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REPLY TO ATTN OF: EH-62:Lynn Judson:301-903-1797

SUBJECT: DEPARTMENT OF ENERGY (DOE) HEALTH BULLETIN 95-02

TO: DOE Public Reading Rooms

Attached is the second in a series of Health Bulletins published by the Office of Epidemiologic Studies in 1995. It summarizes a recent epidemiologic study that may be of interest to workers and management in DOE field operations, as well as to members of the public. Also enclosed is a copy, provided by The Lancet Ltd., of the original article on which this Health Bulletin is based. Please place these enclosures in your DOE public reading room.

This new issue, Health Bulletin 95-02, is entitled "Does Exposure to Low Doses of Radiation Over Long Periods of Time Cause Cancer?" It summarizes a study by the International Agency for Research on Cancer on cancer risk in nuclear industry workers receiving low doses of external ionizing radiation over long periods of time. The article on which it was based, entitled "Direct estimates of cancer mortality due to low doses of ionising radiation: an international study," appeared in the October 15, 1994, issue of The Lancet, Volume 344, pp. 1039-1043.

This is considered a landmark study because of the large size of the population studied (nearly 96,000 workers) and the fact that it is international in scope. The authors claim that it provides the most precise estimates that are available to date of cancer risk due to low-dose radiation exposure.

Please keep this article as a reference document in your public reading room for as long as possible. Thereafter, please transfer it to a DOE Library to be kept indefinitely as a reference material. As additional Health Bulletins are prepared, we will provide a copy of the Bulletin and the original article on which it was based. If you have any questions or comments, please contact Lynn Judson, Technical Information Specialist, at 301-903-1797.

Thank you for your assistance.

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OFFICE OF EPIDEMIOLOGIC STUDIES

HEALTH BULLETIN

U.S. DEPARTMENT OF ENERGY WASHINGTON, D.C.
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Does Exposure to Low Doses of Radiation Over Long Periods of Time Cause Cancer?

Studies of atom bomb survivors and patients treated with high doses of radiation over short periods of time clearly show increases in rates of death from leukemia and other cancers. Until recently, it has been unclear whether much lower doses of ionizing radiation received over longer periods, i.e., 10 to 20 years, cause similar increases in cancer death rates.

The first estimates of cancer risk resulting from exposure to low doses of radiation came from studies of people receiving high doses over very short periods of time. Cancer risk estimates calculated directly from studies on nuclear industry workers who received lower doses over a longer period of time began to be available in the 1970's and 1980's, but risk estimates varied widely between studies.

The largest study to date on cancer risks that are linked to low doses of radiation over long periods of time was published in the October 15, 1994, issue of The Lancet, entitled "Direct estimates of cancer mortality due to low doses of ionising radiation: an international study." This study by the International Agency for Research on Cancer (IARC) combines and analyzes data gathered on 95,673 nuclear industry workers from three countries.

The IARC study combines information on cancer death rates for seven large groups of nuclear industry workers from Hanford, Rocky Flats, and Oak Ridge National Laboratory in the United States; Sellafield, Atomic Energy Authority, and Atomic Weapons Establishment in the United Kingdom; and Atomic Energy of Canada, Ltd., in Canada. Most nuclear industry workers receive relatively low total doses of radiation (less than 50 mSv), whereas the high doses received by atom bomb survivors and patients treated with radiation typically exceed 1,000 mSv.

The purpose of this study was to estimate the risk of leukemia and other cancers among nuclear industry workers exposed to low doses of ionizing radiation. Workers who were monitored for external radiation exposure were divided into dose categories according to the amount of total radiation received during the time they worked in the nuclear industry. Eleven percent of workers included in this study received total recorded doses of 0 mSv (no measurable exposure), nearly 80 percent total doses of less than 50 mSv. Cancer death rates for workers in different dose categories were then compared.

One of the strengths of the study was that the large number of workers included in the analysis allowed for more statistically precise estimates of the cancer risks than was possible from previous smaller studies.

