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Health Effects, Dosimetry and Radiological Protection of Tritium

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Health Effects, Dosimetry and Radiological Protection of Tritium

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TABLE OF CONTENTS

EXECUTIVE SUMMARY ..... **vii**

1. INTRODUCTION **1**

2. PHYSICAL, CHEMICAL AND RADIOACTIVE PROPERTIES OF TRITIUM **2**
2.1 Radioactive Properties 2
2.2 Chemical Forms and Properties 3
2.2.1 Tritiated Water 3
2.2.2 Tritiated Gas 3
2.2.3 Organically Bound Tritium 3

3. ADVERSE HEALTH EFFECTS DUE TO TRITIUM **5**
3.1 Deterministic Effects 6
3.1.1 Lethality 6
3.1.2 Teratogenic Effects 7
3.1.3 Reproductive Effects 9
3.2 Stochastic Effects 11
3.2.1 Carcinogenicity 11
3.2.2 Hereditary Effects 13
3.2.3 Adverse Health Effects of Organically Bound Tritium 14
3.3 Non Radiological Effects of Tritium 16
3.3.1 Transmutation 16
3.3.2 Isotopic Effect of Tritium 17
3.4 Conclusion on Adverse Health Effects 17

4 EPIDEMIOLOGY **21**
4.1 Introduction 21
4.1.1 Types of Epidemiological Studies 21
4.2 Studies of Radiation Workers 23
4.2.1 United Kingdom Atomic Energy Authority Workers 24
4.2.2 Atomic Weapons Establishment Workers 27
4.2.3 Three Groups of UK Classified Workers 28
4.2.4 British Nuclear Fuel Limited Capenhurst 29
4.2.5 Chapelcross Nuclear Reactor Workers 30
4.2.6 Sellafield Nuclear Workers 31
4.2.7 UK National Registry for Radiation Workers: Mortality and Cancer Incidence Following Occupational Radiation Exposure 32
4.2.8 United States: Savannah River Site Workers and Other US Nuclear Workers 33
4.2.9 Canada: Atomic Energy of Canada Limited and Other Canadian Nuclear Workers 35
4.2.10 The International Agency for Research on Cancer Multi-Country Worker Studies 39

4.3 Case-Control Studies of *In Utero* Exposure and of Offspring of Radiation Workers 41
4.3.1 Case-Control and Cohort Studies of Childhood Leukaemia Around British Nuclear Plants ... 41
4.3.2 Congenital Malformations and Occupational Exposure to Low-Level Ionizing Radiation at the Hanford Site ... 47
4.3.3 Congenital Anomalies in Offspring of Ontario Hydro Power Workers ... 48
4.4 Studies of Environmental Releases and People Living in the Vicinity of Nuclear Facilities ... 51
4.4.1 Childhood Leukaemia in Communities Around Nuclear Installations in Britain ... 51
4.4.2 Congenital Malformations, Childhood Leukaemia and Mortality in Communities Around Nuclear Sites in the United States ... 54
4.4.3 Birth Defects, Childhood Leukaemia, Infant Mortality and Other Health Indicators in Communities Around Canadian Nuclear Facilities ... 56
4.4.4 Childhood Cancer and Leukaemia in Communities near German Nuclear Power Plants ... 59
4.4.5 Incidence of Childhood Leukaemia Near Nuclear Sites in France ... 67
4.4.6 Meta-Analysis of Childhood Leukaemia in Proximity to Nuclear facilities . 70
4.4.7 Authoritative Reviews of Epidemiological Studies of Childhood Leukaemia Around Nuclear Facilities ... 71
4.5 Review of Tritium Epidemiological Studies ... 73
4.5.1 United Kingdom Report of the Committee Examining Radiation Risk of Internal Emitters ... 73
4.5.2 The Independent Advisory Group on Ionizing Radiation's Review of Epidemiological Studies of Exposure to Tritium ... 74
4.6 Discussion ... 75
4.7 Conclusions ... 78

5 RELATIVE BIOLOGICAL EFFECTIVENESS ... 80
5.1 RBE Literature Reviews and Experimental Studies ... 81
5.1.1 Straume and Carsten (1993) ... 81
5.1.2 Advisory Group on Ionizing Radiation Report (HPA, 2007) ... 82
5.1.3 Little and Lambert (2008) ... 84
5.1.4 Kocher, Apostoaei and Hoffman (2005) ... 85
5.1.5 Dietze and Alberts (2004) ... 85
5.1.6 Fairlie, I. (2007) ... 86
5.1.7 Environment Canada/Health Canada – Releases of Radionuclides From Nuclear Facilities (Impact on Non-Human Biota) ... 87
5.1.8 Myers and Johnson (1991) ... 87
5.2 Summary of Relative Biological Effectiveness Determinations ... 88
5.2.1 *In Vivo* Studies Using X-rays as the Reference Radiation ... 88
5.2.2 *In Vivo* Studies Using Gamma Rays as the Reference Radiation ... 90
5.2.3 *In Vitro* Studies Using X-rays as the Reference Radiation ... 94
5.2.4 *In Vitro* Studies Using Gamma Rays as the Reference Radiation ... 96
5.2.5 Relative Biological Effectiveness Studies – Summary ... 102
5.3 Factors Affecting RBE ... 105
5.3.1 Reference Radiation ... 105
5.3.2 Dose and Dose Rate Effects ... 106

5.3.3 Dosimetric Considerations 108
5.3.4 Experimental Environments 108
5.3.5 Biological Endpoints 109
5.3.6 Electron Energy and Ionization Path Lengths: Why Tritium Radiation Is More Effective Than Gamma Radiation 109
5.4 Summary and Conclusions 112

6 DOSIMETRY AND BIOKINETICS 114
6.1 Overview of Current ICRP Models for Tritiated Water and Organically Bound Tritium 114
6.2 Internal Dosimetry of Tritiated Compounds using the ICRP HTO Model 115
6.2.1 The ICRP Model for the Inhalation and Ingestion of Tritiated Water 115
6.2.2 Absorption of HTO Through Skin 117
6.2.3 Inhalation of Elemental Tritium Gas 117
6.2.4 Tritiated Hydrocarbons 117
6.2.5 Metal Tritides 118
6.2.6 Summary of Dose Coefficients Based on the ICRP HTO Model 118
6.3 Internal Dosimetry of Tritiated Compounds Using the ICRP OBT Model 119
6.4 Intakes of Tritium in Relation to Pregnancy and Nursing 121
6.4.1 Pregnancy and Tritium Intake 121
6.4.2 Nursing and Tritium Intake 123
6.5 Review of Currently Available Information About the Biokinetics of Tritiated Compounds 124
6.5.1 Dosimetry of Tritiated Compounds Using the HTO Model 124
6.5.2 Absorption of HTO Through Skin 127
6.5.3 The inhalation of elemental tritium gas 128
6.5.4 Intake Resulting From Skin Contact With Tritium-Gas-Contaminated Surfaces 129
6.5.5 Ingestion of Organically Bound Tritium 130
6.5.6 Biokinetics of Tritiated DNA Precursors 134
6.6 Summary and Conclusions 135

7 OPTIONS FOR ASSESSING AND CONTROLLING RISKS ASSOCIATED WITH TRITIUM EXPOSURE 138
7.1 The ICRP's Approach to Radiation Protection From Internal Emitters 138
7.1.1 Change the Radiation Weighting Factor (w_R) 140
7.2 Summary and Conclusions 143

8 CONCLUSIONS 145

9 GLOSSARY 148

10 ABBREVIATIONS 167

11 UNITS 170

12 REFERENCES 171

LIST OF TABLES AND FIGURES

Figure 2.1: Decay Formula for Tritium 2

Table 3.1: Overview of Studies Showing Lowest Concentration or Administered Dose of Tritum to Produce an Adverse Effect 18

Table 4.1: Summary of the UKAEA Cohort and Prostate Cancer Standardized Mortality Ratios (1946–79) 24

Table 4.2: Summary of the UKAEA Cohort and Prostate Cancer Standardized Mortality Ratios (1946–97) 26

Table 4.3: Rate Ratios (and Numbers of Deaths) Among Workers Monitored for Tritium in Three United Kingdom Radiation Workforces 29

Table 4.4: Comparison of Estimates of Excess Relative Risk per Sv (and 90% Confidence Intervals) for Cancer in the NRRW and the Japanese Atomic Bomb Survivors 33

Table 4.5: Summary of Cancer Mortality Excess Relative Risk Results (1956–85) 36

Table 4.6: Summary of Cancer Mortality Excess Relative Risk Results 38

Table 4.7: Summary of Cancer Mortality Excess Relative Risk Results 40

Table 4.8: Lymphatic Leukaemia and Non-Hodgkin's Lymphoma: Observed and Expected Numbers With Relative Risks by Father's Assessed Exposure to Tritium Prior to Child's Conception 43

