains regarding the categorization of these risks as deterministic vs. stochastic, which has major implications for radiation protection.

The most recent external report of the evidence of space radiation effects was published in 2006 by the NCRP (NCRP 2006). The stated purpose of this report was to identify and describe the information that is needed to make radiation protection recommendations for space missions beyond low Earth orbit (LEO). The report contains a comprehensive summary of the current body of evidence for radiation-induced health risks and makes recommendations on areas requiring further research. For the non-cancer, late effects of radiation, the authors of this report recommend that experiments be conducted using protracted or extended exposure times and low dose rates of protons, heavy ions, and neutrons in energy ranges that are relevant to space radiation exposure scenarios. Specifically, the authors of the report recommend that analyses should be conducted on the effects of protracted exposures on the lens, whole-body vasculature, gastrointestinal tract, gonadal cell populations, and hematopoietic and immune systems, as well as fertility.

1. Cataracts in Astronauts

Cucinotta et al. (2001) reported epidemiological evidence for an exposure-dependent increase in the risk of cataract formation in astronauts. Health records for 295 astronauts who were enrolled in the NASA Longitudinal Study of Astronaut Health, which spans more than 3 decades, were evaluated for incidence and type of cataract. Data were analyzed for astronaut

age at the time at which the cataract appeared or the duration between the first mission and cataract appearance (Figure 5). Astronauts were grouped by individual occupational radiation exposure records that allowed for the separation of exposures from low-LET diagnostic x-rays, atmospheric radiation that was received during aviation training, and exposure that was received during space flight. These data reveal an increased cataract incidence in astronauts who have a higher lens dose-equivalent (average of 45 mSv) of space radiation relative to that of other astronauts with zero or low lens doses (average 8 mSv). These studies also show a significant association between radiation quality and cataract incidence. Astronauts who flew on high-inclination (>50 deg) and lunar missions, which are associated with a higher flux of high-LET heavy ions, had a higher incidence of cataract formation than those who flew on low-inclination missions, in which a large proportion of the dose is from low-LET trapped protons. Further evidence for the link between cataract formation and exposure to space radiation was presented in a 2002 study of cosmonauts and astronauts (Rastegar et al. 2002), in which a trend for increased opacification in the posterior cortical and posterior capsule regions of the lens was evident in a group of cosmonauts and astronauts compared with the controls. As astronauts were screened for vision at entry into the Astronaut Corps and were observed with distinct methods, comparisons to other studies are inconclusive. In fact, it is very likely that astronauts, prior to their exposure to space radiation, have a baseline incidence of cataracts that is well below that of members of the general population.
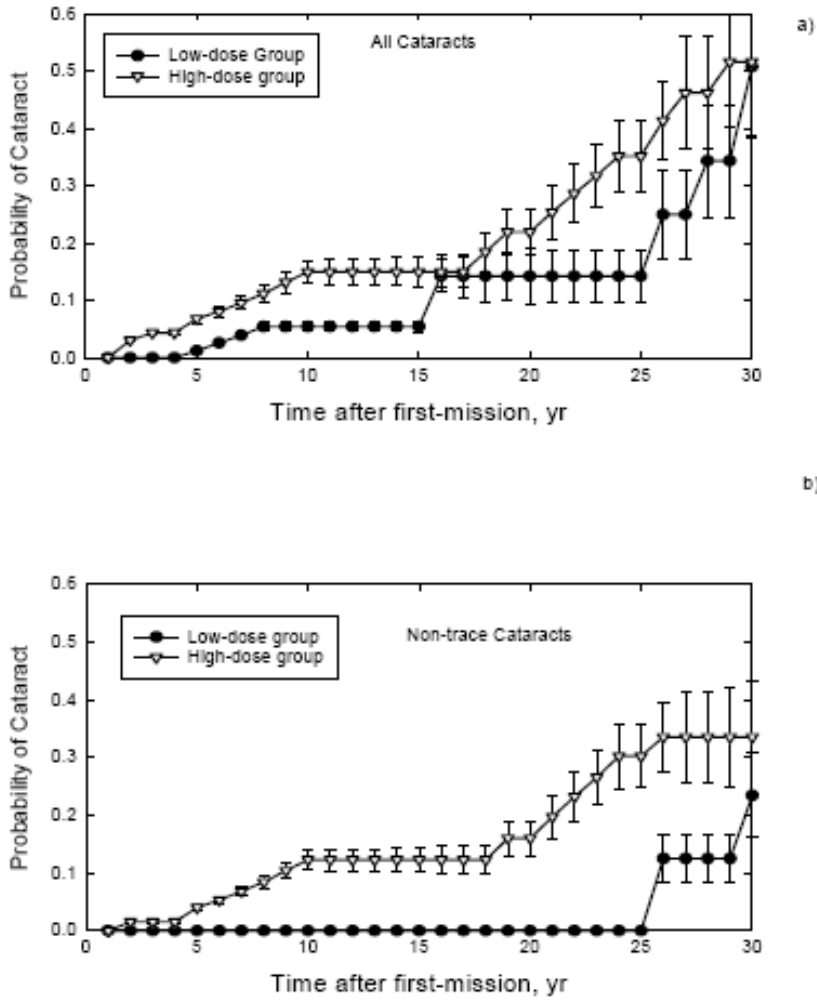
Figure 5. Results regarding the probability of survival without cataracts vs. time after the first space mission for NASA astronauts in a low-dose group (closed symbols) with a lens dose below 8 mSv (average 4.7 mSv) and a high-dose group (open symbols) with a lens dose above 8 mSv (average 45 mSv). Error bars indicate standard errors of the mean. The upper panel is for all cataracts, and the lower panel is for non-trace (vision-impairing or large-area) cataracts. Only cataracts occurring after a first space mission are included (Cucinotta et al. 2001).