This study found that the risk of all leukemias, excluding chronic lymphocytic leukemia (CLL) a type of leukemia thought to be unrelated to radiation, increased in a linear manner with greater lifetime radiation dose. This risk was 22 percent higher for nuclear industry workers exposed to a total lifetime dose of 100 mSv or greater (less than 1 percent of workers) than for workers who received no measurable dose of external ionizing radiation. The risk of all leukemias, excluding CLL, increased 2.2 percent for each additional 10 mSv of total dose. The risk of all other cancers combined, however, was no greater among exposed workers than among unexposed workers. As in all studies of human populations, the study must be viewed cautiously. For example, errors in the measurement of radiation dose or cause of death could affect the estimates of cancer risk.

According to the authors of this study, the estimates of cancer risk obtained from this study are consistent with earlier estimates derived from studies of atom bomb survivors and patients receiving high doses of radiation in a short period. Therefore, the authors indicated that their results are consistent with the current recommendations of the International Commission on Radiation Protection, which primarily are based on these earlier high-dose studies.

Two additional papers that explain the methods and results of this study in greater detail will be published in the near future, and Health Bulletins on these reports will be distributed as soon as the papers are available.

DOE, in cooperation with the National Institute for Occupational Safety and Health, will continue to evaluate the health of its current and former employees and to make these findings available to the public. For a copy of this article from The Lancet, check with your local DOE reading room or contact the Office of Epidemiologic Studies at (301) 903-5328. For extra copies of this Health Bulletin, please contact the Office of Epidemiologic Studies at (301) 903-5328.

This Health Bulletin is one in a series of routine publications issued by the Office of Health Studies to share data from health studies throughout the DOE complex. The authors' conclusions do not necessarily reflect those of the Department. For more information contact: Lynn E. Judson, Office of Epidemiologic Studies, U.S. Department of Energy, Washington, D.C. 20585; Telephone (301) 903-1797.

Articles

Direct estimates of cancer mortality due to low doses of ionising radiation: an international study

*IARC Study Group on Cancer Risk among Nuclear Industry Workers**

Summary

When setting standards for protection against ionising radiation it has been usual to extrapolate from experience with high-dose short-term exposure—studies based on atom bomb survivors and patients exposed to radiation therapeutically. Those who work in the nuclear industry are exposed to low-level predominantly γ radiation for longer periods, and provide an alternative direct source of information. We have combined mortality data from seven cohort studies on nearly 96 000 nuclear industry workers monitored for external radiation in Canada, UK, and USA to assess directly the carcinogenic effects of protracted low-dose exposure to ionising radiation.

The excess relative risk for death from leukaemia, excluding chronic lymphocytic leukaemia, was 2·2 per Sv (90% CI 0·1 to 5·7). This estimate is intermediate between the linear estimate of 3·7 per Sv and the linear-quadratic estimate (as used in recent leukaemia risk assessments) of 1·4 per Sv derived from Japanese atomic bomb survivors' data. The excess relative risk for death from all cancers, excluding leukaemia, was −0·07 per Sv (90% CI −0·4 to 0·3). This estimate is consistent with a range of risks varying from negative to nearly twice those estimated from atomic bomb survivors (0·18 per Sv).

These are the most precise direct estimates so far made of carcinogenic risk after protracted exposure to low-dose ionising radiation. They provide little evidence that the estimates that form the basis of current radiation protection recommendations are appreciably in error.

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See Commentary page 1037

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Introduction

Current protection standards for environmental and occupational exposures to ionising radiation are mainly based on estimates of radiation-induced cancer risk derived from studies of atomic bomb survivors in Hiroshima and Nagasaki, Japan, and of patients irradiated for therapeutic purposes.[1-4] The use of data from populations who have received comparatively high radiation doses over short periods to predict carcinogenic effects in populations receiving generally lower doses over longer time involves uncertain extrapolations.[1,2,5,6]

A direct assessment of the carcinogenic effects of protracted, generally low-level radiation exposure can be made from studies of cancer risk among workers in the nuclear industry. Estimates of radiation-induced risk from individual studies of such workers in the USA, UK, and Canada have been published;[7-20] combined analyses have also been carried out in the USA and the UK.[21-23] Considered individually, estimates of risk from these studies were consistent with a wide range of possibilities—from negative effects to risks an order of magnitude greater than those on which the current radiation protection recommendations have been based.