Table 4.9: All Leukaemias and Non-Hodgkin's Lymphoma: Observed and Expected Numbers with Relative Risks by Father's Assessed Exposure to Tritium Prior to Child's Conception 44

Table 4.10: All Leukaemias and NHL: Observed and Expected Cases by Potential Exposures to Tritium and Trichloroethylene 44

Table 4.11: Odds Ratios for Leukaemia Cases Among Offspring of Workers Monitored for Tritium in Ontario 49

Table 4.12: Adjusted Odds Ratios for Aetiological Groups of Congenital Anomalies According to Tritium Exposure (Recorded Dose 60 Days Before Conception vs. None) 51

Table 4.13: Observed and Expected Number of Cases of Acute Childhood Leukaemia within Circles with the Radii Shown 54

Table 4.14: Summary of Childhood Leukaemia Relative Risks in the Vicinity of German Nuclear Power Plants, 1980–95 60

Table 4.15: Summary of Childhood Leukaemia Standardized Incidence Ratios Near the Krümmel Nuclear Power Plant in Hamburg, Germany, 1990–2005 61

Table 4.16: Estimated Parameters From the Conditional Logistic Regression Model with Continuous Exposure (1/distance in km) for Leukaemia and Subtypes (under 5 years of age) 63

Table 4.17: Estimated Odds Ratios for Two Distance Categories for All Leukaemias and Subtypes (Under 5 years of Age) 63

Table 4.18: Comparison of Leukaemia Odds Ratios for Different Categories of Distance, as Derived from Regression and Categorical Analysis 65

Table 4.19: Leukaemia Odds Ratios as Derived from Previous Ecological Studies and the Case-Control Study 65

Table 4.20: Distribution of Childhood Leukaemia Cases and Standardized Incidence Ratios for Different Distances from Nuclear Power Plants Operating in France between 1990 and 1998 67

T**able 4.21:** Distribution of Observed and Expected Numbers of Childhood Leukaemia Cases by Age and Category of Estimated Dose Due to Gaseous Discharge in the Vicinity of 23 Nuclear Sites in France (1990–2001) 69

Table 4.22: Distribution of Leukaemia Cases in Children less than 5 Years of Age and SIRs at Different Distances from France's 19 Operating Nuclear Power Plants between 1990 and 1998 70

Table 5.1.1: *In Vivo* Studies using X-rays as the Reference Radiation 98

Table 5.1.2: *In Vivo* Studies using Gamma Rays as the Reference Radiation 99

Table 5.2.1: *In Vitro* Studies using X-rays as the Reference Radiation 100

Table 5.2.2: *In Vitro* Studies using Gamma Rays as the Reference Radiation 101

Table 5.3: Statistical Summary of Studies Determining the RBE of Tritium Radiation under Different Experimental Conditions 103

Table 5.4: Track Average LET in Water for Various Radiations Based on a Cut-Off Energy, Δ, of 100 eV 110

Table 6.1: Parameters Describing the Distribution and Retention of Tritium after Acute Intakes of Tritiated Water 116

Figure 6.1: ICRP Model for the Biokinetics of Tritiated Water 116

Table 6.2: ICRP Dose Coefficients Based on the ICRP HTO Model for Various Tritiated Compounds, Modes of Intake and Age Groups 118

Table 6.3: ICRP Dose Coefficients for HTO Inhalation for Various Age Groups 119

Figure 6.2: ICRP Model for the Biokinetics of Organically Bound Tritium 120

Table 6.4: ICRP (1993) Partitioning between HTO and OBT after Dietary Intakes of OBT 121

Table 6.5: ICRP (1996) Dose Coefficients based on the ICRP OBT Model for Various Modes of Intake and Age Groups 121

Table 6.6: ICRP (1996) Dose Coefficients for OBT Ingestion for Various Age Groups 121

Table 6.7: ICRP (2001) Selected Prenatal and Infant Dose Coefficients 123

Table 6.8: ICRP (2004) Selected Nursing Infant Dose Coefficients 124

Table 6.9: Selected Tritium Retention Half-Lives in Humans Following Intakes of Tritiated Water 125

Table 6.10: Parameters for the HTO Model Recommended by Taylor (2003) 127

Table 6.11: Adult Dose Coefficients from Physiologically-Based OBT Biokinetic Models 133

Table 7.1: Recommended Radiation Weighting Factors 141

EXECUTIVE SUMMARY

In January 2007, the Canadian Nuclear Safety Commission (CNSC) held public hearings related to the licensing of a tritium handling facility. During these hearings, questions arose on the following issues:

- handling, control and releases of tritium
- tritium drinking water limits
- tritium's fate in the environment
- health effects of tritium exposure

To expand the body of knowledge on tritium and to identify opportunities to further enhance regulatory oversight of tritium-related activities in Canada, the Commission Tribunal directed CNSC staff to undertake tritium-related research. In response, staff initiated the Tritium Studies Project, which involved several information gathering and research activities that extended to 2010. A fact sheet detailing the objectives and schedule of these studies is available at nuclearsafety.gc.ca.

This report on the *Health Effects, Dosimetry and Radiological Protection of Tritium* has been prepared as part of the Tritium Studies Project. The study's objectives were to:

- conduct an independent review of scientific literature to assess the health risk to workers and the public from exposures to tritium
- assess Canadian and international dosimetry practices for tritium intakes
- review the current approaches for limiting exposure to tritium

To meet these objectives, this report provides:

- an overview of tritium's physical, chemical and radiological properties
- a detailed analysis of the health effects of tritium radiation, including reviews of laboratory and epidemiological studies
- a review of experimental studies estimating the relative biological effectiveness (RBE) of tritium radiation
- a description of biokinetic models and dosimetry of tritium
- a review of the approach taken by the International Commission on Radiological Protection (ICRP) for protection from tritium and possible modification of the radiation weighting factor (w_R)

Physical, Chemical and Radiological Properties of Tritium

Tritium, the only radioactive isotope of the element hydrogen (symbol T or ^3H), has a nucleus that contains one proton and two neutrons. Its atoms can replace hydrogen atoms in any molecule. Tritium can also replace hydrogen in water molecules to form tritiated water (HTO), in organic molecules to form organically bound tritium (OBT), and in air to form tritiated gas (HT).

Tritium occurs both naturally and as a byproduct of the operation of nuclear power and research reactors. It can pose a health risk if it is ingested through drinking water or food, or if it is inhaled or absorbed through the skin in large quantities.

Tritium is one of the lowest energy beta particle emitters; therefore, when it enters the body, it gives a lower radiation dose, per disintegration, than other radioisotopes.

Health Effects of Tritium

Laboratory Studies

To date, no human studies have demonstrated that tritium causes cancer. However, laboratory studies using animals have demonstrated that tritium — like other sources of radiation — can interfere with the development of an embryo or foetus, and that it can induce genetic and reproductive effects and cell death but only if delivered at doses that are millions of times higher than those to which members of the public are exposed. Tritium has also been shown to induce and promote cancer in animals under some experimental conditions, but only at similarly high doses. It is important to note that the quantity of tritium required to induce these effects is in the order of gigabecquerels (that is, billions of tritium atoms decaying and emitting a beta particle per second) per gram of body weight and at doses above 500 millisieverts (mSv). In comparison, the public dose limit for non-medical, man-made sources of radiation is just 1 mSv per year and the worker dose limits are 50 mSv per year or 100 mSv over a 5-year period.

Epidemiology Studies

Epidemiological studies based on good-quality radiation exposure data provide the best source of evidence for estimating human health risks from radiation exposure. This is because such studies assess actual health outcomes in humans from radiation exposure.

Many epidemiological studies involving tritium-exposed radiation workers, their offspring, and members of the public living near nuclear facilities and several major authoritative reviews of the scientific literature have been reviewed for this report. Although the studies reviewed provide much information on the relationship between exposures to radiation and the occurrence of health effects such as cancer, they do not contain enough data to specifically estimate the health risks of tritium exposure.

However, based on extensive epidemiological research and the lack of excess risk found from total radiation exposures there is little evidence to suggest that increased birth defects, cancer incidence or mortality occurs in populations exposed to tritium at current environmental or occupational levels.

The lack of current evidence of an excess risk among these populations suggests that any tritium-specific related health risk would be negligible and not distinguishable from similar risks observed in the general population.

Future studies could be based on epidemiological studies of workers with tritium-specific exposures and good-quality dosimetric information. However, the limited number of tritium workers in the individual countries (such as Canada, UK, USA and France) and their generally small tritium exposures would make it difficult to detect any health effects of tritium exposure

with confidence (that is, the studies would have low statistical power). An international collaborative study combining the tritium workers data from multiple countries would be required to provide the necessary study power to assess tritium risk properly.

Health Effects – Conclusions

Tritium exposures are highly unlikely to cause adverse health effects in members of the public or in workers, given that the doses to which these groups are exposed are far below those doses where effects have been shown.