More recently, the NASA Study of Cataracts in Astronauts (NASCA) (Chylack et al. 2009 and 2011) studied cataracts in a population of 224 astronauts and a comparison group of 200 ground controls from the LSAH and military aviators using clinically validated objective measures of posterior subcapsular (PSC), cortical, and nuclear cataracts. A major goal of the NASCA study was to investigate whether the rates of progression of cataracts were increased by space radiation. NASCA confirmed the association between space radiation and cortical and PSC cataracts. The longitudinal phase of the study required 5 lens exams per subject; however, the study ended early after an average of 3.7 exams per subject. Even with the incomplete

study data, the progression rates for cortical cataracts were shown to be associated with space radiation exposures (Chylack et al. 2011).

The NASCA cross-sectional analyses of baseline data (Chylack et al. 2009) revealed (a) the median size and variance in size of cortical opacities were greater in exposed astronauts (P=0.015); (b) within-astronaut group PSC severity (area) was greater in subjects exposed to higher radiation doses (P=0.016); (c) galactic cosmic radiation (GCR) was possibly linked to increased PSC area (P=0.056) and the number of PSC centers (P=0.095); and (d) no relationship was found between density (severity) of C opacification and space radiation exposure. The longitudinal analyses revealed the following: (a) the estimated median rate of progression of C opacification was an increase C %-area opacity of 0.25/yr/Sv in exposed astronauts (P=0.062); (b) neither the area of PSC opacification nor the increase in numbers of centers of PSC opacification was significantly associated with space radiation exposure (yes/no) (however, the NASCA results were influenced by the absence of a large number of PSC cases among astronauts due to lens implants or other reasons as described in the report); (c) within the time frame of the study, there was no evidence that space radiation exposure is related to faster rates of increase in various measures of N opacification; and (d) no impact of space radiation on visual acuity was apparent over the approximately 5 years of follow-up time.

These observations, along with several other epidemiological studies (see Table 2.4 of ICRP 2012), have been used by the ICRP to support a recommendation for a lower lens dose limit for radiation workers (ICRP 2012). The very low doses at which increased rates of cortical cataracts were observed and the likelihood that PSC would also be increased suggest that the possibility of vision-impairing opacities could occur for the much higher doses to crew (up to 40-fold higher than NASCA average lens doses) within the timeline of a 3-year Mars mission. However, NCRP 2014 notes that "the annual limit to the lens of the eye for radiation workers in the United States is 0.15 Sv (150 mSv) (equivalent dose), although the European Union has recently modified their annual limit for the lens of the eye to 0.02 Sv (20 mSv) (equivalent dose), averaged over 5y, based on the recommendation from ICRP (2012). ICRP (2012) recommended this change based on new evidence, from both human and animal studies, that supports a low radiation dose for the induction of cataracts. There remains discussion on the suitability of this revised limit and particularly how it can or will be applied in medical situations and perhaps by extension to space missions."