Recognising that these studies collectively provided most of the available information for direct quantification of the carcinogenic effect of protracted low-dose exposure to ionising radiation, the various study investigators in 1988 agreed in principle on a combined analysis of original data from studies published at that time. A major objective was to provide more precise risk estimates for comparison with estimates derived through extrapolation from studies of atomic bomb survivors and other high-dose populations. Because the definitions of study populations and the analytical strategies used differed, formal combined analyses of original data was preferred to meta-analysis of published results. This allowed the application of similar methodology to all studies and permitted a better understanding of differences and similarities between study populations. The International Agency for Research on Cancer (IARC) Study Group on Cancer Risk among Nuclear Industry Workers was set up to facilitate these analyses. This paper presents risk estimates for all cancers excluding leukaemia and for leukaemia excluding chronic lymphocytic leukaemia (CLL, which is not thought to be induced by radiation),[1] the main causes of death for which risk estimates have been provided by national and international committees, and compares these with corresponding estimates from high-dose studies. A full report of the more detailed analyses, including those for specific cancer sites, will be published elsewhere.

Materials and methods

Seven cohorts of nuclear industry workers in three countries were included in the combined analyses (table 1). They were selected on the basis of availability of adequate dosimetric, demographic, follow-up, and mortality data. In all cohorts, most workers had potential for external occupational exposure to ionising radiation and were monitored by personal dosimeters. Some workers were also at risk of internal exposure through the ingestion or inhalation of radioactive material but information on such exposures has not been recorded in a standard way and is not included in the analyses. Table 1 indicates the types of activity carried out. Additional details are described in the original publications.[8-16,18-20]

For the combined analyses, the study population was restricted to workers employed in a study facility for at least six months and who had been monitored for external radiation exposure. To restrict the study to those who had been exposed at a relatively low dose-rate, 19 workers with at least one annual dose of 250 mSv or greater were excluded.

Although radiation exposure in the nuclear industry has been measured more accurately than exposure to most other occupational carcinogens, the exposure measurements were made to monitor adherence to radiation protection guidelines and not for epidemiological purposes. For the combined analyses, it was important to evaluate the comparability of dose estimates across facilities and at different times. It was also important to evaluate the extent to which recorded doses approximated doses to specific organs because risk estimates from high-dose studies have been based on organ doses.

An international committee of dosimetry experts reviewed historical dosimetric practices in and across the various facilities. Their detailed results and conclusions will be reported elsewhere. They concluded that most of the dose to workers was external, from higher energy (100 keV to 2·5 MeV) X and γ rays, and that this, as well as the dose from tritium, had been measured reasonably comparably in different facilities and at different times. Relative uncertainties in the recorded dose were, however, judged to be greater for measurements made near the detection threshold of the dosimetry system in use and in the earlier years of the industry. There was little evidence of any practice that would, overall, cause significant bias in recorded doses for workers with predominant higher energy photon exposure. At low doses, when there was potential for bias in the recording of subthreshold doses and missing exposure measurements, re-estimations of dose were made where possible.[24,25] The bias in using recorded whole body doses as estimates of organ doses was considered to be small, the main exception being bone marrow where recorded dose probably overestimated dose by about 20%. A small proportion of workers received a substantial portion of their dose from exposure to radiation of lower energies, from neutrons, or from internally deposited radionuclides. It generally has not been possible to determine whether recorded dose estimates from these radiations were comparable over time and across facilities.

