

A SUMMARY OF BEIR VII

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INTRODUCTION

A Phase I committee of the National Academies [slide 2] was asked to review all data since the BEIR V report¹ was published in 1990 and determine whether sufficient new information existed to warrant a Phase II BEIR VII study. In its 1998 report², the Phase I committee recommended that there was sufficient new data for a BEIR VII committee to update risk estimates for exposures to low doses of low-LET ionizing radiation. In particular, the report pointed out that the U.S. Department of Energy (DOE) had initiated a low-dose research program and a new dosimetry was being developed for the Radiation Effects Research Foundation (RERF). So the 7th committee in a series of the Biological Effects of Ionizing Radiation (BEIR VII) was formed³ and began a Phase II in 1999. BEIR VII held 11 meetings and received input from scientists and the public in 6 of those meetings. The final report⁴ was released June 19, 2005, more than 2 years later than initially anticipated, primarily due to a delay in the finalization of the new dosimetry for RERF (DS02). The government sponsors are listed in [slide 3] and the 18 committee members and their affiliations are listed in [slide 4] and [slide 5]. The study director was Dr. Rick Jostes [slide 6].

The charge to BEIR VII is summarized in [slide 7] and [slide 8]. The primary task was to develop the best possible risk estimate for human exposure to low-dose, low-LET ionizing radiation. To do that, the committee was charged to conduct a comprehensive review of all relevant biological, physical, and epidemiological data since BEIR V. “Low dose” was defined as 0-100 mSv or less than 0.1 mGy/min over months or a lifetime [slide 9]. There is data in humans in this dose range since more than 60% of the A-bomb survivors received doses of less than 100 mSv. The problem is illustrated in [slide 10] where the regulation levels and levels of interest extend so low that endpoints such as cancer and mutations are not necessarily measurable with statistical significance. One would like to know the shape of the response curve in the low-dose region since several theoretical models have been proposed—three of which are illustrated in [slide 11] (LNT, linear-quadratic, and threshold). Two other models are not illustrated here—hormesis and supralinearity. The goal of BEIR VII was not to disprove or

¹ National Research Council. *Health Effects of Exposure to Low Levels of Ionizing Radiations: Time for Reassessment?* National Academy Press, Washington, DC. 1998

² National Research Council. *Health Effects of Exposure to Low Levels of Ionizing Radiation: BEIR V.* National Academy Press, Washington, DC. 1990

³ BEIR VII Committee included: Richard R. Monson (Chair), James E. Cleaver (Vice-Chair), Herbert L. Abrams, Eula Bingham, Patricia A. Buffler, Elisabeth Cardis, Roger Cox, Scott Davis, William C. Dewey, Ethel S. Gilbert, Albrecht M. Kellerer, Daniel Krewski, Tomas R. Lindahl, Katherine E. Rowan, Krishnaswami Sankaranarayanan, Daniel W. Schafer, Leonard A. Stefanski (through May 2002), and Robert L. Ullrich. Consultants included John D. Boice, Jr., and Kiyohiko Mabuchi. Rick Jostes was study director. Donald A. Pierce served as research advisor.

⁴ National Research Council. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.* The National Academies Press, Washington, DC. 2005

prove existing theoretical models; rather, it was to develop a model that best fits the physical, biological, and epidemiological data. The charge to the committee was not to recommend policy decisions related to regulations or radiation protection standards or to conduct cost/benefit analyses.

FINDINGS

The committee found that there was considerable new data since BEIR V in 1990 as summarized in [slide 12]. RERF data had matured where there were now 10,000 cancer deaths compared to 6,000 that were available to BEIR V. RERF cancer incidence data was now available (13,000 cancers compared to 0 in BEIR V) and there was now evidence for non-cancer health outcomes (such as cardiovascular disease and stroke), albeit at higher exposure levels. Significant progress has been made related to estimating heritable effects of radiation as a result of advances in human molecular biology and it has become possible to project risks for more classes of genetic diseases such as those with more complex patterns of inheritance [slide 13]. Advances in cell and molecular biology have also contributed new information on mechanisms for responses to radiation-induced damage and to the close associations between DNA damage and cancer development.