2. Cardiovascular Disease in Astronauts

Reynolds and Day (2010) and Cucinotta et al. (2013a) provided evidence that U.S. astronauts should be considered to be at lower risk for circulatory diseases and enjoy a longer life span compared to the average U.S. population. This is borne out by analysis of Kaplan-Meir survival curves (Figure 6) and standard mortality ratios (SMRs) (Table 7), where the cohort of NASA astronauts was compared to the average U.S. population and populations of U.S. never smoker (NS), U.S. normal weight (NW), or U.S. NS-NW model populations (Cucinotta et al. 2013a). The results are strongly indicative of a healthy worker effect for astronauts, as they show a longer longevity and reduced SMR for circulatory diseases compared with the average U.S. population and are more similar to a population of NS among NW individuals.
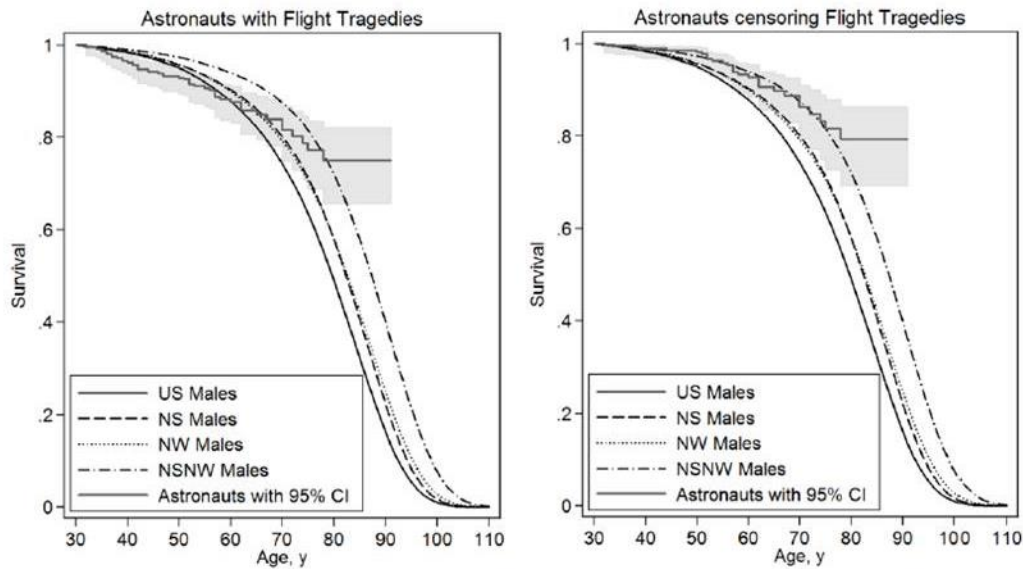
Figure 6. Kaplan-Meier survival versus age for astronauts and payload specialists compared to U.S. males and projections for never-smoker, NW, and NS-NW males. The left panel includes occupational deaths related to flight accidents or training, and the right panel censors occupational deaths (Cucinotta et al. 2013a).

Table 7. Standard mortality ratio for astronauts and payload specialists relative to other model populations for coronary heart disease and stroke (Cucinotta et al. 2013a).

Comparison	SMR
Astronauts vs. U.S. average	0.33 [0.14, 0.80]
Astronauts vs. NS average	0.43 [0.18, 1.04]
Astronauts vs. NW average	0.47 [0.19, 1.12]
Astronauts vs. NS-NW average	0.67 [0.28, 1.62]

It is also interesting to note the differences in SMRs for death from circulatory diseases between NASA astronauts and Soviet/Russian cosmonauts. Reynolds et al. (2014) reported that: "Cosmonauts have only 11% the risk of death due to any cause compared to the general population (for whom circulatory disease is a major killer), but are at more than three times the risk of death from circulatory disease compared to U.S. astronauts." This highlights again the potential heterogeneity found within different populations that can contribute to confounding factors in epidemiological analyses.

3. Influence of Genetic/individual Susceptibility on the Degenerative Radiation Risk

As noted above, the differences between population cohorts, including genetic, environmental, and lifestyle factors, can contribute significantly to variations in risk between those populations. It is very likely that individual gene profiles might inform and influence risks. The NCRP 2010 report details this potential impact of individual genetic susceptibility on radiation-induced risks for astronauts and recommends "that no genetic testing of astronauts be carried out at this time. The probability of individual astronauts having genetic susceptibility factors for radiation-induced cancer or other radiation-induced diseases is low." This is because human genetic disorders, such as ataxia telangiectasia (ATM), ATM-like disorder, Nijmegen breakage syndrome, severe combined immune deficiency (SCID), ligase IV syndrome, and Seckel syndrome, are all disorders that are rare and have phenotypes that are readily apparent and therefore not likely to be present in the astronaut population (NCRP 2010, ICRP 2012). NCRP 2010 concludes that "it is generally not possible to predict an individual's inherent genetic susceptibility to the long-term risk of cancer or other diseases associated with radiation exposure." This is partly because of the relatively little amount of information available on specific genetic characteristics that are known to affect the risk of radiation-induced cancers or non-cancer health effects in humans and partly because of the dearth of data for HZE effects. However, with the recent advances in genomics research and "omics" data in general, it is likely that current and future research will provide for an avenue to predict the risks of radiation based on genetic susceptibility.

