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Protocol for a Cohort Mortality Study of Occupational Radiation Exposure Based on the National Dose Registry of Canada

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INTRODUCTION

CANADA IS in a fortunate position with respect to the conduct of epidemiological studies of occupational radiation exposure. The National Dose Registry (NDR) operated by the Department of National Health and Welfare is one of the most comprehensive centralised radiation exposure record-keeping systems in the world. The NDR currently contains radiation exposure records for approximately 500,000 individuals. Virtually all monitored radiation workers in Canada are included in the NDR, with some records providing in excess of 39 years of exposure data [1]. In addition, the Registry includes 80 different job categories ranging from nuclear power generating station workers to hospital radiologists and dentists.

Vital statistics including cause of death and other information derived form the death certificates are also maintained centrally in Canada. Specifically, the Canadian Mortality Data Base (CMDB) maintained by Statistics Canada [2] contains vital statistics dating back to 1950. Computerised record linkage (CRL) techniques allow for relatively inexpensive linking of the exposure data (radiation records in the NDR) with possible health effects (death registration records in the CMDB). In collaboration with the Epidemiology Unit of the National Cancer Institute of Canada, Statistics Canada has developed a CRL system called Generalized Record Linkage System (GRLS) [3, 4]. This system has been successfully used in a variety of epidemiological studies [5] including a study of the mortality experience of over 320,000 Canadian male farm operators [6, 7]. The main advantages of computerised linking are increased speed, reduced cost, and the large volume of records that can be processed in the study [8, 9].

Given the continued concern over the potential adverse health effects due to occupational exposure to ionising radiation, and the extensive amount of information on occupational exposures in the NDR, a retrospective cohort mortality study linking the NDR with the CMDB was initiated. This study will permit a comparison of the mortality experience of the cohort with that of the Canadian population. Comparisons will also be made between the exposed and non-exposed members of the cohort (almost half of the cohort received no measurable level of radiation exposure). Specifically, the study objectives are as follows:

1. to compare the mortality of the cohort of workers monitored for ionising radiation with that of the overall population of Canada;
2. to determine whether or not there is a difference in the mortality rate between the exposed and non-exposed members of the cohort;
3. to determine if death from specific diseases occurs more frequently in the exposed members of the cohort than in the non-exposed members;
4. to determine if a dose–response relationship can be established between the level of exposure and the mortality of the cohort; and
5. if no dose–response relationship can be established, to determine an upper limit on the potential level of risk associated with radiation exposure.

The fact that radiation is a risk factor for several forms of human cancer is well established. The purpose of this study is thus not to confirm this finding, but rather to establish limits on occupational cancer risks faced by radiation workers in Canada, and to evaluate these limits in light of previously reported findings. Even if no dose–response relationships can be established, it will still be possible to establish an upper limit on the residual level of risk associated with occupational radiation exposure.

This initial study will focus primary on cancer mortality. However, other causes of death will also be considered. Once historic cancer incidence data are available at the national level, a follow-up study of cancer morbidity will be initiated.

RADIATION CARCINOGENESIS

Human exposure to ionising radiation can lead to cancer in a number of organs and tissues [10–13]. Epidemiological evidence of radiation carcinogenesis is based largely on studies of survivors of the atomic bombings of Hiroshima and

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Nagasaki, people exposed to fall-out from nuclear weapons tests, patients subjected to therapeutic doses of radiation, nuclear power plant workers, miners and radiologists, people exposed to high levels of naturally occurring radiation, and people involved in nuclear accidents. Of these study populations, the Hiroshima and Nagasaki bomb survivors continue to provide much of our current knowledge about the carcinogenic effects of ionising radiation in humans [14, 15].

External radiation

Studies of the Japanese atomic bomb survivors have indicated increased mortality due to leukaemia [16], with a total of 202 leukaemia (other than chronic lymphocytic) deaths versus expected occurring between 1950 and 1985 [11]. Elevated leukaemia mortality has also been noted in patients treated with X-rays for ankylosing spondylitis [17], in women given fractionated doses of radiation for carcinoma of the cervix [18], and in patients given radiation therapy for cancers at other sites [11]. An increased incidence of acute leukaemia and chronic granulocytic leukaemia has been noted in radiologists occupationally exposed to X-rays prior to the implementation of modern safety standards [11].

Radiation has been associated with an excess of some forms of lymphoma including multiple myeloma, in which malignant lymphocytes proliferate primarily in bone marrow, and non-Hodgkin's lymphoma, which occurs primarily in the lymph nodes. Excess mortality from multiple myeloma has been observed among the atomic bomb survivors, although with a longer latent period (in excess of 20 years) than with leukaemia [19]. Similar effects have been seen in patients followed for 25 or more years after radiation therapy for ankylosing spondylitis [17], and in nuclear power plant workers in the United States [20] and Britain [21, 22]. Although mortality from non-Hodgkin's lymphoma has not been shown to be elevated in the Japanese atomic bomb survivors [11], mortality is increased in ankylosing spondylitis patients [17].

Mortality due to cancer of the breast, oesophagus, lung and stomach is also elevated in survivors of the Hiroshima and Nagasaki bomb blasts [23, 24]. Cancer of the colon is also responsible for increased mortality in these study populations.

Additional evidence of radiation-induced breast cancer is provided by studies of women receiving repeated fluoroscopic examinations (25–28). Darby and associates [17] noted an increased risk of oesophageal and lung cancer in the cohort of patients given radiation therapy for ankylosing spondylitis. The risk of lung cancer was also increased in women treated with radiation for cancer of the cervix [29]. Although the Japanese atomic bomb survivors provide the strongest evidence that human exposure to ionising radiation can increase the risk of stomach cancer, a similar association has been observed in patients irradiated for peptic ulcers [30].

Internal radiation

Iodine radionuclides. Although carcinoma of the thyroid was one of the first solid tumours observed with increased frequency among the Japanese atomic bomb survivors [31], internally deposited iodine radionuclides emitting primarily beta particles are also a risk factor for thyroid cancer in humans. The effects of iodine radionuclides have been studied in patients receiving ^{131}I for both therapeutic and diagnostic reasons [11]. Studies of people on the Marshall Islands exposed to iodine radionuclides as a consequence of nuclear weapons tests have provided further evidence of thyroid carcinogenesis [32, 33].