Analyses were based on a constant linear relative risk model, in which the relative risk was assumed to be of the form $1+\beta Z$, where Z is the cumulative dose in Sv, and β is the excess relative risk (ERR) per Sv. This model has been used in analyses of atomic bomb survivors data[26] and for the derivation of current radiation risk estimates by international and national committees.[1-3] Estimates of ERR were adjusted by stratification for age, sex, calendar period, facility, and, with the exception of AECL, for socioeconomic status. To allow for a latent period between exposure and disease, doses were lagged by 2 years for leukaemia and by 10 for other cancers. These choices of latent period are the same as used in recent risk assessments.[1]

To permit comparison between the ERRs estimated for the nuclear industry workers and from the atomic bomb survivors cohort,[26] follow up data to 1985 from the latter cohort were analysed at IARC in a similar way. The study population for these analyses was restricted to men exposed between the ages of 20 and 60 years, the subgroup most comparable to the population of nuclear workers. Bone marrow doses were used to obtain the risk estimate for leukaemia and stomach doses for the risk estimate for all other cancers. A quality factor of 20 was assumed for neutrons and the population was further restricted to those who had bone marrow dose equivalents below 4 Sv.[1] A linear-quadratic model was also fitted to the data on leukaemia since it is the preferred model for prescribing radiation-induced leukaemia mortality in analyses of the atomic bomb survivors data.[1,24]

The risk estimates for nuclear workers were also compared with the constant linear ERR estimates for men exposed at the age of 20 or above derived from atomic bomb survivors data by the UN Scientific Committee on the Effects of Atomic Radiation (UNSCEAR).[2] These estimates, reduced by a dose and dose-rate effectiveness factor of two, form one of the bases for the current recommendations of the International Commission for Radiological Protection (ICRP).[4] Comparisons with the estimates derived by the US National Academy of Sciences BEIR committee,[1] which incorporated dependencies of risk on age at exposure, time since exposure, and sex, were also carried out; detailed results and discussion of the effect of time-related factors on cancer risk will be reported elsewhere.

Facility*	Ref	Study period	Types of activity†
United States			
Hanford	15, 19, 21, 22	1944–86	Manufacture, power generation, chemical separation, purification of plutonium
Rocky Flats	12, 21, 22	1951–79	Plutonium fabrication
ORNL	9, 16, 21, 22	1943–84	Nuclear research and development plant, reactors
United Kingdom			
Sellafield	10, 23	1947–88	Nuclear reactors, replacement, reprocessing, waste treatment, fast reactor fuel fabrication
AEA	8, 18, 23	1946–88	Research and development reactor processing
AWE	13, 23	1951–88	Weapons research
Canada			
AECL	11, 20	1956–85	Nuclear reactor, research and related technologies

*ORNL=Oak Ridge National Laboratory; AEA=Atomic Energy Authority (3 facilities: Harwell [with London and Culham], Dounreay, and Winfrith); AWE=Atomic Weapons Establishment; AECL=Atomic Energy of Canada Ltd. †During study periods.

Table 1: **Facilities included in combined analyses**

Results

The main characteristics of the study population are presented in table 2. Of the 95 673 workers, 16·5% were known to have died during the study periods. The distribution of doses was very skewed (figure 1); 11% had a cumulative dose of 0; close to 60% had doses below 10 mSv and 80% below 50 mSv; less than 1% and 0·1%, respectively, had doses greater than 500 mSv and 1 Sv. By contrast, 9% of atomic bomb survivors received doses greater than 500 mSv and 4% received doses above 1 Sv. For comparison, the current ICRP recommendations are to limit occupational doses to 100 mSv over 5 years (not to exceed 50 mSv in 1 year) and doses to the public to 1 mSv in 1 year.[4] It is noted that lagging doses by 2 and 10 years reduced the collective dose of 3843 Sv to 3805 and 3057 Sv, respectively.

