NATIONAL RESEARCH COUNCIL
COMMISSION ON LIFE SCIENCES

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BOARD ON RADIATION EFFECTS RESEARCH

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January 21, 1998

Dr. Jerome Puskin
US Environmental Protection Agency
Radiation Studies Branch
401 M Street, SW Washington, DC 20460

Dear Dr. Puskin:

The Environmental Protection Agency Office of Radiation and Indoor Air asked the National Research Council to evaluate whether sufficient new data exist to warrant a reassessment of health risks reported in *Health Effects of Exposure to Low Levels of Ionizing Radiations (BEIR V)* in 1990. To respond to this request, the National Research Council assembled the Committee on Health Risks of Exposure to Low Levels of Ionizing Radiations. The work of the committee was conducted in what was called the BEIR VII phase 1 study. To assist the committee during its deliberations, various scientists were consulted for advice, and a workshop on the impact of biology on risk assessment was held in collaboration with the Department of Energy Office of Health and Environmental Research. The intent of the workshop was to address the implications of new understanding of the biologic basis of radiation injury and carcinogenesis for risk assessment. Through this letter, we are providing you in advance a summary report of the committee's recommendations. This is being done in order to enable you to begin to move forward as soon as possible in making a decision on the appropriateness of undertaking additional study of the subject.

The following is a synopsis of the conclusions of the BEIR VII phase 1 study:

In the committee's judgment, information that has become available since publication of the 1990 *Health Effects of Exposure to Low Levels of Ionizing Radiations (BEIR V)* makes this an opportune time to proceed with BEIR VII phase 2–a comprehensive reanalysis of health risks associated with low levels of ionizing radiations. Such a study should begin as soon as possible and is expected to take about 36 months to complete.

The committee based that judgment on the following considerations:

- Substantial new epidemiologic evidence has accumulated since the 1990 BEIR V report was published. The present committee's phase 1 report will cite 39 new epidemiologic studies that fall into this category (see Table 1). Additional studies that have a direct bearing on the subject should become available in the next 3 years, the estimated period required to complete the phase 2 study.
- Some of the new epidemiologic data are on subjects on which information had been sparse, such as cancer mortality in those exposed to whole-body irradiation in childhood.
- Studies of carcinogenesis completed since publication of the last BEIR report have focused on mechanisms and the cellular and molecular events that are involved in the neoplastic process. The understanding of molecular events involved in carcinogenesis has increased significantly. Mechanisms that might be involved in radiation carcinogenesis have been identified. Further knowledge of these mechanisms that should become available in the next 3 years might affect estimation of the radiation-response curve at low doses.
- Over the next few years, investigators will be applying two closely linked approaches using animal models of carcinogenesis. These will likely contribute to a

better understanding of mechanisms of radiation-induced cancer. In the first of these two approaches, genetically engineered mice having alterations in specific genes will be used to determine the influence of these genes on the susceptibility of the mice to radiation-induced cancer. In the second approach, studies will be conducted of the inherent differences in susceptibility to radiation-induced cancer among different mouse strains, the objective being to identify the genes involved in controlling susceptibility. Researchers responsible for this new generation of animal studies are taking advantage of the current rapid developments in molecular genetics. Progress on both approaches should be substantial over the next few years. Significant results of relevance to risk estimation are expected to be available for the proposed BEIR VII phase 2 study.

- Evidence regarding specific biologic events that can affect the shape of the dose-response curve at low doses is also accumulating. Information on such phenomena as DNA repair, signal transduction, chromosomal instability, and adaptation, although preliminary, might eventually affect risk analyses of low-dose and low-dose-rate exposures.

The committee recommends that the group responsible for the proposed phase 2 study

- Include a comprehensive review of all relevant epidemiologic data related to low-LET (low linear energy transfer), i.e. sparsely ionizing, radiation.
- Define and establish principles on which quantitative analyses can be based, including requirements for epidemiologic data and cohort characteristics. In this respect, the group should consider biologic factors (such as the dose and dose-rate effectiveness factor, relative biologic effectiveness, genomic instability, and adaptive responses) and appropriate models (favoring simple as opposed to complex models) to develop etiologic models, estimate population detriment, and attribute causation in specific cases.

- Assess the current status and relevance to risk models of biologic data and models of carcinogenesis. This should include a critical assessment of all data that might affect the shape of the response curve at low doses, in particular, evidence of thresholds or the lack thereof in dose-response relationships and the influence of adaptive responses and radiation hormesis.
- Consider potential target cells and problems that might exist in determining dose to the target cell.
- Consider any recent evidence regarding genetic effects not related to cancer. Any such data, even if obtained from high radiation exposures or at high dose rates, should be considered.