Radon. The carcinogenic effects of radon in exposed underground miners have been well documented. As early as 1556, excess deaths due to an unusual and fatal chest disease were recorded among Central European miners. However, it was not until 1879 that bronchogenic carcinoma was identified as the cause of death. By the 1920s, radon was suspected as the cause of lung cancer. Following a lengthy scientific debate, which lasted into the 1960s, radon and its decay products were eventually confirmed as one of the causes of this disease [34]. Miners experienced chronic low-level exposure to internally deposited high-LET alpha emitters.

The epidemiological evidence implicating radon as a risk factor for lung cancer in humans has recently been reviewed by the International Agency for Research on Cancer [35]. Citing elevated lung cancer rates in studies of uranium and other miners, the Agency concluded that there is sufficient evidence for the carcinogenicity of radon and its decay products in humans. Because of the elevated lung cancer risk in miners exposed to high levels of radon, questions have been raised about potential risks due to lower levels of radon present in homes and buildings. While case-control studies in New Jersey [36] and Sweden [37, 38] have provided some evidence of elevated lung cancer risks, studies in China [39] and Canada [40] have been negative. Radon is known to act synergistically with tobacco smoke in the induction of lung cancer [10, 41–43].

NATIONAL DOSE REGISTRY

The National Dose Registry of Canada is a centralised occupational radiation dose record-keeping system, which includes all available records for monitored workers in Canada from 1951 to the present. The Registry is operated by the Radiation Protection Bureau (RPB) of the Department of Health in Canada. Data in the Registry include the records of the National Dosimetry Services (NDS), as well as records submitted by nuclear power generating stations, Atomic Energy of Canada Limited (AECL), and uranium mines (radon daughters).

File structure

At the start of this study, the National Dose Registry was composed basically of four files [44]. The **Master Identification File** (MIF) contained personal identifying information such as surname, given names, sex, year of birth, and assigned identification numbers used to identify the individuals' dose records. The **Lifetime Annual History File** consisted of a sequential file summarising each individual's dose history in a series of records, one for each year. In addition to the individual's numerical identifier and dose information, this file contained the province in which the individual worked, a serial number identifying the organisation, and the type of work as of the last reported record for the year. The **Cumulative File** was a database that contained cumulative radiation doses for the current and previous year as well as the individual's lifetime dose. The **Discrete History File** consisted of a microfilm record

of each dose entry and dose changes made to an individual's record.

The MIF of the NDR was used in the identification of individuals' records to be linked at Statistics Canada. This file was assembled by reviewing the paper records for each in the 15,000 organisations on the National Dosimetry Services. All available identification information (i.e. social insurance number (SIN), surname, first and second given names, sex, and complete date of birth) was extracted and encoded into machine-readable form. At the beginning of the study in 1984, the MIF was given to Statistics Canada for editing and further processing [45].

In 1986, the National Dose Registry was restructured to consist of a single database called the **Lifetime Dose History System** (LDHS) and a **Discrete Transaction File** [44]. The LDHS contains all identifying information and annual summary records for each organisation where the individual was monitored. Combinations of personal identifiers or any of the organisational codes can be used to search through the NDR.

The Discrete Transaction File consists of an index file of approximately one year's duration. Data more than one year old are stored on microfilm in a format similar to that of the original Discrete History File. The data elements of the LDHS and the Discrete Transaction File are shown in Tables 1–3.

During the development of the new LDHS, annual dose records prior to 1977 were taken from a copy of the NDR's Lifetime Annual History Files. Data prior to 1964 were available for two time periods (1951–1957 and 1958–1963) on one machine-readable file. From 1977 onward, dose records were taken from the Discrete Transaction Files. 11 shows the relationship between the files in the original Registry and those in the restructured system.

File contents

Numerical identifiers. The original records from 1951 to 1964 were identified alphabetically by surname, initials, and year of birth. For convenience, an arbitrary numerical identifier was assigned to help with the initial loading of the records into the new LDHS and to allow linkage of these records to the MIF file at Statistics Canada.

From 1964 to 1967, a five-digit numerical identifier was used. This is now referred to as the 'old namecode' or 'asterisked namecode'.

From 1968 to 1972, a six-digit numerical identifer, now referred to as the 'new namecode', was used. All early records of individuals monitored in 1968 were converted to the new namecode, but some of the early microfilms only recorded the old namecode. No machine-readable cross-referencing between the old and new namecodes was available. Cross-referencing information was encoded from old printouts.

From 1973 to 1977, a new seven-digit number referred to as the 'RPB number' was used. This number was assigned to all individuals whether or not they were still being monitored. Cross-referencing information between the RPB number and the old and new namecodes was available in machine-readable form.

When reapplying for monitoring service, some individuals could not remember or did not provide their old number. These individuals were therefore assigned a new number, resulting in fragmentation of their dose records. Because of these and related problems, the SIN has been used as the key to individual records from 1977 onwards. This has resulted in significantly fewer problems with fragmented records.

Table 1. Record layout for analysis files

(a) Individual data file	
ID number	(Statistics Canada linkage number to SC new sequence number)
Record type	(value to distinguish from yearly records in part (b) below)
Birth data	(NDR file)
Death date	
Cause of death	(ICDA as of death year)
Death linkage weight	
Sex	
Available for discrepancy flag	
Available for further flags	
(b) Annual dose records	
ID number	
Radiation type	
Radiation year	
Province	
Group-class	
Service-type	
Group-serial	
Job class	
Annual dose body	
Annual dose skin	
Dose count	
First period	
Last period	
Error-flag	
(c) Individual file with cumulative values	
ID number	
Birth year	
Sex	
First year monitored (gamma)	
Last year contact (gamma)	
First year monitored (tritium)	
Last year contact (tritium)	
First year monitored (radon)	
Last year monitored (radon)	
First year monitored (overall)	
Last year contact (overall)	
Cumulative dose—whole body	
Cumulative dose—tritium	
Cumulative dose—radon daughters	
Province	
Last job class	
Last group-serial (organization)	
Service-type	
Group-class	

Files (a) and (b) represent the main analysis file. File (c) may also be used in analysing cumulative exposure.