BIOLOGICAL AND BIOCHEMICAL FINDINGS

Some of the major biological advances since 1990 are outlined in [slide 14]. In particular, genetic influences related to the gain of function of certain genes and the loss of function of repressor genes have added understanding to mechanisms of carcinogenesis. Molecular pathways for repair and misrepair of DNA damage such as double-strand breaks (DSBs) have been elucidated and relationships between DNA DSBs, chromosome aberrations, and cancer have been revealed, including implications for genomic instability and telomere involvement. Relationships between locally multiply damaged sites (LMDS) and dose response have been characterized, especially comparing differences between DNA damage resulting from ionizing radiation damage compared to damage resulting from naturally occurring oxidation processes. There is more data available related to dose and dose rate effectiveness factors (DDREF) and phenomena have been explored such as adaptive responses, bystander effects, and hyper radiation sensitivity (HRS). These new biological advances are discussed in considerable detail in BEIR VII, including some assessment as to whether or not they should expect to influence radiation-induced health effects at the low doses of interest in this study.

At low radiation exposures, the number of low-LET radiation traversals of cells should be proportional to the dose and the number of traversals can be very small at the lowest doses. Figure 1-8 from BEIR VII [slide 15] illustrates the primary and secondary electron tracks that result and the arrows in Panel A point to the clusters of ionization events that occur. The arrow in Panel B points to an ionization cluster near a DNA molecule and illustrates the possibility of LMDS. So DNA damage resulting from even a single ionizing radiation traversal of a cell is expected to be potentially different from the biochemical damage resulting from normal oxidative processes. A sensitive biomarker of DNA damage and repair (γ H2AX) has been

identified and used to study changes in chromatin conformation from DNA DSBs, excision repair, and DNA replication [slide 16]. Rothkamm and Löbrich⁵ have used this sensitive biomarker to examine the formation and repair of γ H2AX foci in normal human cells at very low doses of ionizing radiation. [slide 17] illustrates that DSBs are formed as a linear function of dose down at least to background radiation dose levels and repair of most of the DSBs is complete by 24 hours. Since the BEIR VII committee's assessments, Löbrich and coworkers⁶ have shown linearity for DSBs in patients in vivo after CT examinations at doses of 4.8-17.4 mGy as illustrated in [slide 18].

GENETIC EFFECTS FINDINGS

Radiation-induced heritable diseases have not been demonstrated in humans and studies based on 70,000 children of A-bomb survivors (RERF F1 studies) suggest that radiation doses less than 0.2 Gy are unlikely to double the risk of untoward pregnancies [slide 19]. Studies of nuclear workers' children have also not convincingly linked exposure to heritable diseases, ICRP 1999⁷ estimated genetic risk at about 0.2% per Gy (or 1 case in 500 live births per Gy), and UNSCEAR 2001⁸ estimated the “doubling dose” at about 1 Sv. Extensive data in mice, however, provide evidence for radiation-induced mutations in mammals. BEIR VII estimated a “doubling dose” using human data on spontaneous mutation rates of disease-causing genes and mouse data on induced mutation rates.

EPIDEMIOLOGICAL FINDINGS

For epidemiological evidence, the BEIR VII committee turned to four major groups of data—the RERF A-bomb survivor studies, the studies of occupational exposures (such as the 3-country pooled study of nuclear workers⁹ and the UK National Registry of Radiation Workers study¹⁰), studies of medically exposed populations, and studies of environmental exposures (such as the populations exposed at Chernobyl, Semipalatinsk, or the Ural Mountains) [slide 20]. In particular, the RERF [slide 21] data was used by BEIR VII because of the strengths of the A-bomb survivor studies summarized in [slide 22]; those strengths have been major reasons why

⁵ Rothkamm, K. and M. Löbrich. From the cover: evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. *Proc Natl Acad Sci USA* 100:5057-5062 (2003)

⁶ Löbrich, M., M. Rief, M. Kühne, M. Heckmann, J. Fleckenstein, C. Rübe, and M. Uder. *In vivo* formation and repair of DNA double-strand breaks after computed tomography examinations. *Proc Natl Acad Sci* 102:8984- (2005).