4. Summary

In summary, the link between exposure to acute doses of 0.5 Gy or more of ionizing radiation and the development of degenerative diseases is clearly established, while the health risks of low-dose and low-dose-rate ionizing radiation remain largely unknown. These risks are more difficult to assess because multiple factors are believed to play a role in the etiology of the diseases (BEIR VII 2006). Similarly, no human data are available on the effects of high-LET radiation on the development of degenerative heart and cardiovascular complications.

## V.	COMPUTER-BASED SIMULATION INFORMATION

Computer models of radiation-induced degenerative risks have been proposed and are being developed at this time. Epidemiological data are severely lacking, precluding an approach that is similar to those that were used to project cancer risks. Only a few biological models that describe the degenerative processes that are caused by ionizing radiation and that would be needed to form a computer model are available. This is probably because these processes are less studied than radiation carcinogenesis and are, in many cases, complicated by other lifestyle factors that influence the disease process. A mechanistic model for radiation-induced atherosclerosis was proposed by Little et al. (2009). Based on experimentally derived parameters, the assumption that the excess cardiovascular risk seen in the epidemiology data is primarily due to atherosclerosis, as well as several other assumptions noted in the paper, the model suggests a linear dose response down to relatively low doses.

There are other systems biology approaches available for the mathematical modeling of cardiovascular disease; although they do not include radiation effects, they may be modified to describe radiation-induced degenerative risks. MacLellan et al. (2012) reviewed systems-based approaches to modeling cardiovascular diseases. Ramsey et al. (2010) also proposed a systems-biology approach to atherosclerosis involving interacting systems at multiple levels and including genetic and environmental factors (Figure 7). Finally, in silico modeling of atherosclerosis is being developed by the NIH in conjunction with Entelos and the Biomarker Consortium and will result in a publicly accessible model that has the potential for modification to include radiation exposure as a risk factor (http://www.fnih.org/work/research-partners/atherosclerosis-computer-modeling-metabolic-disorders).
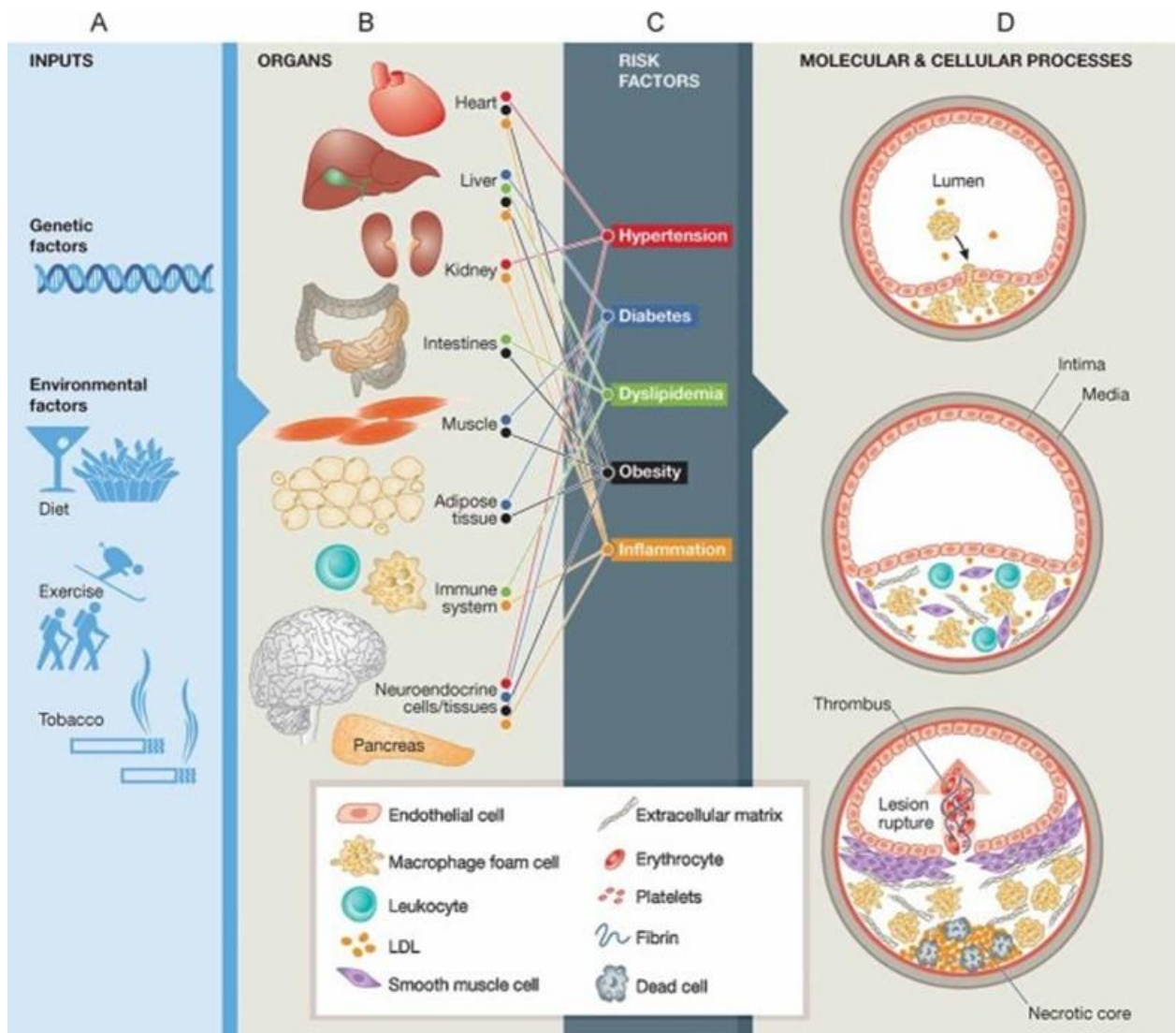