Types of radiation. The NDR has been designed in such a way as to allow the inclusion of any type of radiation dose ranging from external gamma exposures to effective dose equivalents for radioisotopes such as ^{14}C. With the exception of radon daughter exposures, the doses are divided into penetrating (whole-body) and non-penetrating (skin) doses, and are expressed as dose equivalents in millisieverts (mSv). Currently, the NDR contains dose estimates for the types of radiation listed in Table 4.

Table 2. Lifetime dose history system data elements

ID number (SIN)
Surname
1st Given name
2nd Given name
Alternate surnames
Alternate ID numbers (RPB number, namecodes, miner's X-ray numbers)
Sex
Date of birth (DD/MM/YY)
Place of birth code
For each organisation and year or span of years, which the individual was monitored, the following information is also included:
Radiation type
Year of dose
Job classification code
Group numbers—province code
—group-class code
—service code
—serial
Annual dose—body
Annual dose—skin

In order to evaluate the impact of exposure to several different types of radiation, it is necessary to express radiation exposures in common units [46]. The dose equivalent H is defined by $H = DQN$, where D is the absorbed dose, Q is the quality factor, and N is the product of other modifying factors. The absorbed dose D is the amount of energy deposited in the tissue (expressed in grays (Gy) where 1 Gy = 1 J/kg of tissue). The quality factor Q is a measure of the biological damage different types of radiation may inflict. In the NDS, quality factors for X-ray, gamma, and beta are taken as 1.0, while the quality factor for neutrons is taken as 10.0. Although the International Commission on Radiological Protection has recently recommended a quality factor of 20.0 for neutrons [47], this has not been universally accepted. The factor N is assumed to be 1.0 [48].

Table 3. Discrete transaction file

ID number (SIN)	
Radiation type	
Surname	
1st Given name	
2nd Given name	
Sex	
Date of birth (DD/MM/YY)	
Job classification code	
Dosimetry entry	—year
	—period
	—dosimeter number
Group number	—provincial code
	—class code
	—service code
	—serial
Body dose	
Skin dose	
Record code	
Date of transaction (DD/MM/YY)	

For the purposes of clarity, only data fields containing relevant information have been included.

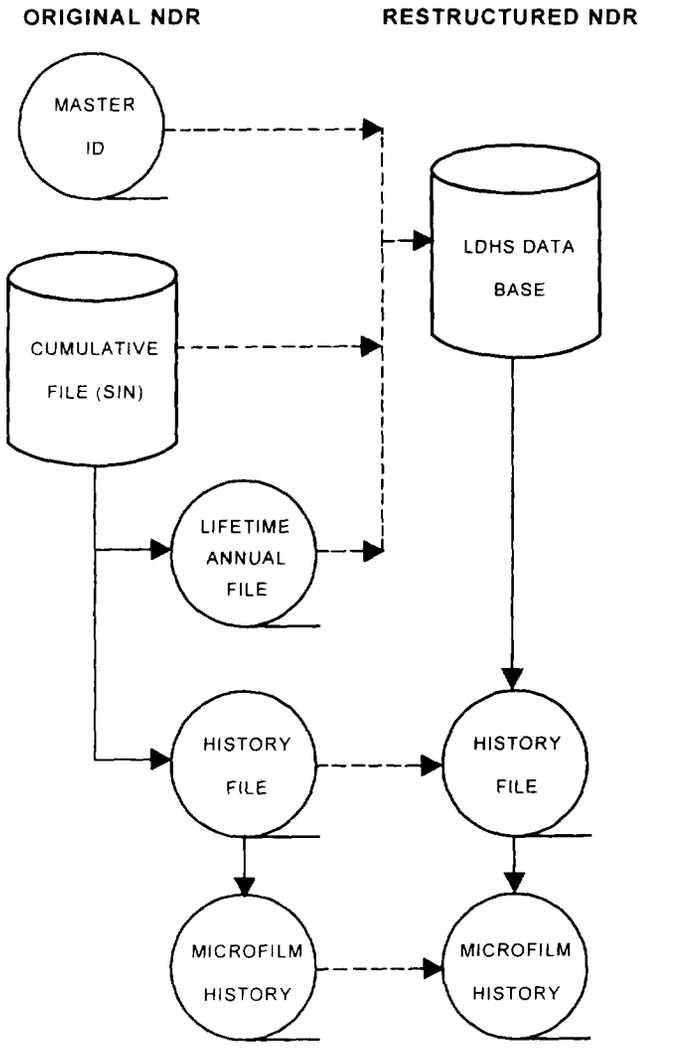

Figure 1. NDR data flow diagram.

Radon daughter records were first entered into the NDR in 1977. Since that time they have been routinely entered on a quarterly basis in all uranium mines and in some non-uranium mines where radon is a problem. Radon daughter exposure records are submitted to the NDR in working level months (WLM). A WLM corresponds to exposure of a miner to the concentration of the short-lived radon daugh-

Table 4. Types of radiation included in the national dose registry

Radiation type	NDR exposure category
X-ray	External whole-body, skin and extremity
Gamma	External whole-body, skin and extremity
Neutron	External whole-body, skin and extremity
Beta	External skin and extremity
Internal tritium	Internal whole-body and skin
Radon daughter	Radon daughter exposures

ters of one working level (WL) for a period of 170 h (a working month). Most records in the NDR are estimates based on area monitoring and occupancy times. Annual records from the 1950s to 1977 are based primarily on the data obtained in a study of the Ontario miners [49], which was incorporated into the NDR in the mid-1980s. The Ontario miners' data prior to 1968 are based on estimated working levels in the mines. Information obtained directly from Ontario mines for the period 1968–1976 have been used to update the NDR records. Data prior to 1977 for Saskatchewan miners consist of a single total exposure level prior to 1977, and may not be available for all uranium miners in Saskatchewan. Gamma monitoring for the miners started in 1981.