⁷ International Commission on Radiological Protection (ICRP). Risk estimation for multifactorial diseases. *Ann ICRP* 29:1-144.

⁸ United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). *Heredity Effects of Radiation: The 2002 Report to the General Assembly with Scientific Annex*. United Nations, New York (2001)

⁹ E. Cardis *et al.* Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res* 142:117-132 (1995)

¹⁰ C. Muirhead *et al.* Occupational radiation exposure and mortality: second analysis of the National Registry for Radiation Workers. *J Radiol Protection* 19:3-26 (1999). NOTE: The International Agency for Research on Cancer (IARC) 15-country pooled study of radiation workers—E. Cardis *et al.* Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *Brit. Med. J.* 331:77-82 (2005)—was not available in time for thorough assessment by the committee but is discussed in an appendix of the BEIR VII report.

the risk assessment work of RERF is often referred to as the “gold standard” for radiation epidemiology. Since BEIR V, RERF has developed an improved dosimetry system (DS02), has 15 additional years of mortality follow-up, has cancer incidence data for both Hiroshima and Nagasaki, and has identified an association between non-cancer mortality and radiation exposures [slide 23]. BEIR VII mortality data is based on 10,127 solid cancer deaths (versus 5,588 in BEIR V) and 293 leukemia deaths (versus 202 in BEIR V), and survivors exposed at age 10 or 30 have now entered their most cancer-prone years [slide 24]. One of the strengths of the RERF studies is the range of individual radiation doses reconstructed for the survivors. The distribution of doses is shown in [slide 25] and it should be noted that 62% of the survivors received exposures in the low-dose range of 5-100 mSv. RERF’s analyses by Preston and his coworkers¹¹ have shown that applying the new dosimetry (DS02), in which gamma doses increased slightly and neutron doses decreased in the range of interest, produced a slight decrease (~7%) in the previous RERF cancer risk estimates and had no appreciable impact on dose-response shape, gender risk differences, or age-time patterns. In 80,180 subjects with 2,083,988 person-years follow-up, 13,454 solid cancers have been recorded with an excess of 853 estimated for an attributable risk of 6.3%. The dose response for the solid cancer incidence is shown in [slide 26] with no evidence of nonlinearity for weighted colon doses of 0-2 Sv.

BEIR VII RISK MODEL

The RERF Life Span Study (LSS) cohort played a principle role in the BEIR VII development of cancer risk estimates. Risk models were developed primarily from cancer incidence data for the period 1958-1998 and based on DS02. Data from studies involving medical and occupational exposure were also evaluated. Models for estimating risks of breast and thyroid cancer were based on pooled analyses that included data on both the LSS cohort and medically exposed persons. To use models developed primarily from the LSS cohort for the estimation of lifetime risks for the U.S. population, BEIR VII makes assumptions regarding uncertainties such as the DDREF and the transport of risk estimates from the Japanese population. The committee’s preferred estimates of the lifetime attributable risk of incidence and mortality are presented in BEIR VII for all solid cancers and for leukemia, and for males and females, along with 95% subjective confidence limits.

BEIR VII Figure ES-1 [slide 27] shows estimated excess relative risks (ERRs) of solid cancer versus dose (averaged over sex and standardized to represent individuals exposed at age 30 who have attained age 60) for A-bomb survivors, with doses in each of 10 dose intervals at less than 2 Sv. For solid cancers, the linear-quadratic model did not offer a statistically significant improvement in fit, so the linear model was used. For leukemia, a linear-quadratic model (insert in Figure ES-1) was used since it fitted the data significantly better than the linear model. An example of how the data-based risk models can be used to evaluate the risk of radiation exposure is illustrated in [slide 28]. On average, assuming a sex and age distribution similar to that of the entire U.S. population, the BEIR VII lifetime risk model predicts that approximately 1 person in 100 would be expected to develop cancer (solid cancer or leukemia) from a dose of 100 mSv above background, while approximately 42 of the 100 individuals would be expected to develop

¹¹ Preston, D.L., D.A. Pierce, Y. Shimizu, H.M. Cullings, S. Fujita, S. Funamoto, and K. Kodama. Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat Res* 162:377-389 (2004)

solid cancer or leukemia from other causes. The BEIR VII report also presents example estimates for each of several specific cancer sites and other exposure scenarios.