Figure 7. Systems biology approach to modeling atherosclerosis (Ramsey et al. 2010).

VI.   RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS

A.   Projections for Space Missions

No existing biophysical model projects all degenerative risks for the entire range of particle types and energies that are found in space. The large RBEs that are found in the few studies that have been performed suggest that organ dose-equivalent based on radiation quality factors can be used to make a first approximation for risk estimates; however, the shape of the dose-response curve for specific diseases and dose-rate modifiers is unknown. Dose-rate modifiers could be higher than those observed for cancer risks because of the possibility of threshold effects. Cucinotta et al. (2013b) presented %REID assessments for extended LEO and exploratory missions, including the prediction of a combined cancer and circulatory disease %REID for a Mars mission. The authors used the excess relative risk (ERR) results of Little et al. (2012) and noted that the inclusion of the circulatory disease risk increased the overall risk by 40% from cancer alone and reduced the overall age at exposure dependence of the %REID (Table 8).

	a_E, y	Cancer Risk		Combined Cancer and Circulatory Disease Risk	
		US Avg. Population	Never-smokers	US Avg. Population	Never-smokers
Male	35	209 (205)	271 (256)	173 (163)	208 (193)
	45	232 (227)	308 (291)	187 (173)	222 (214)
	55	274 (256)	351 (335)	206 (194)	256 (235)
Female	35	106 (95)	187 (180)	115 (107)	159 (149)
	45	139 (125)	227 (212)	123 (118)	183 (171)
	55	161 (159)	277 (246)	142 (129)	201 (191)

Calculations are for average solar minimum with 20 g/cm^2 aluminum shielding. Values in parenthesis are the case of the deep solar minimum of 2009.
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Table 8. Safe days in deep space (defined as the maximum number of days with the 95% CI below the NASA 3% REID limit) for males and females at different ages at exposure (Cucinotta et al. 2013b).

NCRP 2014 notes that this approach for combining cancer and circulatory disease risks is comprehensive but should be considered "preliminary", largely due to the assumptions "of risk in the low-dose domain for circulatory disease that are far from conclusive." The estimates for ERR per Sv, which were provided by studies of the A-bomb survivors, are not sufficient to estimate risk for astronauts because a risk transfer approach is needed together with estimates of RBE and dose-rate modifiers. Additionally, there is significant heterogeneity between different populations - the baseline risk of coronary heart disease (CHD) is several-fold larger in the U.S. than in Japan, while the risk of stroke is comparable. NCRP 2014 suggests that "it would be preferred to have less heterogeneous and more comparable populations to generate risk coefficients." To determine the cancer risks, the NCRP suggests using multiplicative and additive transfer models to transfer risks between populations." Thus, "it is essential that additional experimental data with HZE particles be acquired using relevant model systems and relevant doses to provide robust input to refine the current model of cardiovascular risk from space radiation" (NCRP 2014).