Until 1977, all monitoring done by the NDS was performed using Kodak radiation monitoring film for gamma, X-ray, and beta exposures, and Kodak NTA nuclear emulsion film for neutron exposures. In 1976, the National Dosimetry Services initiated a partial thermoluminescent dosimetry (TLD) program utilizing lithium fluoride: two lithium fluoride chips were used, one for measuring the penetrating dose, the other for measuring the non-penetrating dose. Conversion of the service to TLD was completed by 1981. In 1988, neutron dosimetry in the NDS was converted from film to a new technology using polycarbonate (CR-39) elements as detectors [50].

All nuclear power stations now use TLD and make quarterly submissions of the external doses to the NDR. Ontario Hydro used the RPB film service until 1976 when it started its own lithium fluoride TLD program. Quebec Hydro remained on the RPB film service until 1980, at which point it started its own lithium fluoride TLD program. New Brunswick Power has, since the beginning of its nuclear programme, run its own lithium borate-based TLD program. AECL has always performed its own dosimetry changing from film to a lithium fluoride-based TLD program in 1973. All nuclear power stations and AECL perform their own bioassays for tritium. The dose equivalent in mSv is determined from urinalysis [51].

The NDS has used a variety of reporting thresholds since its inception in 1951. Doses below the threshold of reporting were recorded as zeros from 1951 to 1963. Between 1964 and 1972, the reporting threshold was 1 mR (0.01 mSv) and exposures below this value were recorded as 1 mR (0.01 mSv). From 1972 to 1977, the threshold was 5 mrem (0.05 mSv) for X-rays and beta radiation and 20 mrem (0.20 mSv) for gamma radiation. Values below the threshold were recorded as zeros. With the introduction of the TLD service in 1977, the reporting threshold was fixed at 0.20 mSv with values below this limit being included as zero.

Procedures for reporting thresholds for submitted records vary for the nuclear generating stations and AECL. The minimum reporting levels are shown in Figure 2. With one exception, doses below the minimum reporting levels are included in the cumulative dose records as zeros. The exception occurred between 1964 and 1969, when the value of 0.01 mSv (1 mrem) was used for doses below the minimum reporting threshold in the NDS.

Because of these threshold reporting limits, it is possible that cumulative annual exposures may be overestimated or underestimated. For example, if an individual was monitored with every second week and received doses just below

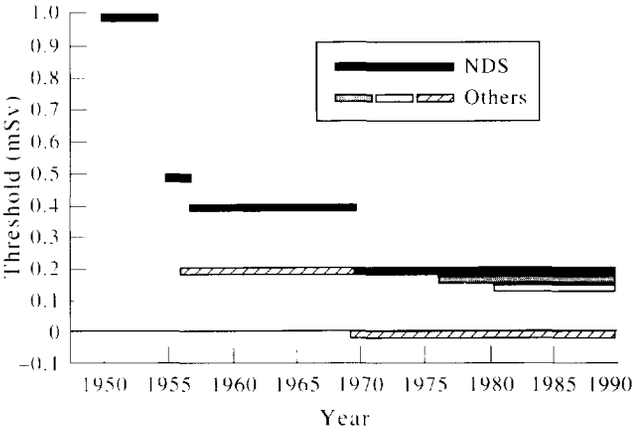

Figure 2. Minimum reporting thresholds.

0.2 mSv, his/her annual dose could theoretically be underestimated by $0.2 \times 26 = 5.2$ mSv if these values were recorded as zeros. While the number of dosimeters with readings below the reporting threshold can be determined manually for each individual from the microfilm transaction records, it is not feasible to do this for all members of the cohort because of the large number of records. The possibility of taking this source of error into account will be pursued by the study team.

The external whole-body doses reported by each of the nuclear generating stations and AECL are generally comparable. These facilities participate in national and international intercomparison studies along with the National Dosimetry Services, the results of which are usually published. A recent national intercomparison for external dosimetry showed comparability to within ±20% between facilities whose records are in the NDR [52]. In the case of early records, dosimetry for nuclear facilities other than AECL was performed by the National Dosimetry Services. The intercomparability in tritium dose equivalents is considered to be better than that for external dosimetry.

Systematic differences may also result from administrative procedures or policies that may differ from one facility to another. For example, trigger levels for the investigation of high exposures may differ, and could influence the accuracy of dose records assigned to an individual. This potential source of bias is very difficult to take into account.

CANADIAN MORTALITY DATA BASE

The Canadian Mortality Data Base (CMDB) contains records for all registered death events from the provinces and territories since 1950. These records exist in both machine-readable and microfiche formats. The machine-readable records consist of provincial records that have been converted into a standardised format on magnetic tape under the custody of Canada's central statistical agency, Statistics Canada [2, 53].

The CMDB is ideally suited for long-term follow-up epidemiological studies. These can be defined as studies involving large cohorts identified on the basis of a common characteristic (e.g. exposure to a specific environmental, or subject to a specific medical treatment, diagnostic or therapeutic procedure) followed over a specified time to assess the effect of the characteristic under-study on a particular health outcome (e.g. death).

In recent years, the completeness and accuracy of reporting of the various kinds of personal identifying information on the death registration forms is high. However, lack of personal identifiers on the cohort nominal roll records (based on NDR files) used to initiate the search of the CMDB will affect the ability of the record linkage software to identify true links between the two files.

The Statistics Act protects the confidentiality of all records [54]. All studies involving long-term medical follow-up must satisfy a rigorous review and approval process prior to a search of the CMDB being conducted.

RECORD LINKAGE

Record linkage is the process of bringing together two or more separately recorded pieces or information pertaining to the same individual [8, 9]. The procedures for computerised probabilistic linkage have become exceedingly sophisticated, and have been elaborated in detail elsewhere [55, 56]. Statistics Canada has developed a generalised record-linkage system (GRLS) that is particularly useful for studies of the type discussed here [3, 4]. This software is capable of handling both one-file (internal) and two-file linkages.