With respect to modeling, the committee recommends that the group responsible for the proposed phase 2 study

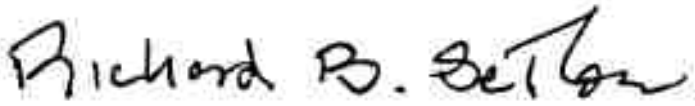
- Develop appropriate risk models for major cancer types and other outcomes, including benign disease and genetic effects. Specifically, the responsible group should develop models appropriate for probability-of-causation tables and should consider the fitting of purely empirical models to original data from studies or combined studies, the fitting of purely empirical models with meta-analytic techniques, and the fitting of semiempirical biology-based models to epidemiologic data.
- Provide examples of specific risk calculations based on the models and explain the appropriate use of the risk models.
- Describe and define the limitations and uncertainties of the risk models and their results. The group conducting the proposed phase 2 study should be directed to develop

best-risk estimates as opposed to developing conservative models for purposes of radiation protection.
- Discuss the role and effect of modifying factors, including host (such as individual susceptibility and variability, age, and sex), environment, and lifestyle.
- Identify critical gaps in knowledge that should be filled by future research.

To accomplish the above charge, the membership of the group responsible for the proposed BEIR VII phase 2 study will require expertise in epidemiology, biostatistics, radiation physics and dosimetry, molecular biology, risk assessment, cancer modeling, animal and cellular radiation biology, somatic cell genetics, cell-cycle regulation and apoptosis, and ionizing radiation-induced DNA damage and its repair. The committee recommends that the experts chosen have adequate resources and access to data for the computing, statistical analyses, and modeling required to complete the study.

We trust that this synopsis of the recommendations of the committee will meet your current needs. The complete report of the committee will be published and provided to your office when it has received the committee's final approval and has been subjected to the National Research Council peer-review process.

Sincerely,



Richard B. Setlow, Ph.D.
Chairman, Committee on Health Effects of Exposure to Low
Levels of Ionizing Radiations (BEIR VII Phase 1)

Table 1 is a summary of the more important epidemiologic data that have been published since the 1990 publication of the BEIR V report. Included are studies that are expected to provide new and useful data during the 3-year term of the proposed BEIR VII, Phase II, study. Although not exhaustive, the list should serve as a guide to some of the pertinent new and upcoming epidemiologic data on the subject.

Table 1. Summary of Epidemiologic Studies of Low-LET Ionizing Radiation and Cancer, 1990

STUDY	REFERENCE	TYPE OF STUDY	SERIES	SEX	NO. IN STUDY	YEARS OF FOLLOW-UP	CANCER SITES REPORTED
Ankylosing spondylitis patients	Weiss et al. Cancer mortality following x-ray treatment for ankylosing spondylitis. Int J Cancer 1994;59:327-338.	Cohort	Mortality	Male and Female	15,577	1935-1992	All cancer and multiple cancer sites
	Weiss et al. Leukemia mortality after x-ray treatment for ankylosing spondylitis. Rad Res 1995;142:1-11.	Cohort	Mortality	Male and Female	14,767	1935-1992	Leukemia
Atomic-bomb survivors	Preston et al. Cancer incidence in atomic-bomb survivors. Part III: leukemia, lymphoma, and multiple myeloma 1950-1987. Rad Res 1994;137:568-597 (2 suppl).	Cohort	Incidence	Male and Female	93,696	1950-1987	Leukemia, lymphoma, multiple myeloma
	Thompson et al. Cancer incidence in atomic-bomb survivors. Part II: solid tumors, 1958-1987. Rad Res 1994;137:517-567.	Cohort	Incidence	Male and Female	79,972	1958-1987	Multiple cancer sites (solid tumors)
	Ron et al. Incidence of benign gastrointestinal tumors among atomic-bomb survivors. Amer J Epi 1995;142:68-75.	Cohort	Incidence	Male and Female	80,311	1958-1989	Benign tumors of stomach, colon, and rectum
	Pierce et al. Studies of the mortality of atomic bomb survivors. Report 12, Part 1. Cancer:1950-1990. Rad Res 1996;146:1-27.	Cohort	Mortality	Male and Female	86,572	1950-1990	Non leukemias, leukemia, and multiple cancer sites
Atomic-bomb survivors (case-control study)	Land et al. A case control interview study of breast cancer among Japanese A-bomb survivors. I. Main effects. Cancer Causes and Control 1994;5:157-169.	Case-control		Female	Cases: 196 Controls: 566	1955-1981	Breast cancer
	Land et al. A case-control interview study of breast cancer among Japanese A-bomb survivors. II. Interactions with radiation dose. Cancer Causes and Control 1994;5:167-176.						
Atomic-bomb survivors (in utero cohorts)	Delongchamp et al. Cancer mortality among atomic-bomb survivors exposed in utero or as young children, October 1950-May 1992. Rad Res 1997;147:385-395.	Cohort	Mortality	Male and Female	17,601	1950-1992	Non leukemias, leukemia, and multiple cancer sites