B.   Synergistic Effects with other Flight Factors

The space environment includes many other stressors besides radiation, such as microgravity, altered oxygen levels and circadian rhythms, nutritional deficiencies, and immune dysregulation. These are currently unknown modifiers of cardiovascular and degenerative tissue disease risks from space radiation. Few reports have been published that directly address synergistic effects of non-radiation risk factors on the risks from space radiation.

For exploration-class missions, NASA has proposed to use varying levels of oxygen in the vehicles (Norcross et al. 2013). This raises the issue of what, if any, effects these oxygen levels may have on radiation-induced degenerative diseases. Hyperbaric hyperoxia (increased oxygen levels at pressures higher that atmospheric conditions) has been used as a radiosensitizer for cancer radiotherapy. However, conditions of hyperoxia would only be present during EVAs (4.3 psia and 85-100% O_2), which are characterized by mild hypobaric hyperoxia and short durations on the order of hours. Currently, there are no plans for long-term exposure to high O_2 concentrations at hyperbaric pressures in any of NASA's design reference missions (Norcross et al. 2013). Therefore, the effects of the planned hypobaric hyperoxia on this risk are likely to be negligible. The difference between hyperbaric or normobaric and hypobaric hyperoxia should be noted as well. One study published results showing oxidative lung damage from synergies of exposures of radiation and hyperoxia "relevant" to space travel (Pietrofesa et al. 2013). However, exposure conditions were not relevant to the space environment; low-LET gamma radiation was used at high doses (total dose of 3 Gy), and the hyperoxia was in a normobaric environment, not the proposed hypobaric hyperoxia that is planned for NASA's missions.

Conversely, there may be some benefit to the use of a hypoxic environment for mitigating radiation effects. The proposed vehicle exploration atmosphere of 8.2 psia and 34% oxygen presents a mildly hypobaric hypoxic environment and would only be used in the exploration habitat during high EVA frequency portions of a mission. A standard sea-level atmosphere (14.7 psia/21%) would be used for the transit to and from the exploration destination (moon, Mars, asteroid) (Norcross et al. 2013). Additionally, previous research has shown that the body will acclimatize to this type of mildly hypobaric, hypoxic environment starting after approximately 2 weeks of exposure (Powell et al. 2000; Barratt and Pool 2008). Given the relatively short exposure times in this hypobaric hypoxic environment, it also seems likely that the effects of these types of oxygen levels are negligible.

Immune dysregulation has been noted during exposure to short periods of microgravity (Crucian et al. 2015). However, no studies have evaluated the combined effects of radiation and microgravity over long periods relevant to the degenerative risks. One study by Zhou et al. (2012) specifically investigated the effects of microgravity and radiation on the immune system using a hindlimb suspension mouse model and gamma or proton radiation. They concluded that synergies were present, but the time points for data collection were all less than a week. Similarly, Alwood et al. (2010) irradiated unloaded mice with 0.5 Gy iron ions but only examined effects 3 days after irradiation. It remains to be seen whether any long-standing effects will occur from microgravity and radiation exposure combined.

The CSRR, established by NSBRI in 2014, will conduct a 3-year focused research effort to investigate the effects of space radiation on cardiovascular disease. Additionally, a portion of their research will include the investigation of combined stressors of microgravity and SPE-like

proton exposures to provide insight into early, acute effects on the hematopoietic system, heart, and retina.

C.   Potential for Biological Countermeasures

Much of the indirect cell damage produced by ionizing radiation is mediated through reactive oxygen species (ROS) that are immediately generated from the interaction of the charged particle with water and other cell components (Li et al. 2014). Excessive production of free radicals produces oxidative damage to cellular structures, which includes proteins, DNA, and lipids, and contributes to the radiation-induced degenerative changes that are associated with aging, cardiovascular disease, and cataract formation. This extensive ROS profile can also induce persistent metabolic changes that result in a chronic inflammatory response. The subsequent recruitment of inflammatory cells, such as macrophages, which also generate ROS and pro-inflammatory signals, feeds into a loop of oxidative stress, inflammation, and cell damage (Zhao and Robbins 2009). The identification of safe and effective agents that will protect and mitigate against these effects of radiation exposure is a high priority both for radiotherapy purposes, where the sparing of normal tissue is critical, and for the health of the general public in the event of a terrorist attack with nuclear weapons (Kennedy 2014).