Records of the NDR are accessible by computer, as are the death registrations on the CMDB. Linkages of the two sorts of records on an individual basis is dependent, in principle, on the availability of sufficient personal identifying information common to the two sorts of records, to ensure against ambiguous matches and mistaken identities.

The personal identifying information pertaining to NDR registrants had to be put through a considerable number of steps in order to: (i) determine the quality and quantity of data available; (ii) group all records corresponding to the same individual; (iii) define the cohort in terms of the individuals to be included; and (iv) put these data into a format suitable for linkage with the CMDB. The details of this work have been described previously [45].

ANALYSIS METHODOLOGY

Cohort definition

The cohort for the NDR mortality study consists of all workers whose exposure records were contained in the National Dose Registry as of 31 December 1983. This includes records from the National Dosimetry Service, as well as records routinely submitted by Atomic Energy of Canada Limited, nuclear power stations and uranium mines (radon daughter exposure estimates).

There are approximately 255,000 workers in the cohort with a collective dose (external whole-body + tritium) of 1480 Sv, and an average lifetime dose of 5.9 mSv as of 31 December 1987. The collective dose summarised by job category is shown in Table 5.

The National Dose Registry provides detailed information on occupational exposures to ionising radiation (external whole-body, tritium, radon daughters) experienced by approximately 500,000 Canadians dating, in some cases, back to 1951. Depending on the type of radiation and the levels of exposure anticipated within specific job categories, radiation exposure records have been collected annually, quarterly, monthly, or biweekly. Each year, a summary measure of the annual dose experienced by each individual is recorded in the Lifetime Dose History System (LDHS). The annual exposure records maintained in the LDHS will be used as the basis for examining potential relationships between occupational radiation exposure and health status.

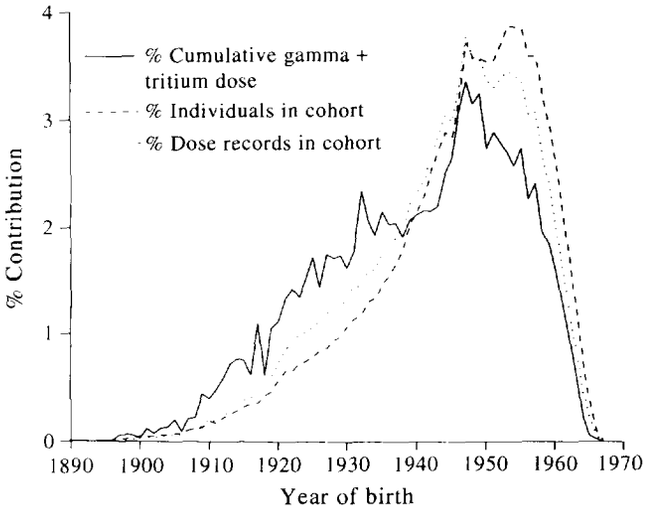

Figure 3. Distribution of collective dose (gamma + tritium) by year of birth.

The individual data in the LDHS also permit the calculation of a cumulative lifetime dose for each individual. The distribution of lifetime radiation exposures experienced by Canadians by year of birth is summarised in Figure 3. Although individuals will not experience the same level of exposure each year, an average annual dose for an individual can be obtained by dividing the cumulative lifetime dose by the number of years that have elapsed since the time of first exposure. Statistical analysis can be based on the cumulative lifetime dose, the average annual dose, or the annual doses as recorded by the LDHS. The use of annual doses is necessary in the presence of dose-rate effects known to exist with ionising radiation [43].

These summary measures of exposure can be calculated for the cohort as a whole, and for specific subgroups of interest such as workers with specific job titles. Summing the cumulative lifetime dose across all individuals in the cohort yields the collective dose for the cohort as a whole.

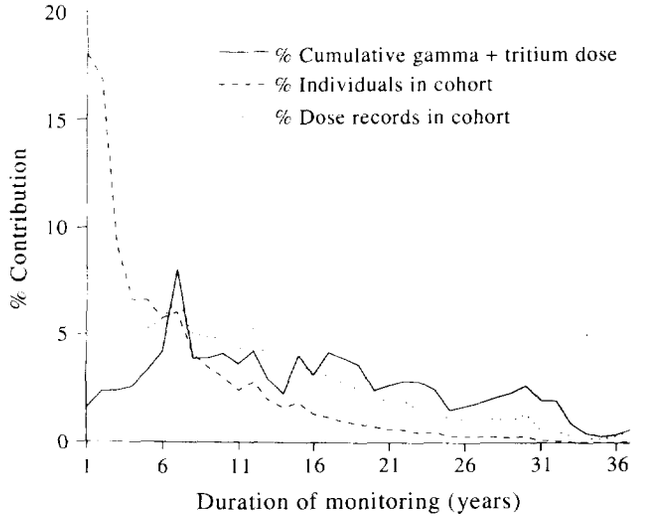

Figure 4. Collective dose (gamma + tritium) as a function of years of monitoring.