STUDY	REFERENCE	TYPE OF STUDY	SERIES	SEX	NO. IN STUDY	YEARS OF FOLLOW-UP	CANCER SITES REPORTED
Canadian fluoroscopy	Howe. Lung Cancer Mortality between 1950 and 1987 Following Exposure to fractionated moderate dose rate ionizing radiation in the Canadian Fluoroscopy Study and a comparison with lung cancer mortality in the Atomic Bomb Survivors Study. Radiat Res 1995; 142:295-304.	Cohort	Mortality	Male and Female	64,172	1950-1987	Lung cancer
	Howe and McLaughlin. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate dose rate ionizing radiation in the Canadian fluoroscopy study and a comparison with breast cancer mortality in the Atomic bomb survivors study. Rad Res 1996;145:694-707.	Cohort	Mortality	Female	31,917	1950-1987	Breast cancer
Cervical cancer patients	Kleinerman et al. Second primary cancer after treatment for cervical cancer. Cancer 1995;76:442-452.	Cohort	Incidence	Female	86,193	1935-1990	Multiple cancer sites
Contralateral breast (Denmark)	Storm et al. Adjuvant radiotherapy and risk of contralateral breast cancer. J Nat Cancer Inst 1992;84:1245-1250.	Case-control in a cohort		Female	Cohort: 56,540 Cases: 691 Controls: 691	1943-1986	Breast cancer
Contralateral breast (U.S.A.)	Boice et al. Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992;326:781-785.	Case control within a cohort		Female	Cohort: 4,109 Cases: 655 Controls: 1,189	1935-1987	Breast cancer
Fallout from Nevada Test Site	Kerber et al. A cohort study of thyroid disease in relation to fallout from nuclear weapons testing. JAMA 1993;270:2076-2082.	Cohort	Incidence	Male and Female	2,473	1965-1986	Thyroid cancer and other thyroid disease
	Simon et al. The Utah leukemia case-control study: dosimetry methodology and results. Hlth Phys 1995;6814:460-471.	Case-Control		Male and Female	Cases: 1,177 Controls: 5,330	1952-1981	Leukemia
Massachusetts fluoroscopy	Davis et al. Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. Cancer Res 1989;49:6130-6136.	Cohort	Mortality	Male and Female	13,385	1929-1986	Multiple cancer sites
	Boice et al. Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. Rad Res 1991;125:214-222.	Cohort	Incidence	Female	4,940	1925-1986	Breast cancer

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Multiple diagnostic x-rays of scoliosis patients	Hoffman et al. Breast cancer in women with scoliosis exposed to multiple diagnostic x-rays. J Natl Cancer Inst 1989;81:1307-1312.	Cohort	Incidence	Female	1,030	1935-1986	Breast cancer
Nuclear industry workers (combined analysis)	Cardis et al. Direct estimates of cancer mortality due to low doses of radiation: an international study. Lancet 1994;344:1039-1043.	Cohort	Mortality	Male and Female	95,673	1943-1988	Multiple cancer sites
	Cardis et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. Rad Res 1995;142:117-132.	Cohort	Mortality	Male and Female	95,673	1943-1988	Solid tumors and leukemia
Nuclear workers at Mayak Production Association	Koshurnikova et al. NCRP Proceedings, 1996, 113:T2, 113-122.	Cohort	Mortality	Male and Female	18,879	1948-1993	Lung cancer and leukemia
Pelvic radiotherapy for benign gynecologic disease	Inskip et al. Leukemia, lymphoma and multiple myeloma after pelvic radiotherapy for benign disease. Rad Res 1993;135:108-124.	Cohort	Mortality	Female	12,955	1929-1985	Multiple hematopoietic cancers
Pooled analysis of external radiation and thyroid cancer	Ron et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Rad Res 1996;141:259-277.	Cohort Case-control	Incidence	Male and Female	120,000	1926-1990	Thyroid cancer
Radiation treatment for benign head and neck conditions (benign thyroid tumors)	Wong et al. Benign thyroid tumors: general risk factors and their effects on radiation risk estimation. Amer J Epi 1996;144:728-733.	Cohort	Incidence	Male and Female	544	1939-1991	Benign thyroid nodules
Radiation treatment for benign head and neck conditions (thyroid cancer and thyroid nodules)	Schneider et al. Dose-response relationships for radiation-induced thyroid cancer and thyroid nodules: evidence for the prolonged effects of radiation on the thyroid. J Clin Endocrinol Metab 1993;77:362-269.	Cohort	Incidence	Male and Female	4,296	1939-1990	Thyroid cancer and nodules
Radiation treatment for breast cancer	Curtis et al. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. N Engl J Med 1992;326:1745-1751.	Case-control within cohort		Female	Cohort: 82,700 Cases: 90 Controls: 264	1973-1985	Leukemia
Radiation treatment for peptic ulcer	Griem et al. Cancer following radiotherapy for peptic ulcer. J Natl Cancer Inst 1994;86:842-849.	Cohort	Mortality	Male and Female	3,609	1937-1985	Multiple cancer sites