Two main types of countermeasures have been used to protect normal vasculature from ionizing radiation: sulfhydryl or thiol compounds and antioxidants. Both of these classes of compounds function by scavenging the free radicals that are produced by the interaction of ionizing radiation with water. WR2721, which is also known as amifostine and gammaphos, is the best-described member of the sulfhydryl class and is the only drug that is approved by the Food and Drug Administration (FDA) to help prevent excess damage to normal tissues during radiotherapy. The mechanism of action of this drug is thought to be the scavenging of free radicals that are produced by radiation and H-atom donation to protect against the damage that is done by free radicals. This compound has been tested as a countermeasure for both cataract formation and vascular damage (Kador 1983; Mooteri et al. 1996; Warfield et al. 1990; Plotnikova et al. 1988). Radical scavenging vitamins such as C and E have also been shown to protect the lens and vascular system (Bantseev et al. 1997; Jacques et al. 1997; Taylor and Hobbs 2002). In addition, growth factor treatments have been shown to decrease blood vessel stenosis (Fuks 1994). In all of these examples, the compounds were administered prior to radiation exposure.

Dietary supplements and antioxidants have also been used as mitigators for radiation-induced cataracts. Davis et al. (2010) showed that exposure to 1 GeV/nucleon proton (3 Gy) or iron-ion (50 cGy) radiation significantly increased the cataract prevalence and severity in CBA/J mice to levels above the baseline levels of age-induced cataract formation in this mouse strain. However, treatment with a soybean-derived protease inhibitor or an antioxidant formulation significantly reduced the prevalence and severity of the lens opacifications in the mice 2 years after being exposed to heavy ion radiation.

Similarly, the Center for Space Radiation Research (CSRR) will also investigate the use of gamma tocotrienol, an isoform of vitamin E, as a mitigator for space radiation-induced effects on the cardiovascular system. γ-tocotrienol is a potent inhibitor of the cholesterol biosynthesis pathway and has previously been show to act as a protective agent against vascular radiation

injury due to high doses of whole-body gamma-ray exposures (Berbée et al. 2009). The CSRR will use mice models to measure in vivo effects of γ-tocotrienol as a mitigator against cardiovascular effects of low-dose, high-LET radiation.

Given the chronic inflammatory response that may occur from the low dose and dose-rates experienced in space, the use of anti-inflammatory drugs for the prevention of radiation-induced effects is also a possibility (Wilson et al. [2011] used corticosteroid therapy to improve the conditions of radiation-induced pneumonitis and pneumonopathy), but it should be approached with caution. Consideration must be given to evidence pointing to immune dysregulation noted in microgravity (Crucian et al. 2015). The use of a long-term anti-inflammatory drug may synergize with the depressed immune function to significantly increase the risk of infection and even cardiovascular disease (Hsu and Katelaris 2009).

Another potential avenue for biological countermeasures is the use of statins, a class of pharmaceuticals currently used to slow or prevent cardiovascular disease. A recent study has utilized simvastatin to mitigate the effects of radiation-induced cardiovascular disease (Lenarczyk et al. 2015), albeit after very high doses of whole-body irradiation (10 Gy gamma-rays).

VII. GAPS

Current research is focused on closing the following knowledge gaps:

Degen - 1: How can tissue specific experimental models be developed for the major degenerative tissue risks, including cardiovascular, lens, and other tissue systems (e.g. immune, endocrine, respiratory and/or digestive) in order to estimate space radiation risks for degenerative diseases?

Degen - 2: What are the mechanisms of degenerative tissue changes in the cardiovascular, lens, digestive, endocrine, and other tissue systems? What surrogate endpoints do they suggest?

Degen - 3: What are the progression rates and latency periods for radiation-induced degenerative diseases, and how do progression rates depend on age, sex, radiation type, or other physiological or environmental factors?

Degen - 4: How does individual susceptibility, including hereditary predisposition, alter radiation-induced degenerative disease processes and risk estimates? Does individual susceptibility modify possible threshold doses for these processes in a significant way?

Degen - 5: What quantitative procedures or theoretical models are needed to extrapolate molecular, cellular, or animal results to predict degenerative tissue risks in astronauts? How can human epidemiology data best support these procedures or models?

Degen - 6: What are the most effective biomedical or dietary countermeasures to mitigate degenerative tissue risks? By what mechanisms are the countermeasures likely to work? Are these CMs additive, synergistic, or antagonistic to other Risks?