Table 5. Collective dose (up to December 1987) by job classification

	Job classification	External whole-body (Sv)	Tritium (Sv)	Radon (WLM)
000	Not available	389.6	3.1	2324.7
001	Administrator	1.0	0.0	1.0
002	Office staff	5.1	0.1	11.7
003	Safety officer	1.0	0.0	
004	Other (administration)	1.4	0.0	0.0
010	Chiropractor	1.6		0.0
011	Dentist	4.9		1.0
012	Gynaecologist	0.7		
013	Laboratory technician (medical)	8.1	0.0	
014	Medical physicist	1.9	0.0	
015	Nurse	23.6	0.0	
016	Physician	14.8	0.0	
017	Radiological technician (diagnostic)	76.4	0.0	
018	Radiological technician (therapeutic)	12.1	0.0	
019	Radiologist (diagnostic)	24.3		
020	Radiologist (therapeutic)	3.9		
021	Veterinarian	2.8	0.0	
022	Ward aid/orderly	6.2		
023	Other (medical)	12.4	0.0	
024	Isotope technician (nuclear medicine)	24.1	0.0	
025	Dental hygienist	1.7		
040	Dial painter	1.7	0.0	
041	Instructor (non-medical)	0.6	0.0	
042	Instrument technician	7.8	0.6	
043	Laboratory technician (industrial)	14.5	0.1	
044	Well logger	11.9		
045	Industrial radiographer	91.0	0.2	
046	Scientist engineer (field)	6.5	0.9	
047	Scientist/engineer (laboratory)	10.4	0.0	
048	Other (industrial)	77.8	25.2	0.0
049	Fuel processor	4.4	0.0	
070	Janitorial staff	0.5	0.1	22.8
071	Salesman	0.4	0.0	
072	Student	9.6	0.0	
073	Visitor	0.0		
074	Other (miscellaneous)	0.9		
500	Reactor–scientific/professional	104.8	34.0	6.2
510	Reactor–administration	13.2	1.1	
520	Reactor–health physics	1.4	0.1	
530	Reactor–chemical & radiation control	29.7	3.0	
540	Reactor–electrical maintenance	12.3	1.6	
545	Reactor–industrial radiographer	0.0	0.0	
550	Reactor–mechanical maintenance	80.0	14.2	
560	Reactor–general maintenance	26.7	2.9	
570	Reactor–fuel handling	16.2	1.9	
580	Reactor–operations	86.2	22.3	
590	Reactor–control technicians	14.2	4.1	
596	Reactor–summer student	0.0	0.0	
597	Reactor–training	0.2	0.0	
598	Reactor–construction	16.4	2.1	
599	Reactor–visitor	0.3	0.0	
601	Uranium mine underground personnel	101.8	0.0	156,623.7
602	Uranium mine surface personnel			11.4
603	Uranium mine visitors			0.2
604	Uranium mine office staff	0.0		22.1
610	Uranium mine underground miner	0.4		1608.0
615	Uranium mine nurses			0.3
620	Uranium mine support workers	0.0		608.2
630	Uranium mine underground maintenance	0.0		
650	Uranium mine surface miner	0.0		42.7
660	Uranium mine surface support workers	0.1		56.3
670	Uranium mine surface maintenance	0.0		663.0
680	Uranium mine mill maintenance	0.0		147.3
690	Uranium mine mill workers	0.2		287.9
801	Non-uranium mine underground personnel	1.5		11,961.5
810	Non-uranium mine underground miner	0.0		
820	Non-uranium mine support workers	0.0		2.3
Total		1362.5	117.8	174,402.4

Table 6a. *Total cumulative dose distribution up to* 1987

Radiation type	Sex	Number of people	Cumulative dose	Number of records
External	All	247,074	1362.5	1,444,805
Tritium	All	20,469	117.8	131,935
Radon	All	17,271	174,402.4	101,826
External	Males	125,822	1143.6	788,683
External	Females	115,757	206.4	636,495
External	Unknown	5495	12.6	19,627
Tritium	Males	16,052	116.4	115,323
Tritium	Females	1895	0.2	8848
Tritium	Unknown	2522	1.3	7764
Radon	Males	16,695	173,870.6	99,132
Radon	Females	446	291.1	1692
Radon	Unknown	130	240.6	1002

The distributions of the collective dose as a function of the number of years of exposure monitoring is shown in Figure 4. Descriptions of the study cohort according to type of radiation exposure (external whole-body, tritium, and radon daughters) are given in Tables 6a and 6b. Annual doses by year by radiation type are given in Table 7.

Statistical analysis

The major goal of the analysis of the NDR cohort is to identify and quantify effects of radiation exposures on mortality. Several methods are available to examine cohort data for evidence of differences in death rates as a function of job class or monitored radiation exposures. Evidence of dose–response relationships is of particular interest. Some grouping of cohort data into categories defined by sex, age, calendar period, cumulative exposure, and other fixed or time-varying factors will be necessary to reduce this massive database on approximately 250,000 individuals into a form suitable for statistical analysis.

Comparing mortality rates within different subgroups of the cohort is straightforward when the subgroups are defined on the basis of factors that do not vary with time. Each subgroup is then treated as a separate cohort and the usual allocation of deaths and calculation of person-years by age and time is carried out separately for each subgroup. Since a study member contributes person-years to only one subgroup, there is no ambiguity about the assignment of observation time.

However, to make comparisons between subgroups defined on the basis of time-dependent variables, e.g. cumulative dose, person-years at risk needs to be computed carefully. In this case, person-years of follow-up are assigned to the exposure category to which a death would be assigned if the death should occur at that time. Thus, subjects whose exposure classifications change with time will contribute person-years to several exposure categories.

In all analyses, person-years will be regarded as the unit of analysis, with each person-year assigned values for cumulative radiation dose, age, calendar year, and vital status. Workers are assumed to be alive at the end of the follow-up period if they have not been identified as dead.

Standardised mortality ratios. The standardised mortality ratio (SMR) is defined as the ratio of the number of deaths observed in the study cohort to the number of deaths expected on the basis mortality rates in a suitable reference population. In the present study, the mortality experience of radiation workers will be compared with that of the Canadian population. Person-years will be calculated for males and females separately within five-year age and calendar-year categories. The person-years are multiplied by corresponding age, sex, and calendar-specific rates for Canada in order to estimate the expected number of deaths for each cause of interest. The statistical significance of the SMRs is evaluated under the assumption that the observed number of deaths follows a Poisson distribution. A two-sided test will be used to determine whether any of the SMRs differs significantly from unity [57]. Trends in SMRs with degree or duration of exposure will be examined [57].