RECOMMENDATIONS (RESEARCH NEEDS)

BEIR VII identified 12 research needs that are recommended for obtaining additional information that would improve understanding of radiation risk assessment. One of those in particular (number 8) [slide 29] and [slide 30] is very relevant to today's session (medical radiation studies). The committee encouraged future medical radiation studies that should rely on exposure information collected prospectively, including cohort and nested case-control epidemiological studies. Those studies should explore effects of modifiers of radiation risk and gene-radiation interactions to provide information on potential sensitive subpopulations. Epidemiological studies were encouraged of persons receiving CT, especially children, infants receiving cardiac catheterization, those receiving recurrent exposures, and premature babies receiving repeated x-rays. It was suggested that there should be consideration of organizing a worldwide consortia for CT, PET, and SPECT data.

CONCLUSIONS

CANCER RISKS

Radiation induction of cancer is clearly significant at doses greater than 100 mSv for adults exposed to A-bomb radiations in Hiroshima and Nagasaki [slide 31]. Cancer is significant at doses greater than 10 mSv for children exposed in utero. A linear-no-threshold (LNT) model represented a reasonable fit for solid cancers while a linear-quadratic model fit for leukemia. A Bayesian analysis produced estimates for a DDREF from 1.1-2.3; 1.5 was used in the risk analyses. The committee concluded that current scientific evidence is consistent with a LNT dose-response relationship between exposure to ionizing radiation and the development of solid cancers in humans. ERRs and Excess Absolute Risks (EARs) were estimated for incidence and mortality and with respect to sex, age, and attained age—and for 11 specific cancer sites. In general, the magnitude of estimated risks for total cancer mortality has not changed drastically from past reports as illustrated in [slide 32]. The BEIR VII ERR per Gy is compared to the estimates from the nuclear worker studies in [slide 33].

GENETIC RISKS

BEIR VII estimated a “doubling dose” of 1 Sv using human data on spontaneous mutation rates of disease-causing genes and mouse data on induced mutation rates [slide 34]. Those estimates are 3,000-4,700 cases per 10^6 F1 children per Gy or 0.4-0.6% of a baseline of 738,000 cases in 10^6 of which chronic diseases are estimated to be 650,000 per 10^6 . BEIR V had estimated 2,400-5,300 cases per 10^6 F1 per Gy or 5-14% of baseline, but BEIR V did not include chronic diseases in the baseline.

OTHER RISKS

BEIR VII concluded that radiation appears to increase the risk of diseases other than cancer, particularly cardiovascular disease, following high doses in therapeutic medicine and modest doses in A-bomb survivors [slide 35]. However, there is no direct evidence for increased risk at low doses and data are inadequate to quantify this risk if it exists.

THE BOTTOM LINE

BEIR VII judged that balance of evidence from epidemiologic, animal, and mechanistic studies tend to favor a simple, proportionate relationship at low doses between radiation dose and cancer risk [slide 36]. Uncertainties on this judgment are recognized and noted in the BEIR VII report. Current knowledge on adaptive responses, genomic instability, and bystander signaling among cells that may act to alter radiation cancer risk was judged to be insufficient to be incorporated in a meaningful way into the modeling of epidemiologic data at this time [slide 37]. The committee concluded that genetic variation in the population is a potentially important factor in the estimation of radiation cancer risk. But modeling studies suggest that strongly expressing mutations that predispose humans to cancer are too rare to distort appreciably population-based estimates of risk—they are a significant issue in some medical radiation settings. The BEIR VII report concludes [slide 38] that the current scientific evidence is consistent with a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans, but notes that at low doses that risk will be small. And while adverse health effects have not been observed in the children of exposed parents, extensive data in mice suggests that there is no reason to believe that humans would be immune to this sort of genetic harm, but the risk is also low.