Degen - 7: Are there synergistic effects from other spaceflight factors (e.g. altered gravity (μ-gravity)**,** stress, altered circadian rhythms, altered immune function, or other) that modify space radiation-induced degenerative diseases in a clinically significant manner?

Degen - 8: Are there research approaches using simulated space radiation that can elucidate the potential confounding effects of tobacco use on space radiation circulatory disease risk estimates?

VIII. CONCLUSION

The association between ionizing radiation exposure and the long-term development of degenerative tissue effects such as heart disease, cataracts, immunological changes, and premature aging is well-established for moderate to high doses of low-LET radiation. The majority of this evidence is derived from epidemiological studies on the A-bomb survivors in Japan, radiotherapy patients, and occupationally exposed workers and is supported by laboratory studies using animal models (Blakely et al. 2010) and studies of cataracts in astronauts (Cucinotta et al. 2001; Chylack et al. 2009; 2011). The risks for these diseases from low dose-rate exposures and HZE nuclei are much more difficult to assess due to their multifactorial nature and long latency periods where animals must be observed; therefore, these risks remain debatable for ISS or short-term lunar missions but are more likely in long-term lunar or Mars missions. It also remains unclear whether low-dose (<0.5 Gy) exposures influence the same biological pathways that have been shown to be involved in disease progression following moderate- to high-dose radiation exposures (Little et al. 2008). NASA has established short-term dose limits to prevent clinically significant deterministic health effects, including performance degradation in flight. These dose limits and accumulated evidence will be reviewed by NCRP in the next five years to establish whether there are sharp thresholds or whether there may still be some risk at lower doses. In the near-term, cell or animal models of degenerative risks need to be developed and applied to determine the mechanisms of cardiovascular disease and other degenerative risks and to determine appropriate risk assessment data for models, including the existence of dose thresholds, role of individual susceptibility, relative biological effectiveness, and dose-rate dependencies for different space radiation ions at NASA Space Radiation Laboratory (NSRL) (Gaps Degen 1-4). Research to address the possible role of chronic inflammation and increased oxidative stress associated with space radiation exposure will also need to be conducted. As mission duration increases, there could be degenerative risks to other tissues related to digestive diseases and pulmonary changes that become a concern. A long-term goal will be to consider such possible changes in animal validation studies made at the extended-duration GCR facility under development at NSRL (anticipated completion in 2016). The possibility of synergistic risks with other flight factors must also be considered (Gap Degen-7).

Space radiation is a large obstacle to mission success, and the long-term health of astronauts and recent evidence suggests that the risk of degenerative diseases may be of much larger concern than previously thought. Therefore, the risk of degenerative diseases potentially presents a risk that is comparable to the already well-documented risks of mortality and morbidity from cancer. It will be essential to obtain additional information to address the risk knowledge gaps to successfully mitigate the degenerative risk to astronauts for lunar and Mars missions.

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XI. LIST OF ACRONYMS

A-bomb	Atomic bomb
BEIR	Biological Effects of Ionizing Radiation
BFO	Blood-Forming Organs
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CNS	Central Nervous System
CuZn	Copper-Zinc
CVD	Cardiovascular Disease
DDREF	Dose- and Dose-Rate Effectiveness Factor
DNA	Deoxyribonucleic Acid
DDR	DNA Damage Response
EBIS	Electron Beam Injector System
ERR	Excess Relative Risk
FDA	Food and Drug Administration
GCR	Galactic Cosmic Rays
Gy	Gray
HZE	High Charge and Energy
IARC	International Agency for Research on Cancer
ICRP	International Commission on Radiological Protection
IHD	Ischemic Heart Disease
ISS	International Space Station
LEO	Low Earth Orbit
LET	Linear Energy Transfer
LSAH	Lifetime Surveillance of Astronaut Health
LSS	Life Span Study
MeV	Megaelectron Volt
mGy	milliGray
mGy-Eq	milliGray-Equivalent
mSv	milliSievert
NAS	National Academy of Sciences
NCRP	National Council on Radiation Protection and Measurements
NRC	Nuclear Regulatory Commission
NSRL	NASA Space Radiation Laboratory
NS	Never Smoker
NW	Normal Weight
PEL	Permissible Exposure Limit
RBE	Relative Biological Effectiveness
REID	Risk of Exposure-Induced Death
ROS	Reactive Oxygen Species
SMR	Standard Mortality Ratios
SPE	Solar Particle Event

Sv   Sievert
USAF   U.S. Air Force