- In Canada, doses to members of the public from tritium releases from nuclear facilities are far below the public dose limit. In fact, doses from tritium exposures among people living near Canadian nuclear facilities are in the range of 0.0001 to 0.1 mSv/year. These are not only well below the limit, but also are negligible compared to natural background radiation, (approximately 2 to 3 mSv/year depending upon geographic location).
- Workers in tritium handling facilities receive only a small part of their total radiation doses from tritium, and receive a typical total average dose of under 1 mSv per year.

Relative Biological Effectiveness

Relative Biological Effectiveness (RBE) is a value that is used to compare the effectiveness of different types of radiation in causing the same biological result. By correcting for the RBE of different types of radiation, it helps form a special unit of dose — the sievert (Sv) — which can be used for protection from all types of radiations. It is also useful in conducting what is called retrospective studies. These studies are done when a more exact measurement of the dose is desired such as when there has been an exposure high enough to require medical treatment or in epidemiological studies where you need the best estimate of each individual dose.

Much of the discussion in this report and others has focused upon choosing an appropriate single value for the RBE of tritium radiation. There are more than 50 different estimates of the RBE for tritium. However, considerable variation and uncertainty in the radiobiological data exists making it difficult to choose a single RBE value. The RBE data largely differs because its reference radiation also has variations: that is, the two types of radiation (x-rays and gamma rays) usually used as the reference radiation have different RBE values of their own.

Studies to determine a single value for tritium radiation's RBE indicate that:
- where x-rays are chosen as the reference radiation, an RBE value of about 1.4 would be appropriate.
- if gamma radiation is chosen as the reference, an RBE value closer to 2.2 would be indicated.

Gamma radiation appears to be the preferred choice of reference, based on the arguments presented in ICRP 92 (2003), which states that the atomic bomb survivors were mostly exposed to gamma radiation. As such, gamma radiation is also usually the radiation studied in experiments that examine the effects of chronic (long-term) radiation exposure and is the largest source of radiation exposure to workers.

For chronic occupational and public exposures, the most relevant health outcome for the determination of an RBE is cancer caused by radiation.

The use of a RBE of 1 in the current ICRP radiation protection framework has not decreased the level of protection afforded to workers or members of the public. This is because implementation of optimization has resulted in exposures to tritium that are very low and well below doses at which an increased risk of cancer has been observed.

Dosimetry

Radiation doses from tritium cannot be measured directly and so are usually estimated by measuring the tritium in bioassay samples (such as urine) or through environmental monitoring. Once an estimate of the quantity of tritium in the body is made, the dose can be calculated by using biological models that estimate the concentration of tritium in organs and tissues.

To estimate the dose resulting from the intake of tritium, compounds that contain tritium are often categorized as one of the following: those that behave as tritiated water after they have entered the body, and those that behave as organically bound tritium after entering the body. This report also addresses tritium absorbed through the skin from HT-contaminated surfaces. The biokinetics of tritiated compounds in relation to pregnancy and to nursing are also discussed.

The ICRP recommends two main metabolic models to estimate the dose from compounds that contain tritium:

1. **the ICRP HTO model**, estimates the dose resulting from intakes of tritiated water or other tritiated compounds that partially convert to HTO after being taken into the body.
   - This model is used to assess doses from intakes of HTO in the form of liquid and for HTO formed from intakes such as tritium gas (HT), tritiated hydrocarbon vapours and gases (such as methane), and tritiated particulates (for example, airborne particles that contain tritium). The compounds in this category that give the greatest dose-per-unit intake are tritiated particulates of moderate and low solubility as well as tritiated water. Tritiated water by far results in the highest doses from intakes of tritiated compounds by workers and the public.
   - In the case of pregnancy, maternal intakes of tritiated water result in doses to the foetus of about twice those received by adults for equal intakes of tritium.

2. **the ICRP OBT model**, estimates doses from intakes of various tritiated organic compounds.
   - This model applies to the inhalation and ingestion of organically bound tritiated compounds, which yield dose-per-unit intakes about double those of tritiated water. It is used to estimate doses to the public resulting from dietary intakes of organically bound tritium; for example, from tritium bound to nutrients.

A new model (Taylor, 2003) has recently been proposed for HTO. This model differs from the ICRP model in its treatment of OBT formed in the body after tritiated water is inhaled or ingested. It currently applies only to adults and would need to be expanded to account for

various age groups before it could be used to estimate doses to members of the public in a regulatory context. While the ICRP OBT model appears to be generally consistent with experimental results, it does not account for the different ways that OBT deposits in organs versus tissues. The validation and incorporation of models, such as the Taylor (2003) model, in computer codes would make it easier to assess doses from OBT. Furthermore, the expansion of such a model to include age dependency for all age groups — including the breast-feeding infant exposure pathway — would be valuable particularly in situations of very high exposures such as in accidents. Overall, for current public and worker exposures to tritium the ICRP models provide reasonable estimates of dose and hence of risk.

Options for Assessing and Controlling Risks Associated with Tritium Exposure

As the world's foremost group in radiation protection, the ICRP has formulated what it believes to be a practical, working system of radiation protection that is scientifically based with straightforward assumptions. The ICRP's principles and recommendations from ICRP 60 (1991) have been adopted both in Canada and internationally to protect radiation workers and members of the public from radiation.

The ICRP radiation protection framework is based upon three key principles:

- Justification: the benefit to the exposed individuals or society from an activity using radiation must offset the harm it causes.
- Optimization: Doses have to be kept as low as reasonably achievable (ALARA), taking into account economic and societal factors and limitations.
- Application of dose limits: Doses to persons, other than from medical exposures, should not exceed the appropriate ICRP specified limits.

The ICRP has developed a broad, but simplified system of protection to implement this framework. The system allows exposures from all types of radiation to be added together, and it provides limits to reduce the likelihood of both stochastic risks (such as cancer) and deterministic risks (such as skin reddening and radiation burns).

The ICRP has designed the sievert (Sv) to give a measure of dose for all ionizing radiations. This is achieved by applying weighting factors (w_R) for the different types of radiation (i.e., alpha, beta and gamma) and for the radiation sensitivities of different organs and tissues.

However, it should be noted that the sievert is strictly a unit used for radiation protection purposes. It provides a single unit for dose from all ionizing radiations for optimazation purposes and for comparison against dose limits. In addition doses are gender neutral such that equivalent and effective doses are calculated for a "representative person" based on a population of males and females, ethnicity and age.

The ICRP approach has been criticized in how it treats exposure to tritium. The ICRP assigns a w_R weight of 1 to all low-linear energy transfer (LET) radiation, including tritium's beta radiation, despite the extensive evidence that suggests that the RBE for tritium-induced cancer may be more than twice that of other low-LET radiation.

The radiation weighting factor w_R is a factor by which an absorbed dose (in gray) is weighted for the purpose of determining the equivalent dose (in sievert). The w_R for a specified type and energy of radiation has been selected to be representative of values of the RBE of that radiation (e.g. tritium beta radiation) in causing stochastic effects (e.g. cancer) at low doses.

Using a different w_R for tritium to reflect the RBE value (e.g. 2.2 relative to gamma radiation) would best reflect the radiation risk for tritium. However it is important to consider that:

- The apparent improvement in correlation with risk may be misleading given the existence of many other uncertainties due to other significant variables (sex, age, weight, metabolic rates, genetic susceptibilities, etc.)
- It would be inconsistent with the ICRP system of radiattion protection due to the fact that
    - There are no other isotope specific w_R
    - It would be difficult to compare radiation protection practices nationally and internationally

Conclusions

Overall, the *Health Effects, Dosimetry and Radiological Protection of Tritium* study has come to the following conclusions:

1. The lines of evidence, based on both epidemiological and laboratory studies reveal that adverse health effects due to tritium exposure at current exposure levels in Canada are highly unlikely.
2. The results of over 50 experimental studies related to the determination of a single RBE value for tritium confirm that tritium beta radiation is about 1.4 times more biologically effective than radiation from x-rays of 250 kVp and 2.2 times more biologically effective than gamma ray radiation.
3. Current dosimetry and biokinetic models for assessing dose are acceptable for radiation protection purposes.
4. Canada's current regulatory framework is satisfactory for controlling tritium exposures.

1 INTRODUCTION

In Canada, in addition to the CANDU nuclear power plants that produce tritium, there are several nuclear facilities that use tritium in their product lines and are licensed by the Canadian Nuclear Safety Commission. In January 2007, during public hearings related to the licensing of one such facility, questions arose on the handling practices, control and releases of tritium, tritium drinking water limits, tritium's fate in the environment and the health effects to humans due to exposures of tritium from CNSC-licensed activities. To better understand tritium-related issues, the Commission Tribunal directed CNSC staff to initiate research studies in the areas cited above. In response, CNSC staff initiated in 2007 a Tritium Studies Project with several information-gathering and research activities extending to 2010 (a fact sheet detailing the objective and schedule of these studies is available on the CNSC's Web site at nuclearsafety.gc.ca).