In the total study population there were 15 825 deaths, of which 3830 were from cancers other than leukaemia and 119 were from leukaemia excluding CLL. Most (85·4%) of the study subjects were men and they had received 98% of the total collective dose. Of the 119 leukaemia deaths, 6 occurred among workers with a cumulative radiation dose of 400 mSv or above, a dose-

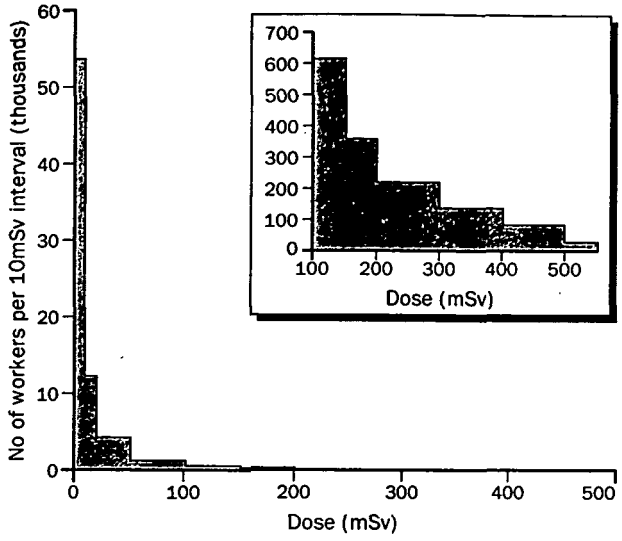

Figure: **Distribution of cumulative radiation doses among workers included in analyses**
For doses of 100 mSv or more numbers shown more clearly in insert.

Study population	All cancers excluding leukaemia	Leukaemia excluding CLL
Nuclear workers*†	−0·07 (−0·39 to 0·30)	2·18 (0·1 to 5·7)
Atomic bomb survivors		
Linear‡	0·18 (0·05 to 0·34)	3·67 (2·0 to 6·5)
Linear-quadratic‡§	NA	1·42 (<0 to 6·5)
UNSCEAR	0·24 (NA)	3·70 (NA)

*Estimates of organ dose and recorded whole body dose were used, respectively, in analyses of data from atomic bomb survivors and nuclear industry workers (see Methods).
†Estimates were adjusted for age, sex, calendar period, facility, and, with exception of AECL, for socioeconomic status.
‡Analyses done at IARC; restricted to men exposed between the ages of 20 and 60 years; estimates are adjusted for age, city, and calendar period.
§Preferred model for describing leukaemia mortality in recent analyses of atomic bomb survivors data[1,24]
NA=not applicable or not available.

Table 3: **ERR estimates per Sv (and 90% CI) for all cancers, excluding leukaemia, and for leukaemia excluding CLL, for nuclear workers, male atomic bomb survivors, and published estimates of risk from high-dose studies**

range comparable to the lowest dose-range in which leukaemia mortality excesses were demonstrated among the atomic bomb survivor population.

The ERR for leukaemia (excluding CLL) in the nuclear industry workers was 2·2 per Sv with 90% CI 0·1 to 5·7; the excess was significant (one-sided p=0·05). For mortality from all cancers excluding leukaemia, the ERR was −0·07 per Sv with 90% CI −0·39 to 0·30 (table 3). The estimates for leukaemia excluding CLL and all cancers excluding leukaemia correspond, respectively, to relative risks of 1·22 and 0·99 for a dose of 100 mSv versus zero dose. When, as recommended by the dosimetry committee, we applied a factor of 1·2 to correct for the probable overestimation of bone marrow dose, the resulting ERR for leukaemia became 2·6 per Sv (90% CI 0·1–7·0).

The ERR for leukaemia excluding CLL was between the value for atomic bomb survivors estimated from a liner extrapolation to low doses (3·7 per Sv) and that estimated from a linear-quadratic extrapolation (1·4 per Sv). The ERR for all cancers excluding leukaemia was less than the linear estimate derived from atomic bomb survivors (0·18 per Sv) (table 3). In both cases, the 90% CIs about the ERR estimates for nuclear workers included values of the order of twice the linear estimates obtained from the atomic bomb survivors. The UNSCEAR estimates of the ERR bore a similar relation to the estimates obtained from the nuclear workers. They differed slightly, however, from the estimates we obtained from the atomic bomb survivor data (table 3) because of differences in analytic strategies (UNSCEAR estimates were based on all men exposed at the age of 20 or above, used a quality factor of 1 for neutrons, truncated doses at 6 Gy, and stratified age at exposure in three categories).