Trend tests. In addition to analyses based on SMRs, which involve comparison of mortality rates experienced by members of the cohort with external rates for the general population, tests for the trend in mortality with increasing exposure to radiation may also be conducted within the cohort. Specifically, tests for the trend in mortality due to the 42 causes of death listed in Table 8 will be performed. Particular attention will be paid to cancer mortality of the following types: stomach, kidney, bladder, brain–nervous system, thyroid, bone, non-Hodgkin's lymphoma,

Table 6b. *Total cumulative dose distribution up to* 1987 *by exposure category*

Exposure category	External whole-body	Tritium	Radon	Number of people	Cumulative dose: External whole-body	Cumulative dose: Tritium	Cumulative dose: Radon
1	–	–	+	7718			43,139.1
2	–	+	–	117		0.2	
3	+	–	–	217,241	698.0		
4	+	–	+	9481	105.4		130,217.0
5	+	+	–	20,280	556.8	117.1	
6	+	+	+	72	2.2	0.5	1046.2

+, records present; –, records not present.

*Table 7. Cumulative dose distribution up to 1987 by year of exposure**

	External whole-body		Tritium		Radon	
Year	Cumulative dose (Sv)	Number of people	Cumulative dose (Sv)	Number of people	Cumulative dose (WLM)	Number of people
1951	0.46	1165	0.00	28	304.67	217
1952	1.37	1499	0.00	30	312.59	241
1953	1.84	1670	0.01	36	326.80	267
1954	3.70	1955	0.01	40	345.89	283
1955	7.49	2675	0.03	53	796.70	263
1956	19.77	4142	0.09	71	2663.64	505
1957	15.60	4949	0.07	84	6027.53	858
1958	33.94	10,548	0.12	102	9669.87	1220
1959	35.09	13,009	0.10	113	11,197.59	1343
1960	30.37	14,721	0.11	126	9940.54	1267
1961	27.77	15,799	0.12	140	11,748.71	1142
1962	26.97	16,869	0.14	162	11,319.30	1148
1963	26.59	16,971	0.16	179	8700.66	1165
1964	32.31	18,836	0.21	205	9139.32	1191
1965	30.04	18,972	0.32	244	5619.71	1168
1966	33.52	21,493	0.39	279	4539.48	1252
1967	33.91	23,314	0.46	313	5462.89	1442
1968	33.90	25,914	2.09	854	2634.25	1457
1969	34.83	29,172	3.19	1135	2724.39	1628
1970	37.94	31,361	4.09	1350	2891.27	1736
1971	40.45	37,295	5.10	1588	2739.47	1788
1972	48.97	42,121	5.70	1735	2439.02	1875
1973	41.51	50,660	6.34	1792	2763.36	2025
1974	56.23	53,046	6.58	1950	2630.31	2324
1975	54.06	54,213	9.84	2672	3206.03	3072
1976	54.40	64,363	7.75	2641	3352.17	4475
1977	48.00	63,809	7.57	5319	4878.52	5462
1978	48.33	68,774	7.40	6136	5414.77	8015
1979	56.48	74,106	7.68	6433	5797.43	8016
1980	61.36	79,199	5.77	8198	5634.49	8161
1981	55.74	89,395	5.29	12,291	6412.52	7943
1982	60.02	93,742	5.18	14,250	5249.45	6762
1983	65.54	94,491	5.74	14,619	4239.45	5441
1984	62.23	86,795	5.15	13,343	3525.05	4650
1985	63.54	78,558	4.04	12,294	3462.15	4341
1986	47.25	72,737	5.00	11,618	3350.73	3923
1987	40.95	66,467	5.96	9512	2941.65	3660

* Cumulative dose is used here to describe summary dose recieved by cohort members in a given calendar year.

leukaemia, leukaemia excluding chronic lymphatic leukaemia, myeloid leukaemia, acute myeloid and monocytic leukaemia, multiple myeloma, and lung. These types of cancer have previously been associated with exposure to ionising radiation.

Darby and Reissland [58] proposed a test for the trend that permits an examination of mortality in the cohort in relation to recorded radiation dose after adjusting for other factors. Prior to application of the Darby–Reissland test, the data are grouped into a number of categories or strata. The strata to be used in the present study are job type, latency, calendar period (in 5-year increments) and age (in 5-year increments).

After allocating observed deaths to the relevant strata, the Darby–Reissland test for the trend in mortality with increasing dose is based on the statistic

$$T = \sum_{i,j} d_j (O_{ij} - E_{ij}).$$

here O_{ij} is the number of deaths observed in the jth dose category of the ith stratum, E_{ij} is the number of deaths expected in the jth dose category of the ith stratum (conditional on the total number of deaths in that stratum calculated under the null hypothesis of no radiation effect), d_j is the mean dose for all individuals in the jth dose category over the entire cohort, and the summation is over all dose categories and over all strata that could provide any information about a trend in death rates with dose. Thus, strata in which there are no observed deaths or where all the person-years fall in a single-dose category are excluded. Under the null hypothesis, the variance of T is given by

$$\mathrm{var}(T) = \sum_i \left[\sum_j d_j^2 E_{ij} - \left(\sum_j d_{ij} E_{ij} \right)^2 \Big/ \left(\sum_j O_{ij} \right) \right],$$

where the subscript i runs over all informative strata. The standardised statistics $T/[\mathrm{var}(T)]^{1/2}$ is approximately nor-

mally distributed. Large values of the statistic provide evidence against the null hypothesis.

Breslow and Day [57] proposed a similar test statistic

$$T = \sum_{i,j} d_j(O_{ij} - E_{ij}).$$

with variance

$$\text{var} = \sum_i \left[\sum_j d_j^2 E_{ij} - \left(\left(\sum_j d_{ij} E_{ij} \right)^2 \Big/ \left(\sum_{i,j} O_{ij} \right) \right) \right].$$

Here, however, the summation is over all strata, not just informative strata. Under the null hypothesis the standardised statistic $T^2/[\text{var}(T)]$ follows chi-squared distribution with one degree of freedom.

Dose–response relationships. A key assumption in the analysis of grouped data is that disease rates are constant within each cell of the multidimensional cross-classification. This assumption can be made more plausible by refining the classifications, although computational difficulties may still arise in coping with a large number of cells and estimating large number of parameters.