This report provides an independent review of scientific literature to assess the health risk to workers and the public from tritium exposure. It also assesses Canadian and international dosimetry practices for tritium intakes. In addition, during the literature review and discussions with members of the International Commission on Radiological Protection (ICRP) and other relevant experts, it became evident that the reasoning behind the recommendations of the ICRP to protect workers and the public from ionizing radiation is not well understood by regulators, members of the public and the scientific community. Since Canada has largely adopted the ICRP recommendations, a discussion of the ICRP approach, and possible alternatives was also included in this report.

The objective and scope of this report provide:

- an overview of tritium's physical, chemical and radiological properties
- a detailed analysis of the adverse health effects of tritium radiation, including reviews of laboratory and epidemiological studies
- a review of experimental studies estimating the relative biological effectiveness (RBE) of tritium radiation
- a description of biokinetic models and dosimetry of tritium
- a review of the ICRP's approach for protection from tritium and possible modification of the radiation weighting factor

The report is a review and interpretation of the scientific and technical information described above and does not make any recommendations.

The information in this report will be analysed by CNSC staff in combination with the results of the other Tritium Studies Project reports to produce a synthesis report. The synthesis report, including any recommendations that may impact oversight and regulation, will be submitted to the commission tribunal.

2 PHYSICAL, CHEMICAL AND RADIOACTIVE PROPERTIES OF TRITIUM

Hydrogen, the simplest and most common element, has three isotopes:

- protium (H-1), which contains only a proton in its nucleus and is by far the most common hydrogen isotope
- deuterium (H-2), which contains a proton and a neutron
- tritium (H-3), which has a proton and two neutrons, and is hydrogen's only radioactive isotope

Tritium is produced:

- naturally through various interactions of cosmic rays and atoms in the atmosphere — the principal one being the neutron irradiation of nitrogen
- as a byproduct of the operation of nuclear and research reactors including the capture of a fission neutron by a deuterium atom, or neutron capture by Boron-10 and Lithium-6

In Canada, tritium is produced through the operation of nuclear power plants (NPPs) and used by several companies in their product lines. The CNSC report *Tritium Releases and Dose Consequences in Canada 2009* (CNSC, 2009) contains further details of tritium production rates and releases in Canada.

2.1 Radioactive Properties

- Tritium decays to a stable form of helium by emitting an electron from its nucleus (beta radiation) and an antineutrino (see Figure 2.1):

Figure 2.1: Decay Formula for Tritium

$$^{3}\mathrm{H} \rightarrow {}^{3}\mathrm{He} + e^{-} + \overline{\nu_e}$$

- It has a radioactive half-life of 12.3 years and a specific activity of 3.56×10^{14} Bq/g.
- The emitted beta particle has a mean energy of 5.7 keV and a maximum energy of 18.6 keV. Despite this very low energy, these particles possess sufficient energy to ionize atoms and molecules.
- Due to its very low energy, tritium's beta radiation has a very short range (approximately 6 mm) in dry air, is completely absorbed by sheets of plastic, glass or metal, and cannot penetrate dead layers of skin. However, this beta radiation can pose a health risk if tritium is taken into the body. The maximum range of a tritium beta particle is approximately 6 µm in living tissue (Carsten, 1979), compared to typical cells (or cell nuclei) that have diameters from about 7 to 30 µm (nuclei of about 6 to 15 µm) (Virsik *et al*, 1980).
- Due to its very low energy, tritium's beta radiation has a low dose per unit activity concentration in the body, compared to that of other radioisotopes. For example, to produce a dose of 1 Gray (Gy) about 1,000 times more tritium disintegrations would be required than from the alpha radiation from Polonium-210.

2.2 Chemical Forms and Properties

Tritium is almost chemically identical to the other hydrogen isotopes and can exist in several chemical forms including:

- tritiated water (HTO)
- tritiated gas (HT)
- organically bound tritium (OBT)

2.2.1 Tritiated Water

The most common form of tritium is tritiated water (HTO), where a tritium atom replaces a hydrogen atom in water (H_2O) to form HTO. HTO has the same chemical properties as water and is also odourless and colourless. Water with a tritium activity of 1 Bq/L, contains less than 1 tritium atom per 100,000 million, million (1 in 10^{17}) molecules. The majority of tritium in the atmosphere is in the form of HTO and can be transferred to humans by inhalation, skin absorption (liquid and vapour) (Pinson and Langham 1957, DeLong *et al* 1954), or ingestion of drinking water or food (ICRP, 1979; Belloni *et al*, 1983). HTO exposure is generally the most important consideration in assessing dose, since HTO quickly reaches equilibrium with water in the body and is distributed uniformly to all soft tissues. ICRP (1979) recommended that internalized HTO be assumed to be completely and instantaneously absorbed and distributed uniformly with all body water. As a result, at all times, the concentration in sweat, sputum, urine, blood, perspiration, and exhaled water vapour is taken to be the same (Hill and Johnson, 1993). HTO is excreted via urine, feces, sweat, and breath (NCRP, 1979).

2.2.2 Tritiated Gas

Tritiated gas (HT) is formed when a tritium atom replaces a hydrogen atom to form a tritium-hydrogen bond. In its elemental form, HT is an invisible, odourless gas chemically identical to hydrogen gas. HT is relatively inert in biological systems and has a very low uptake into body fluids and tissues (Hill and Johnson, 1993). The main exposure pathways of HT include inhalation or skin contact with HT-contaminated surfaces. Releases from tritium processing facilities (such as self-luminous light manufactures, tritium recovery facilities and nuclear fuel processing facilities) represent the primary source of exposure to HT. HT can be oxidized in the atmosphere to HTO. If deposited on the ground, it is converted to HTO through microbial agents near the soil surface (Amano *et al*, 1995).

2.2.3 Organically Bound Tritium

Following an intake of tritium (typically in the form of HTO) by plants or animals, a fraction of the tritium can become incorporated into organic molecules such as carbohydrates, fats, or proteins and is termed organically bound tritium (OBT)[1]. Within the body, OBT can become incorporated into various compounds such as amino acids, sugars, and structural materials

1 Note: OBT is an acronym that stands for organically bound tritium and is not a chemical formula such as HT and HTO.

such as collagen (Rochalska and Szot, 1977; Saito and Ishida, 1989). OBT can also enter the body directly by ingestion of tritiated food, by inhalation of volatile organic vapours or aerosols, or it can be formed *in vivo* from tritium that is present in the general body pools after exposure to other tritium-containing compounds (Diabaté and Strack, 1993). If the tritium atom is attached to a carbon atom in an enzymatically catalyzed reaction, it is essentially fixed to that molecule until the molecule is metabolized. Conversely, tritium atoms bonded to oxygen, sulphur, nitrogen or phosphorous atoms will readily exchange with hydrogen atoms in the surrounding cellular water and are therefore considered as an exchangeable tritium compound (Diabaté and Strack, 1993). While both forms can be regarded as OBT, it is the non-exchangeable carbon-bound tritium that exhibits longer retention time in the body characteristic of organic molecules. Tritium-hydrogen exchange reactions occur in organic molecules with chemical groups such as nitrogen monohydride (NH), hydroxyl (OH), and thiol (SH). Non-exchangeable tritium is incorporated into more stable bonds with carbon atoms by enzyme catalyzed reactions (Diabaté and Strack, 1993).

Recap: Section 2

- Tritium is the only radioactive isotope of the element hydrogen.
- Tritium atoms can replace hydrogen in water molecules to form tritiated water (HTO), in organic molecules to form organically bound tritium (OBT) and in air to form tritiated gas (HT).
- Tritium is one of the lowest energy beta particle emitters. When it is incorporated into the body, more tritium is required than other radioisotopes to cause the same dose.
- Tritium occurs both naturally and as a by-product of the operation of nuclear power and research reactors. It can pose a health risk if it is ingested through drinking water or food, or if it is inhaled or absorbed through the skin in large quantities.

3 ADVERSE HEALTH EFFECTS DUE TO TRITIUM

Tritium beta radiation does not penetrate the dead outer layer of the skin. Therefore, tritium only poses a health risk if inhaled, ingested or absorbed into the body through the skin. If the chemical form is HTO, it will not collect in any specific tissue or organ but will distribute itself uniformly throughout the body. If it is part of an organic molecule, it may be incorporated into specific molecules or tissues. Generally speaking, the proximity of tritium to key molecules — principally deoxyribonucleic acid (DNA) — will determine the importance of the damage it will inflict when it undergoes nuclear transformation and emits a beta particle. Since HTO and most forms of OBT are assumed to be uniformly distributed in body tissues and cells, one would expect intakes of tritium to result in radiation effects similar to that of whole-body exposures from other types of low-linear energy transfer (LET) radiation, such as x-rays and gamma rays. Of course, the severity of the damage would vary according to differences in the relative biological effectiveness (RBE) of the different radiations as well as to dose and dose rate effects.