STUDY	REFERENCE	TYPE OF STUDY	SERIES	SEX	NO. IN STUDY	YEARS OF FOLLOW -UP	CANCER SITES REPORTED
Radiotherapy treatment for Hodgkin's Disease (breast cancer)	Hancock et al. Breast cancer after treatment of Hodgkin's Disease. J Natl Cancer Inst 1993;85:25-31.	Cohort	Incidence and Mortality	Female	885	1961-1990	Breast cancer
Radiotherapy treatment for Hodgkin's Disease (gastro intestinal cancer)	Birdwell et al. Gastrointestinal cancer after treatment of Hodgkin's Disease. Int J Rad Oncol Biol Phys 1997;37:67-73.	Cohort	Incidence and Mortality	Male and Female	2,441	1961-1993	Multiple cancer sites (gastro-intestinal only)
Radiotherapy treatment for metropathia hemorrhagic anemia	Darby et al. Mortality in a cohort of women given x-ray therapy for metropathia hemorrhagica. Int J Cancer 1994;56:793-801.	Cohort	Mortality	Female	2,067	1940-1991	Multiple cancer sites
Radiotherapy treatment for pituitary adenoma	Brada et al. Risk of second brain tumor after conservative surgery and radiotherapy for pituitary adenoma. Br Med J 1992;304:1343-1346.	Cohort	Incidence	Male and Female	334	1962-1986	Multiple cancer sites (solid tumors only)
Radiotherapy treatment for skin, hemangioma in childhood	Furst et al. Tumors after radiotherapy for skin hemangioma in childhood. Act Oncologica 1990; 29:557-562.	Case-control within a cohort		Male and Female	Cohort: 14,647 Cases: 94 Controls: 359	1920-1986	Multiple cancer sites (solid tumors)
Radiotherapy treatment for thymus enlargement	Shore et al. Overview of radiation induced skin cancer in humans. Int J Radiat Biol 1990;57:809-827.	Cohort	Incidence	Male and Female	7,450	1953-1989	Skin cancer
Radiotherapy treatment for uterine bleeding	Inskip et al. Cancer mortality following radium treatment for uterine bleeding. Rad Res 1990;123:331-344.	Cohort	Mortality	Female	4,153	1925-1984	Multiple cancer sites
Tinea capitis (Israel)	Ron et al. Thyroid neoplasia following low-dose radiation in childhood. Rad Res 1989;120:516-531.	Cohort	Incidence	Male and Female	10,834	1950-1986	Thyroid cancer and other thyroid disease
	Ron et al. Radiation induced skin carcinomas of the head and neck. Rad Res 1991;125:318-329.	Cohort	Incidence	Male and Female	27,060	1950-1980	Melanoma, other skin cancer and benign skin tumors
Women treated for infertility	Ron et al. Mortality following radiation treatment for infertility of hormonal origin or amenorrhea. Int J Cancer 1994; 23:1165-1173	Cohort	Mortality	Female	816	1925-1991	Multiple cancer sites

STUDY	REFERENCE	DESCRIPTION
In utero exposure	Doll and Wakeford. Risk of childhood cancer from fetal irradiation, Brit J Radiol 1997; 70:130-139	A review of case-control and cohort studies of childhood cancers.