Discussion

By combining studies of nuclear industry workers, we have estimated the excess risk of cancer associated with increasing cumulative doses of ionising radiation. The estimates are the most precise yet to have been obtained directly from populations with protracted exposures to low levels of X and γ radiation. They suggest that the risk estimates obtained by extrapolation from the studies of atomic bomb survivors are unlikely to be substantially in error.

The effect of both measurement error and confounding needs to be considered when interpreting these results. There are three major sources of dose-measurement error. First, reliable estimates of dose were available systematically only for dose from external exposure to higher-energy photons and from tritium. A few workers received substantial doses of other types of radiation which were not always included in the dose estimates. Second, the recorded doses probably overestimate dose to particular organs, by as much as 20% for the bone marrow. Third, dose estimates are subject to random

	Facility						
	Hanford	Rocky Flats	ORNL	Sellafield	AEA+AWE*	AECL	Total
Numbers of workers	32 595	6638	6591	9494	29 000	11 355	95 673
Male	24 628	6638	6591	8802	26 495	8591	81 745
Female	7967	0	0	692	2505	2764	13 928
Deaths							
All causes	6445	587	1246	2027	4629	891	15 825
All cancers, excluding leukaemia	1452	104	280	533	1227	234	3830
Leukaemia, excluding CLL	47	4	18	10	35	5	119
Person-years	781 549	100 022	173 730	233 090	637 925	198 210	2124 256
Collective dose (Sv)	877·2	241·8	141·4	1309·6	958·6	314·6	3843·2
Male	831·6	241·8	141·4	1294·5	936·4	311·8	3757·5
Female	45·6	0	0	15·1	22·3	2·8	85·8

*For confidentiality reasons, information could not be obtained separately for AWE and AEA workers.

Table 2: **Distributon of workers, deaths, person-years, and collective dose by facility**

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measurement errors for which no adjustment could be made. Our more detailed analysis (to be reported elsewhere) suggests that the first of these sources of error is unlikely to have introduced serious bias. Indeed, the risk estimates obtained after excluding the workers who could be identified as having received substantial doses from neutrons, lower-energy radiations, or contamination with radionuclides did not differ greatly from those reported here. The second and third possible sources of errors are more difficult to assess; both would, most likely, have led to underestimation of the excess relative risk per unit dose.

Although the analyses took account of confounding by age, sex, socioeconomic status, calendar time, and facility, we were unable to adjust for possible confounding by variables such as smoking, diet, and occupational exposure to other carcinogens because the information was not available. Since there was no evidence for an association between cumulative dose and mortality from smoking-related cancers, respiratory diseases, or liver cirrhosis in these data, smoking and alcohol consumption do not appear to be strongly related to cumulative radiation dose. However, the possibility of some bias due to confounding cannot be excluded entirely.

A major issue in radiation risk assessment is whether the cancer risk per unit cumulative dose is different for low-dose protracted exposures than for high-dose acute exposures. The risk estimates derived in this study were generally somewhat lower, but consistent with, estimates derived using constant linear models fitted to the results of high-dose studies. In addition, as will be reported in detail elsewhere, there was little evidence for heterogeneity of risk across study populations. We also compared the risks in workers with those of atomic bomb survivors using the BEIR V models,[1] which incorporated dependencies of risk on age at exposure, time since exposure, and sex. Detailed results and conclusions of these analyses will be reported elsewhere. Again, there was little indication that risks following protracted exposure were seriously underestimated by extrapolation from acute exposure studies.

Experimental studies have provided evidence that linear extrapolation may overestimate such risks and, for this reason, the ICRP recommended reducing linear risks by a dose and dose-rate effectiveness factor (DDREF) of two.[4] BEIR V used a linear-quadratic model for estimating leukaemia risk and also recommended that risks should be reduced to account for lower dose-rate exposures.[1] If we assume that the difference in the risk estimates derived from the nuclear workers and the atomic bomb survivors studies is entirely attributable to the effect of dose and dose-rate, we could infer that the DDREF for leukaemia (excluding CLI) is about 1·7 with a lower limit of 0·6 and an upper limit of 37. There may be other differences, however, and at the present time the need for a DDREF cannot be assessed with certainty.