An exception to these direct interactions is a phenomenon known as the "bystander effect", where non-irradiated cells exhibit the same symptoms as nearby irradiated cells. This has been demonstrated in many studies (UNSCEAR, 2009), using primarily alpha particle and photon irradiation but the effect has also been demonstrated in a study using tritium (Persaud *et al*, 2005). Most of the studies have been conducted *in vitro*, but the bystander effect has been observed in a limited number of *in vivo* studies and it is thought to be due to an unidentified chemical messenger. What is known is that the bystander effect occurs at the cellular level of biological damage and any damage induced by it will have already been accounted for in dose-response assessments.

As with all other forms of ionizing radiation, adverse health effects from tritium exposure can be classified as deterministic or stochastic.

Deterministic Effects:
- occur within relatively short timeframes after exceeding a dose threshold
- there is an increase in severity (e.g., cataracts, skin reddening) as dose increases

Stochastic Effects (cancer and hereditary effects):
- are assumed not to have dose thresholds
- have a greater chance of occurring as dose increases

At low radiation doses (such as those below ≈ 100 mSv), the primary radiation protection concern is cancer or, to a lesser extent, hereditary effects. At higher doses, tritium can cause deterministic effects and even death. To date, the only reported deterministic effects from tritium exposure are the deaths of two Russian workers in 1953 (Soloviev *et al*, 2001; Melintescu *et al*, 2007).

Sections 3.1 and 3.2 review several studies looking at deterministic and stochastic effects, respectively. The review of deterministic effects includes lethality (death), teratogenicity

(birth defects), and reproductive effects. The review of stochastic effects includes carcinogenicity (cancer) and hereditary effects. Section 4 reviews epidemiological studies on workers and in the public that have been exposed to tritium.

3.1 Deterministic Effects

3.1.1 Lethality

Brues *et al* (1952) demonstrated the lethality of tritium by inducing death in mice by administering one-time tritium injections of 0.37 to 1.11 GBq (5–15 Gy to organs). The researchers reported a lethal dose ($LD_{50/30}$) that would kill 50% of the population within 30 days of 37 MBq/g of body weight (BW) (a typical adult mouse weighs about 40g (U. of Iowa, 2002) so the total intake is approximately 1.5 GBq). This dose compares to a $LD_{50/30}$ of about 6 Gy for acute exposures to 250 kV x-rays. A similar result was found by Furchner (1957) who determined a $LD_{50/30}$ value of 8 Gy, by a single injection of about 30 MBq to female mice. Yokoro *et al* (1986) (see also Yamamoto *et al*, 1990) found a $LD_{50/30}$ of about 8 Gy from a single injection of 0.56 GBq in one strain of mice and 0.93 GBq injection in another. The estimated lowest total dose causing haematopoietic death by continuous oral administration was 11.1 Gy. Tritium likely required a higher dose to cause death than acute x-rays because of dose protraction effect; that is, a tritium dose is delivered over several days, as opposed to a dose delivered in just a few minutes via x-ray exposure.

Yamamoto *et al* (1990) investigated chronic intakes of HTO that would be lethal in mice by continuously administered HTO. They found that the concentration of tritium reached a plateau in organs and blood after about 7 days. A typical time of 2 weeks for haematopoietic death occurred following intakes of drinking water with tritium concentrations from 148 to 592 GBq/L. The lowest total dose inducing death was 11 Gy at a drinking water concentration of 148 GBq/L. All observed deaths were due to haematopoietic failure.

Although details are vague, tritium was reported to be the cause of death of two workers in 1953 in Chelyabinsk-40 (now Ozyorsk) Russia. Doses were estimated at 10 to 12 Gy, indicative of massive intakes (Soloviev *et al*, 2001; Melintescu *et al*, 2007).

In summary:

- The radiation dose from tritium necessary to cause death in mice is slightly greater than an acute external irradiation by x-rays or gamma rays, with a tritium $LD_{50/30}$ of about 6–9 Gy. This corresponds to an acute intake in the order of 1 GBq or a chronic dose of about 11 Gy (~ 0.5 GBq) when tritium is orally administered.
- An unusual finding was that haematopoietic death prevailed over the gastrointestinal syndrome following the exposure to radiation from tritium. The latter would have occurred if a similar dose had been given with gamma or x-rays (Yamamoto *et al*, 1990).

3.1.2 Teratogenic Effects

Teratogenic effects occur when an agent interferes with the development of an embryo or a foetus *in utero*. Teratogenic effects are not hereditary; that is, they are not passed on to future generations. In general, a tissue's sensitivity to radiation is directly proportional to the rate of proliferation of its cells. Therefore, a foetus that is rapidly developing from an embryo is expected to be more sensitive to radiation than an infant, child or adult. This inference is supported by the results of experiments in animal models, and by experience with human populations exposed to doses of radiation above 100 mSv (for example, medical exposures, atomic bomb survivors) and by childhood leukaemia cases observed when children had been irradiated in the womb with doses from 10 to 20 mSv (Brenner *et al*, 2003). Radiation's most significant harmful effects to the human foetus include mental retardation, delayed intrauterine growth and childhood cancers (such as leukaemia) (BEIR III, 1980; BEIR VII, 2007).

Straume and Carsten (1993) reviewed current literature looking at tritium exposure during foetal development. They pointed out that some foetal cells rapidly divide during certain stages of development, and differentiate to form organs and tissues while containing others such as neurons or oocytes involve very little or no further cell proliferation. Consequently, tritium that is incorporated into "long-lived" molecules (becoming OBT) could result in large integrated doses over the lifetime of the cells, since the tritium would not be diluted by further cell proliferation. The dose from tritium incorporated into molecules such as DNA and histones of rapidly dividing cells was small compared to the dose from HTO as observed by Commerford *et al* (1982). Conversely, for long-lived cells, the dose from tritium incorporated into DNA and histones could exceed that from HTO. This was also discussed in some depth by the Advisory Group on Ionising Radiation (AGIR) reporting to the UK Health Protection Agency (HPA, 2007) and will be presented in the following discussion on reproductive effects. The AGIR (HPA, 2007) concluded that tritium could be incorporated during pregnancy into the DNA of foetal oocytes and remain there until fertilization decades later; however, it also concluded that DNA is not a stable molecule and that due to a turnover of its molecules over time, although the net effect of this on dose is small. The net radiological impact of this phenomenon is unclear, but would be related to dose and the amount of tritium deposited within the DNA of the long-lived cells. To be deposited within DNA, tritium would have to be bound to a specific organic molecule (such as a nucleic acid) that could become part of a DNA molecule. All OBT compounds represent a fraction (~13%) (Brown, 1995) of the total tritium in the environment, but OBT molecules could be any one of the thousands of different types of organic molecules. It is therefore reasonable to expect that a low number of OBT compounds are used to build DNA. The section of the report on reproductive effects (see section 3.1.3) discusses this phenomenon in more detail.

Dekaban (1968) first summarized radiation-induced teratogenic effects in humans when he reported developmental effects due to medical x-ray treatments in the 1920s and early 1930s, when radiation was widely used to treat many diseases. The report evaluated a group of children who were exposed *in utero* to radiation when their mothers had pelvic x-ray exposures. Doses of 200–300 R (~2–3 Gy) consistently induced foetal damage. The following were the most frequent anomalies identified in children who were irradiated during intrauterine life were:

(1) small size at birth and markedly stunted growth, (2) microcephaly, (3) mental retardation, (4) microphthalmus, (5) pigmentary degeneration of the retina, (6) genital and skeletal malformations and (7) cataracts. However, Mulvihill *et al* (1991) later reported that these effects depend on gestational age and that other case reports of radiotherapy during pregnancy showed that anomalies did not always develop.

Zamenhof and Van Marthans (1979) studied how five generations of rats were affected by pre- and post-natal exposure to HTO. Female rats were given HTO (111 kBq/mL) beginning in adolescence and throughout pregnancy. This exposure to tritium did not produce any signs of radiation illness or increase in cataract formations in the mothers. The courses and outcomes of pregnancy were also normal, but 60% of the newborn rats exhibited hematomas, edemas and subdural haemorrhages. None of these effects lasted beyond 30 days of age.

A study by Laskey *et al* (1973) maintained rats on activities of 0.37–370 kBq HTO/mL of body water from conception of the first generation until delivery of the second generation. The corresponding dose rates were 0.03–30 milligray per day (mGy/d). An exposure to 370 kBq/mL of body water resulted in a 30-percent weight reduction of the testes in the first-generation of adult males, but there was no impairment of growth or reproductive ability. The following were noted in the second-generation of newborns: a relative reduction of brain weights at exposures of 3.7–370 kBq/mL (0.3–30 mGy/d); a decrease in body weight at 37 kBq/mL (3 mGy/d) and 370 kBq/mL (30 mGy/d); a decrease in litter size and an increase in resorption at 370 kBq/mL (30 mGy/d). In their discussion Laskey *et al* (1973) noted that similar effects had not been observed in other studies with comparable doses of Cobalt-60 gamma radiation. Laskey *et al* (1973) did not observe litter size effects or resorption either at or below 37 kBq/mL (~3 mGy/d), although higher dose rates showed statistically significant reductions in the weights of both male and female rats.