Analyses of dose–response relationships will be based on a relative-risk Poisson-regression approach. A major strength of Poisson-regression methods for the analysis of survival data is the ease with which one can include time-dependent covariates, including time itself, in the models. In particular, once the data have been grouped, fitting a model with time-dependent covariates requires no more computation than fitting a model (with the same number of parameters) in which the covariates do not vary with time. The use of Poisson-regression methods for data of this type have been discussed by Breslow and Day [57], Preston and colleagues [59], Frome [60], and Laird and Oliver [61].

Modelling of any observed dose–response relationships will be done using the AMFIT program developed by Preston and colleagues [62]. The generalised risk models available in AMFIT include both relative and absolute risks models as special cases. AMFIT uses a Gauss–Seidel algorithm that allows models to include large numbers of multiplicative stratum parameters. If the number of deaths is sufficiently large this stratification obviates the need to develop explicit models for background rates and leads to a grouped data version of the semi-parametric proportional hazards model [63].

Exposure and response variables considered

The focus of this study is on the relationship between occupational exposure to radiation and mortality due to cancer and other causes. Although exposure to tobacco and other environmental and occupational risk factors will contribute to worker mortality, adjustment for such confounders is not possible in a record-linkage study of this type based on existing administrative databases in which this information is stored.

Cause of death. For the purpose of the present analyses, causes of death will be grouped into the 42 broad categories shown in Table 8. The test for trends with an increasing exposure will be performed for all 42 causes of deaths. The results of the trend test will be used to select those cancer sites that will be subjected to a detailed dose–response analysis using Poisson regression.

Table 8. Categories of death

1	Tongue and mouth
2	Salivary gland
3	Pharynx
4	Oesophagus
5	Stomach
6	Colon
7	Rectum
8	Liver, primary
9	Liver, non-specific
10	Gall-bladder
11	Pancreas
12	Larynx
13	Nose
14	Prostate
15	Testis
16	Kidney
17	Bladder
18	Melanoma
19	Other skin
20	Brain, nervous system
21	Thyroid
22	Bone
23	Connective tissue
24	Non-Hodgkin's lymphoma
25	Hodgkin's disease
26	Leukaemia
27	Leukaemia excluding chronic lymphatic leukaemia
28	Myeloid leukaemia
29	Acute myeloid and monocytic leukaemia
30	Multiple myeloma
31	Lung
32	All cancer
33	Infective and parasitic
34	Endocrine and metabolic
35	Circulatory
36	Respiratory
37	Genito-urinary system
38	Accidents
39	All causes
40	Breast
41	Uterus including cervix
42	Ovary

Types of radiation. The types of radiation included in the NDR are listed in Table 4. In the analysis, doses from X-rays, gamma radiation and neutrons will be combined into a single variable, external whole-body radiation. Trends and dose–response relationships will be investigated for the following four categories: external whole-body; tritium; radon daughters; and combined external whole-body and tritium.

Exposure categories and radiation threshold reporting limits. The cumulative lifetime dose for each individual is obtained by summing the doses experienced during monitoring periods varying from one week to one year. The dose measured during each period is subject to a threshold reporting level, depending both on the quality of radiation and the type of dosimeter. For example, the threshold reporting limit for gamma radiation using current TLD monitors is 0.2 mSv, with doses below the threshold reported as 0.0 mSv. Thus, a null result confirms only that the actual exposure is in the range of 0–0.2 mSv. Combining exposures across reporting periods to construct the

cumulative lifetime dose will increase the range of uncertainty when a number of null readings are included in the total. This uncertainty can be appreciable when many records are accumulated over a period of years.

In the initial analysis of the NDR data, null results will be assumed to correspond to zero exposure. If warranted, a detailed analysis of this source of error will be undertaken.

Job and organisational classifications. The job classifications used by the NDR are given in Table 5. Grouping of job classifications will be considered in the study to reduce the number of different job classification types. Stratification by job category affords an opportunity to adjust to some extent for the potential confounding effect of socioeconomic status (SES).

Subsets of the NDR cohort may be selected for special study on the basis of occupations of special interest, the magnitudes of accumulated lifetime personal doses, on the basis of their likelihood of having received internal exposure, or for the collective dose for the group as a whole. Such subsets include reactor workers, uranium miners, medical and related workers (e.g. radiologists, radiological technicians and nurses), and industrial radiographers. This would involve analysis of mortality rates similar to that for the full cohort.

Time variables. Time variables that are available for analysis include age, calendar year, age at first exposure, latent period, and exposure lag. Because radiation-induced solid cancers are believed to have a minimum latent period, and to aid comparability to other studies, analyses have been conducted in which person-years and cancer deaths were excluded for a period after first exposure. Various latent periods have been examined (0, 2, 5, 10 years) in previous studies. In the present study, a short latent period (2 years or less) is considered to be most appropriate for leukaemia and bone cancer, whereas a longer latent period of up to 10 years may be most appropriate for the remaining sites.

The term exposure lag refers to the time from which an exposure is received until the time at which the disease of interest is induced. By lagging radiation doses by 5 years, doses received in the 5 years previous to death will be ignored. Lag periods of 0, 2, 5 and 10 years will be used in the initial analyses.

Cumulative exposures to different radiation types may vary with time. Therefore, cumulative exposure to external whole body, tritium and radon, and respective exposure categories are time-dependent variables. Cumulative exposures were classified into exposure categories as the subjects moved through the study period. Exposure categories are as follows:

External Whole-body and Tritium Exposure Categories (mSv):

0:	=0.00
1:	>0.00– <0.50
2:	0.50– <5.00
3:	5.00– <10.00
4:	10.00– <20.00
5:	20.00– <50.00
6:	50.00– <100.00
7:	100.00– <200.00
8:	200.00– <400.00
9:	>400.00

Radon Daughters Exposure Categories (WLM):

0:	=0.00
1:	>0.00– <0.20
2:	0.20– <10.00
3:	10.00– <50.00
4:	50.00– <100.00
5:	100.00– <200.00
6:	200.00– <300.00
7:	300.00– <400.00
8:	400.00– <500.00
9:	>500.00

The proposed methodology will be used to quantify the effects of long-term, low doses of radiation on the mortality of the National Dose Registry cohort.

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