The upper confidence bounds presented in this paper are of particular interest because it has been said that the extrapolation process used to assess cancer risk following low-dose protracted exposure may seriously underestimate this risk, possibly by an order of magnitude or more.[6] These analyses indicate that if there has been underestimation, it is unlikely to have been by more than a factor of about two.

These estimates are the most precise direct estimates made so far of carcinogenic mortality risk after protracted exposure to low levels of radiation. They provide little evidence that the estimates that form the basis for current radiation protection recommendations are appreciably in error. Many of the workers in the study cohorts are still quite young; 84·5% are still alive. Additional follow-up and studies of other cohorts of workers are needed to increase the precision of the estimates of radiation-related risk of cancer and thus to strengthen further the scientific basis for setting radiation protection standards.

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References

1 BEIR V. Committee on the Biological Effects of Ionizing Radiation. Health effects of exposure to low levels of ionizing radiation. Washington, DC: National Academy of Sciences, 1990.

2 UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation). Sources and effects of ionizing radiation: 1988 report. New York: United Nations, 1988.

3 National Institutes of Health. Report of the National Institutes of Health Ad Hoc Working Group to Develop Radioepidemiological Tables (*NIH Publ* no 95-2748). Washington, DC: Department of Health and Human Services, 1985.

4 International Commission on Radiological Protection. Recommendations of the International Commission on Radiological Protection: ICRP 60. Oxford: Pergamon Press, 1991.

5 Sagan LA. What is hormesis and why haven't we heard about it before? *Health Phys* 1987; **52:** 521–26.

6 Stewart AM, Kneale GM. A-bomb radiation and evidence of late efects other than cancer. *Health Phys* 1990; **58:** 729–35.

7 Rinsky RA, Zumwalder RD, Waxweiler RJ, et al. Cancer mortality at a naval nuclear shipyard. *Lancet* 1981; i: 231–35.

8 Beral V, Inskip H, Fraser P, et al. Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–1979. *BMJ* 1985; **291:** 440–47.

9 Checkoway H, Mathew RM, Shy CM, et al. Radiation, work experience, and cause specific mortality among workers at an energy research laboratory. *Br J Ind Med* 1985; **42:** 525–33.

10 Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. *BMJ* 1986; **293:** 845–54.

11 Howe GR, Weeks JL, Miller AB, et al. A study of the health of the employees of Atomic Energy of Canada Limited IV: analysis of mortality during the period 1950–1981 (AECL-9442). Chalk River, Ontario, Canada: AECL, Open literature report, 1987.

12 Wilkinson GS, Tietjen GL, Wiggs LK, et al. Mortality among plutonium and other radiation workers at a plutonium weapons facility. *Am J Epidemol* 1987; **125:** 231–50.