Bursian *et al* (1975) looked at effects on rats continuously exposed to HTO concentrations of 0, 37, 370 and 3,700 Bq/mL from conception to birth. The *in utero* exposure to doses as low as 0.66 Gy (370 kBq/mL) produced measurable and persistent decreases in brain weight and increases in norepinephrine concentrations at 21 and 45 days post-natal. No differences from controls were observed in the rate of turnover or the concentrations of dopamine, acetylcholinesterase or monoamine oxidase; although it is unclear what effects would have occurred at different concentrations.

In an experiment by Jones *et al* (1980), drinking water containing HTO was given to pregnant squirrel monkeys at levels ranging from 16 to 1000 times the "permissible level for human consumption." At the time, the maximum permissible concentration for tritium in drinking water was 111 kBq/L or about 16 times higher than the current Canadian drinking water guideline of 7,000 Bq/L. No effects in newborn progeny were seen in terms of body weight, body dimensions, organ weights, hematological patterns, the histology of organs, or tissues, with the exception of the ovaries. Dobson *et al* (1974; 1976) found a decrease in the number of immature oocytes at the highest doses.

In summary, tritium radiation-induced teratogenic effects have been demonstrated in laboratory studies and are consistent with similar effects from external photon radiation. Teratogenic effects in animal studies start to occur at doses of about 0.4–0.6 Gy from chronic intakes of HTO.

3.1.3 Reproductive Effects

Reproductive organs and tissues in both males and females are among the most radiosensitive tissues, with mature gametes being the most sensitive cells. In the male, spermatogenesis is a proliferative and continuous process, where sperm originate from spermatogonial stem cells and undergo many developmental stages, from the primordial germ cell to the mature spermatozoa. This process continues throughout adult life and due to continual replenishment, testis are among the most radiosensitive tissues.

In the female, germ cells are called oocytes. They are produced in the ovary and give rise to the ovum (egg), which can be fertilized. Oocyte formation (oogenesis) occurs in the female during foetal life, with primary oocytes produced in the ovaries of the foetus by the fifth month of pregnancy. About 7 million primary oocytes are initially produced but only about 400,000 remain by puberty. The oocyte development process includes several stages of maturation, from the production of oogonia from primitive germ cells to development of primary oocytes and formation of definitive oocytes at puberty.

Effects in the Female

Since tritium distributes itself throughout the body, it can be taken up by a developing oocyte and incorporated in its DNA. Tritium incorporated into oocyte DNA could theoretically irradiate the oocytes over a period of 30 or more years. Because oocytes do not divide until fertilized, there is little turnover of the DNA molecules which implies that the biological half-life of the tritium imbedded in oocyte DNA could approach the radioactive half-life of tritium, 12.3 years. The AGIR (HPA, 2007) points out that while a biological process gradually exchanges all the components of DNA molecules — including that of tritium-labelled DNA — it would take 50 years to replace 2 to 5% of a cell's genome (DNA). Therefore, most of the tritium incorporated in an oocyte will remain there for its whole life.

Straume and Carsten (1993) reviewed tritium effects on oocytes, reporting that most of the information on radiosensitivity in humans came from autopsies of women who had been exposed to substantial doses of external radiation (Lushbaugh and Ricks, 1972), and from fertility histories of women exposed to radiation from therapy or atomic bombs (Lushbaugh and Casarett, 1976; Baker and Neal, 1977; UNSCEAR, 1982). In all cases, the data were for adult women.

Available data for human females suggest that in adult women, maturing and mature oocytes are more sensitive than immature ones. This is in contrast with observations of mice, whose immature oocytes are by far the most sensitive to radiation killing — about 100 times more sensitive than matures ones (Baker, 1971). In women, an exposure of 2.5–6 Gy will lead to permanent sterility (effect on resting oocytes) (ICRP, 1984; BEIR, 1990). The threshold for

temporary effects on fertility appears to be at least 0.6 Gy of acute x-rays and 1.5 Gy for protracted or fractionated low-LET radiations (ICRP, 1984).

In studies on both mice and rats, Satow (1989a, b) looked at tritium effectiveness in killing oocyte. While the study primarily examined the RBE of tritium, significant oocyte reabsorbtion was found at HTO intakes of 0.17 MBq/g of body weight, corresponding to a total dose of 39 mGy (Baker, 1971).

To assess the risk that tritium radiation would damage oocyte DNA, the AGIR (HPA, 2007) modeled the dose and hereditary risk in a critical group of pregnant women, who consumed an annual total of 24 kg of tritium-contaminated flounder from Cardiff Bay. It was assumed that the flounder had a tritium concentration 50 kBq/kg, which implies that the critical group ingested 1200 kBq of OBT per year. At this rate of intake, the tritium in the body would reach an equilibrium concentration of 175 kBq. The model estimated that approximately 4% of oocytes could experience a tritium disintegration within the next 30 years following intake and that the frequency of severe hereditary effects resulting from this would be expected to be around 1 in 1,000,000 (10^{-6}). This is comparable to the 3–4% rate of spontaneous birth defects that are observable and inheritable.

Overall, female reproductive systems — and principally those of mice — appear to suffer the greatest adverse health effects from tritium exposure. As Baker (1971) reports, the mouse oocyte is about 100 times more radiosensitive than the human oocyte; therefore doses that affect mice oocytes would not be expected to affect human ones.

Effects in the Male

Unlike oocytes, spermatagonia are continuously produced from stem cells throughout adult life. Like all tissues that are rapidly replaced, there are certain germ-cell stages that are highly sensitive to cell killing by ionizing radiation. Experiments in mice have shown that the most sensitive cells are the type A and B spermatagonia, which can be reduced by 50% by doses of only about 0.3 Gy of acute x-rays (Oakberg, 1955; 1959, as reported in Straume and Carsten, 1993). The spermatid and spermatozoa stages are much less sensitive than the spermatogonia stage (Oakberg and Clark, 1964 as reported in Straume and Carsten, 1993). Lambert (1969) found a 27 percent reduction of mouse spermatagonia that were injected with tritiated thymidine (3HDtr) at a dose of 185 kBq/g of body mass and with HTO at a dose of 2,220 kBq/g of body mass (dose to the nucleus of 84 mGy and 49 mGy, respectively).

Although the results are from a single individual, UNSCEAR (1982) reported temporary sterility after doses of only 0.15 Gy of acute x-rays and permanent sterility after acute doses of 3 to 5 Gy (UNSCEAR, 1982). Chronic exposure studies in dogs demonstrate that x-ray dose rates of 1–2 mGy/d do not impair sperm production (BEIR, 1990). If these data were transposed to humans it would imply that the threshold for reduced sperm production in the adult male may be in the order of 10 mGy/d. For continuous exposure, this would add up to 3–4 Gy/y (Straume and Carsten, 1993). A dose of 10 mGy/d due to tritium would require an intake of about 500 MBq/d or about 3,500 times higher than the Canadian drinking water

guidelines of 14,000 Bq/d (assuming a daily consumption of 2 L of water with a tritium concentration of 7,000 Bq/L).

In summary, spermatagonia appear to be particularly radiosensitive with respect to cell killing, but a significant reduction in numbers would require intakes of tritium a million times or more greater than exposure in routine occupational settings or from drinking water at the current Health Canada drinking water guideline.

3.2 Stochastic Effects

3.2.1 Carcinogenicity

Carcinogenicity is the ability of a radiological, chemical or biological agent, to produce cancer. Ionizing radiation was one of the first such agents observed to induce cancer from its early uses in the 1900s. Many of the first researchers were unaware of the risk that radiation presented and succumbed to radiation-induced cancer. The study of populations exposed to radiation such as the atomic bomb survivors, medical patients, and nuclear energy workers, has provided the basis of our current radiation dose limits. Most of the populations studied were those exposed to external radiation, such as x-rays, gamma rays or neutrons. Risks to humans from exposure to internal emitters are largely limited to uranium miners exposed to radon progeny, radium dial painters and patients injected with thorotrast (BEIR, 1988). While epidemiological studies are ongoing, to date no human studies have ever demonstrated tritium-induced cancer (see also Section 4).

Due to a lack of direct experimental evidence, the cancer risk posed by internal emitters to humans has largely been derived from populations that received high, external exposures such as those in the Japanese atomic bomb survivors Life Span Study (UNSCEAR, 2000). Many studies have looked at the incidence of cancer among laboratory animals exposed to gamma radiation and x-rays. While it did not involve exposures to tritium, one of the most comprehensive studies on the effects of radiation was done by Tanaka *et al* (2007), who looked at cause of death and neoplasia in 4,000 mice exposed to Cesium-137 gamma rays at 21, 1.1 and 0.05 mGy/d. Equal numbers of male and female mice were exposed for approximately 400 days with resultant doses of 8,000, 400 and 20 mGy. Compared to the non-irradiated controls, there was a significantly higher frequency of myeloid leukaemia in males, of soft tissue neoplasms and malignant granulosa cell tumours in females, and of hemangiosarcoma in both sexes exposed to 21 mGy/d (8 Gy cumulative dose). The number of multiple primary neoplasms per mouse was also significantly increased in mice irradiated at 21 mGy/d. Both sexes exposed to 21 mGy/d had significantly shorter life spans than control groups, but only the females had significant shorter life spans when exposed to 1.1 mGy/d (0.4 Gy). Females exposed to 0.05 mGy/d (0.02 Gy cumulative dose) also had a shorter average life span by about 8 days, but this was not statistically significant.

Many laboratory studies on animals have clearly demonstrated that tritium can induce cancer, although this has not been studied as extensively as gamma and x-ray exposures.

In Yamamoto *et al* (1995), HTO was administered to mice in drinking water at concentrations that ranged from 9.25 GBq/L (0.240 Gy/d) to 0.37 GBq/L (0.010 Gy/d). Female mice maintained on this drinking water survived for more than 150 days, but 70 to 80% of them developed tumours. In the range from 1.85 to 9.25 GBq/L of HTO (0.048–0.240 Gy/d), the main cause of death was thymic lymphoma. However, at 0.925 GBq/L (0.024 Gy/d), the incidence of thymic lymphoma was lower, while tumour incidence was greater. In addition, tumour types became more diverse at lower concentrations of HTO. The latent period of tumour development was shorter and the life-shortening effect was more marked in this tritium beta irradiation study than in other studies that used x-ray or gamma irradiation. However, Yamamoto *et al* (1995) did not attempt to estimate the RBE of the tritium exposure.

Yamamoto *et al* (1998) administered tritiated drinking water to mice throughout their lives, resulting in dose-rates of 0.2, 0.9, and 3.6 mGy/d. The thymic lymphoma dose-response curve started to increase exponentially at about 0.9 mGy/d, giving a threshold at about 12 mGy/d (although there was no significant difference from controls at 0.9 mGy/d). The group receiving 3.6 mGy/d had significantly shortened life spans compared to controls, while the other groups did not. Increases in body weight were noted for the animals that received lower dose rates (0.9 mGy/d). Yamamoto *et al* (1998) concluded that the threshold dose-rate for tumour induction by HTO is around 12 mGy/d, and that the threshold dose-rate for Cobalt-60 gamma irradiation is higher than that for tritium beta irradiation.

Gragtmans *et al* (1984) estimated the RBE of tritium beta radiation to induce tumours in the breast tissue of rats. Incidence of mammary tumours over time was compared to that of controls in a rat strain where these tumours occur naturally. Tritium was injected intraperitoneally at concentrations of 45 to 370 MBq/100 g body weight followed by four additional injections at two-day intervals, producing doses of 0.46, 0.92, 1.63 and 3.85 Gy. The reference radiation was 200 kVp x-rays delivered over 10 days in doses of 0.29, 0.57, 1.1 and 2.0 Gy. There was early onset of the tumours at 150 days post-treatment for all irradiations when compared to controls. Since these animals would naturally develop mammary tumours, the irradiation likely decreased the onset time of the tumour but did not necessarily increase the overall incidence. Therefore, some care must be taken when interpreting the results.

Johnson *et al* (1995) estimated lifetime incidence of myeloid leukaemia in 7 groups of ~750 mice given single injections of HTO of 90, 180 or 270 MBq each, corresponding to doses of 0.85, 1.86, and 3.04 Gy. The incidence of myeloid leukaemia increased from 0.13% (control) to 6–8% (treated) with apparent excesses at the lowest doses. The calculated RBE for tritium beta rays was 1.0 ± 0.5 to 1.3 ± 0.3 (best estimate 1.2 ± 0.3) using chronic x-ray exposure as the reference radiation. The Johnson *et al* (1995) study primarily aimed to determine an RBE for tritium using myeloid leukaemia as an endpoint and not necessarily as a measure of the induction of myeloid leukaemia and other cancers. Therefore, while they reported on the incidence of other cancers, they did not determine the lowest dose of incidence. Other cancers such as reticulum cell sarcoma did occur, but usually at doses of 2 Gy or higher. Indeed, for some types of cancer, incidence appeared lower than in controls in both the tritium- and x-ray-irradiated animals, but no tests for significance were done to verify this.

Seyama *et al* (1991) examined the cumulative incidence of tumours in mice over different exposure regimes for tritium beta irradiation, neutrons, Cobalt-60 and Cesium-137 gamma radiation. Mice were injected with HTO intraperitoneally at concentrations of 0.14, 0.28, 0.56 and 0.74 GBq, giving doses of 1.97 Gy, 3.95 Gy, 7.90 Gy and 10.53 Gy, respectively. At 400 days, tumour incidence was 4%, 8%, 18% and 24% respectively, but by 500 days, incidences differed little among the groups. This indicated that even the lowest dose (1.97 Gy) was sufficient to elicit the same incidence of tumours, with higher doses simply accelerating the onset. Increased incidence of T cell lymphoma was also induced with 4 weekly injections of similar doses. Increased tumour incidence over controls was seen in the ovary, liver, lung, mammary glands, and uterus. There were also high incidences of lymphoma and leukaemia.

Balonov *et al* (1993) summarized Russian studies that exposed mice and rats to tritium. One of the studies reported (Mushkacheva *et al*, 1992) exposed mice through continuous HTO ingestion of 37–1,850 kBq/g/d, which delivered doses of 1.2 to 2.8 Gy. Damage to DNA was only observed at the end of the intake period in animals with the greatest intake. DNA repair was also found to be slower in this group compared to the controls. The data presented by Balonov *et al* (1993) showed that tritium induced many types of tumour, including leukaemia and solid cancers, in mice and rats.

A literature review by Straume (1993) analyzed the risks, including cancer, of exposure to tritium radiation. Because cancer risk information due to tritium radiation was not available for humans, cancer risk estimates for tritium were derived from human populations exposed to gamma and x-ray radiation and from experimental animal studies. Straume used a Monte Carlo sampling program to generate frequency distributions of excess cancer mortality from chronic, low-level exposure to HTO. He used frequency distributions for dose rate effectiveness factors from 1 to 12 (based upon animal studies), with a central value of the RBE for tritium between 2 and 3 and a range of 0–4.5. His analysis produced a skewed risk distribution with a 50th percentile risk per milligray of 81×10^{-6} with a 90% confidence range of 38 to 185×10^{-6} per mGy. This value is comparable to radiation risk estimates of ICRP (*1991*), BEIR (1990), and UNSCEAR (1988) which are 50×10^{-6}, 79×10^{-6}, and 70 to 110×10^{-6} per milligray, respectively.

Although the above studies demonstrate that tritium's beta radiation is carcinogenic, it remains uncertain at what dose tritium will induce cancer. The lowest dose observed to induce cancer in mice is in the range of about 1 mGy/d. The work by Straume (1993) perhaps gives the greatest insight into tritium-induced carcinogenesis and corroborates the risk factors presented by ICRP (*1991*), BEIR (1990), and UNSCEAR (1988).

3.2.2 Hereditary Effects

It is theoretically possible that damage to the chromosomes in oocytes or spermatagonia may be mutagenic and therefore carried forward in subsequent generations. However, the latest ICRP recommendations (ICRP 103, 2007) maintain that "there continues to be no direct evidence that exposure of parents to radiation leads to excess heritable disease in offspring." Nevertheless, based upon animal experiment results, the ICRP estimates a genetic risk of about 0.2 % per Gy for up to the second generation (grandchildren). For low-LET radiation, the ICRP value for

the probability of severe hereditary effects is 0.5% per Gy, based on extrapolation from male mouse data.

The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (2001) estimated genetic risks:
1) to a population sustaining low-LET, low-dose or chronic irradiation exposure generation after generation and
2) to a population that sustains low-LET, low-dose or chronic irradiation to one generation only.

In the first case, the total genetic detriment was estimated to be ~0.41 to 0.64 percent risk per parental Gy per million progeny above baseline (background incidence) to the first generation and ~0.53 to 0.91 percent risk per Gy per million progeny above baseline to the second generation.

In the second case, the total genetic detriment was again estimated to be ~0.41 to 0.64 percent risk per Gy per million progeny above baseline to the first generation. However, because only the first generation had received the continuous radiation exposure, the risk in the second generation dropped to 0.16 to 0.43 percent risk per Gy per million progeny above baseline.

As for the applicability of these risk estimates to tritium radiation, Straume and Carsten (1993) noted that the genetic effects observed for other low-LET radiations were also present following exposure to tritium, either from HTO or from OBT. By grouping RBE studies with genetic endpoints (such as chromosome aberrations and mutations in mice), they determined that the RBE ranged from 1 to 3, with the higher values associated with low doses and low-dose rates, (due largely to the curvilinear response of the reference radiation).