13 Beral V, Fraser P, Carpenter L, et al. Mortality of employees of the

Atomic Weapons Establishment, 1951–82. *BMJ* 1988; **297:** 757–70.
14 Checkoway H, Pearce N, Crawford-Brown BJ, et al. Radiation doses and cause-specific mortality among workers at a nuclear materials fabrication plant. *Am J Epidemiol* 1988; **127:** 255–66.
15 Gilbert ES, Peterson GR, Buchanan JA. Mortality of workers at the Hanford site: 1945–1981. *Health Phys* 1989; **56:** 11–25.
16 Wing S, Shy CM, Wood JL, et al. Mortality among workers of Oak Ridge National Laboratories: Evidence of radiation effects in follow-up through 1984. *JAMA* 1991; **265:** 1397–402.
17 Kendall GM, Muirhead CR, et al. Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. *BMJ* 1992; **304:** 220–25.
18 Fraser P, Carpenter L, Maconochie N, et al. Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946–1986. *Br J Cancer* 1993; **67:** 615–24.
19 Gilbert ES, Omohundro E, Buchanan J, et al. Mortality of workers at the Hanford site: 1945–1986. *Health Phys* 1993; **64:** 577–90.
20 Gribbin MA, Weeks JL, Howe GR. Cancer mortality (1956–1985) amongst male employees of Atomic Energy of Canada Limited with respect to occupational exposure to external low linear energy transfer ionizing radiation. *Radiat Res* 1993; **133:** 375–80.
21 Gilbert ES, Fry SA, Wiggs LD, et al. Analysis of combined mortality data on workers at the Hanford Site, Oak Ridge National Laboratory and Rocky Flats Nuclear Weapons Plant. *Radiat Res* 1989; **120:** 19–35.
22 Gilbert ES, Cragle DL, Wiggs LD. Updated analyses of combined mortality data on workers at the Hanford site, Oak Ridge National Laboratory, and Rocky Flats weapons plant. *Radiat Res* 1993; **136:** 408–21.
23 Carpenter L, Beral V, Douglas A, et al. Combined analyses of three UK nuclear industry workforces. *Radiat Res* 1994; **138:** 224–38.
24 Inskip H, Beral V, Fraser P, et al. Further assessment of the effects of occupational radiation exposure in the United Kingdom Atomic Energy Authority mortality study. *Br J Ind Med* 1987; **44:** 149–60.
25 Taylor NA. Estimation of dose received when dosimeter results are recorded below a threshold level. *J Radiol Prot* 1991; **3:** 191–98.
26 Shimizu Y, Kato H, Schull WJ. Studies of the mortality of A-bomb survivors 9, mortality 1950–1985, part 2: cancer mortality based on the recently revised doses. *Radiat Res* 1990; **121:** 120–41.

Thrombosis and embolism in long-term central venous access for parenteral nutrition

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Summary

Although the use of silicone catheters for long-term central venous access is widespread, little is known about the incidence of pulmonary thromboembolic complications.

We studied clinical events, lung perfusion scans, and echocardiographic screens in 34 children and adolescents with gut failure who had received cyclical parenteral nutrition for 2 months to 9 years. Major thrombosis and/or embolism was identified in 12 patients and 4 died as a consequence. Actuarial survival free from thrombosis was 53% at 5 years (95% CI, 30–77%). Survival free from fatal pulmonary thromboembolic events was 74% at 5 years (48–99%). 3 patients required surgery to remove right atrial thrombus or pulmonary emboli.

Major right atrial thrombosis and pulmonary embolism are common and potentially fatal complications of parenteral nutrition by long-term venous access in childhood. Anticoagulation is recommended.

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Introduction

Silicone catheters for long-term central venous access have become essential to the management of many patients with cancer or gut failure. Risks of infection and line-tip thrombosis have been studied but thromboembolic events have not been considered a major complication.[1,2] Catheter-related pulmonary emboli with progressive pulmonary hypertension are, however, recognised complications in patients with ventriculo-atrial shunts for hydrocephalus.[3] To assess the extent of thromboembolic complications and to examine factors which might be associated with their development, we studied children receiving long-term cyclical parenteral nutrition (CPN).

Methods

Study population

All 34 patients who received CPN for gut failure for more than 2 months between June, 1983 and July, 1993 at the Hospital for Sick Children, were reviewed. Two patients died of sepsis before the study; both were censored as being free from thrombosis at the time of death. 32 patients remained, of whom 6 no longer required CPN. At the beginning of CPN, patients were aged 1 week to 13 years and by the time of the study had received CPN for 2 months to 9 years. 15 had autoimmune enteropathy (defined as a small intestinal enteropathy resistant to dietary manipulation and associated with circulating enterocyte autoantibodies), 10 had short-gut syndromes after surgery, and 7 had disorders of gut motility.

Parenteral nutrition

8 of 32 patients had CPN prepared by the hospital pharmacy (2 for home use) with heparin 1 unit/mL routinely added (1500–2500 units per day). The remaining 25 received commercially available CPN without heparin. The percentage of