Therefore, it could be concluded that gamma rays were the reference radiation, then the genetic risk estimates from UNSCEAR and the ICRP could be doubled for the risk posed by tritium exposure. It should be noted, however, that this conclusion is based upon animal studies and that genetic effects in humans due to radiation exposure have never been observed to date.

3.2.3 Adverse Health Effects of Organically Bound Tritium

Some of the tritium released into the environment will naturally bind with organic molecules, either through enzymatically catalyzed reactions where a hydrogen atom is replaced by a tritium atom, or through natural exchange reactions. If the tritium atom is attached to a carbon atom in an enzymatically catalyzed reaction, it is essentially fixed to that molecule until the molecule is metabolized. Conversely, tritium atoms bonded to oxygen, sulphur, nitrogen or phosphorous atoms will readily exchange with hydrogen atoms in the surrounding cellular water and are therefore considered as an exchangeable tritium compound (Diabaté and Strack, 1993). Both non-exchangeable and exchangeable compounds are referred to as organically bound tritium (OBT). However, the non-exchangeable tritium will exhibit retention times determined by the metabolism of the molecules concerned, while the exchangeable tritium will be indistinguishable in its retention from that of HTO in cellular water.

OBT is a general term applying to a large group of compounds, where tritium is bound to organic molecules, including tritiated sugars, polysaccharides, lipids (fats), proteins and DNA precursors. The extent of cellular injury caused by an OBT molecule depends largely upon where it is incorporated into a cell and if it is there long enough for the tritium atom to decay. Tritiated DNA precursors, such as ^{3}HTdR, are theoretically more efficient at causing cellular injury since they form part of the basic building block of a DNA strand. On the other hand, tritiated molecules that are more remote from DNA in the cell such as a tritiated fat molecule or a tritiated amino acid in a structural protein, should pose a lesser risk.

Lambert (1969) studied the effects of HTO and ^{3}HTdR on rat spermatagonia and determined an RBE of 1.3 for ^{3}HTdR and 2.3 for HTO. He pointed out that these values should be viewed with caution due to uncertainty on several factors, such as the time of death of the spermatagonia and the amount of tritium that induced it.

One of the few studies looking at effects of tritiated amino acids and nucleosides was done by Furuno-Fukushi *et al* (1987) where they treated mouse lymphocytic leukaemia cells for 50 hours with ^{3}HTdR, lysine, arginine, leucine, and aspartic acid. Doses ranged from approximately 50 mGy to 800 Gy (as interpreted from graphical data). Cell survival decreased linearly for all compounds with effects greatest for thymidine, followed by arginine, lysine, leucine and aspartic acid; similar results were found for cell mutation frequencies. The concentrations for detectable cell killing and mutagenesis ranged from less than 37 kBq/mL for ^{3}HTdR, 37–370 kBq/mL for tritiated amino acids and 18.5–185 MBq/mL for HTO. Furuno-Fukushi *et al* (1987) compared the cell killing results of a previous study that examined the effects of HTO and gamma rays at similar doses and dose rates (Ueno *et al*, 1982), calculated RBEs of 2.9, 2.6 and 5.9 for mutation induction relative to low-dose rate gamma rays for HTO, tritiated amino acids and tritiated thymidine respectively. However, the use of non-concurrent reference radiaton controls places some doubt on these results. They also reported that the tritiated amino acids were distributed homogenously within the cell, as is the case for HTO.

Wang *et al* (1996) examined the effects of OBT on cultured mouse embryonic mid brain cells using ^{3}HTdR, uridine, arginine and glutamic acid. The cells were exposed to different concentrations of the tritiated compounds over a 20-hour period. Assays of cell proliferation and differentiation and DNA and protein content were conducted. To determine the RBE, cultures of cells were also exposed to 150 kVp x-rays at 0.5 Gy/min as the reference radiation. Calculated RBEs were in the range of 4.6 to 8.7 with the largest being for ^{3}HTdR. The study was heavily criticized by Trivedi *et al* (1997a) who pointed out various shortcomings; for example, the reference radiation was over a much shorter period than the tritium exposure, cell cultures were handled improperly and the data analysis was missing information.

In their review of the available studies on OBT, Straume and Carsten (1993) concluded that the RBE of tritium is somewhat larger than that of HTO when it is bound to amino acids, and is about 2 times higher than that of OBT when bound to nuclear bases like thymidine.

In summary, while many studies have examined how OBT is partitioned within the body and within the cell, studies specifically looking at health effects due to OBT are limited. Those

that are available indicate that most organic compounds have about the same RBE as HTO, since they are distributed throughout cells and do not lead to preferential irradiation of the nucleus. Incorporation of ^{3}HTdR, however, can lead to concentration of tritium in the nucleus, resulting in RBE values of about twice that of HTO, calculated on the basis of average cell/tissue dose. With the exception of DNA precursors, it can be concluded that the greater effect of OBT relative to HTO is due to longer retention times, and proportionately greater dose per Bq intake, rather than differences in RBE (see Chapters 5 and 6).

Occupational and public doses due to exposures to OBT would arise from a mixture of tritiated compounds, including amino acids, sugars, fats, nucleic acids and polysaccharides (in the case of public doses). There are some special instances where specific OBT compounds such as ^{3}HTdR would be used (for example, laboratory studies), but these would be under strictly controlled conditions to limit intakes. There are two relevant studies on this subject:

- Steel and Lamerton (1965) measured tritium activity in several different organs in juvenile rats after an injection of ^{3}HTdR. The greatest uptakes of ^{3}HTdR were in the bone marrow, the testis and the lungs. The lungs retained the ^{3}HTdR the longest, although at much lower concentrations than found in the bone marrow. The time for tritium activity to be reduced to half the initial amount ranged from 1 day for the colon to 25 days for the testis, although the retention period changed over the course of the experiment (up to 56 days) likely due to the reuse of the ^{3}HTdR.
- Lambert and Clifton (1968) showed that only about 2% of ingested ^{3}HTdR is incorporated into DNA.

3.3 Non Radiological Effects of Tritium

3.3.1 Transmutation

Transmutation is the conversion of one element to another through radioactive decay. When tritium undergoes decay, it becomes Helium-3 (^{3}He), a stable, inert gas. As a different element, it no longer holds the chemical properties of a hydrogen isotope, which could lead to detrimental consequences in addition to those caused by the radiation. For example, if a tritium atom is bound to a DNA molecule when it decays, most of the kinetic energy will accompany the beta radiation as it is ejected from the nucleus, but some energy will provide a “kick-back” to the ^{3}He atom as recoil energy. Kacena (1967) determined that the recoil energy is too small (about 3 eV) to cause ionization of the DNA molecule on its own. However, the resultant ^{3}He atom would then be attached to a carbon atom with a very weak bond. This bond would tend to break leading to a free helium atom and possibly an ionized DNA molecule. The ionized DNA molecule may then be repaired, or if irreparable, lead to permanent DNA damage.

Myers and Johnson (1991) performed a comprehensive review of transmutation effects. They pointed out that the degree of damage caused by transmutation of tritium to a helium atom could theoretically vary significantly, depending on the position of the tritium atom in specific DNA nucleotides. The studies also covered several test systems from the S13 virus, two strains of the bacterium *E. coli, Drosophila melanogaster* (fruit fly) and cultured mammalian cells. Based on the position of the tritium on the nucleic acid, varying degrees of damage were

noted — in one case, by a factor of 500 in the S13 virus. However, it should be noted that the S13 virus only has a single strand of DNA and therefore does not have the repair capacity of higher organisms. In summary, Myers and Johnson argued that it would be highly conservative to assume that the mutations observed in lower oragnisms would be detectable in mammalian cells, and that the number of detectable mutations in mammals (resulting from transmutation) would not likely exceed 5%.

Carsten (1979) discussed the possibility that such effects would be manifested in humans after ingesting HTO or OBT as food. He suggested that the risk was small enough to pose no significant hazard, primarily because only 2% of the DNA hydrogen is located at the 5-position of the cytosine ring; therefore, damage would be minimal. In their review, Feinendegen and Bond (1971) reached the same conclusion: "the effects of intracellular tritium are overwhelmingly due to beta irradiation of the nucleus" and "transmutation effects do not produce a measurable effect."

In any event, if DNA damage did occur from transmutation, it is unlikely that it could be discerned from radiation-induced damage and would be accounted for in the RBE. The AGIR (HPA, 2007) drew a similar conclusion.

3.3.2 Isotopic Effect of Tritium

With two additional neutrons, a tritium atom has approximately three times the mass of a conventional hydrogen atom (protium). While chemically equivalent to hydrogen, tritium has slightly different physical properties due to its increased mass. Diabaté and Strack (1993) noted that reaction rates decreased as atomic mass increased, causing a significant isotopic effect. Therefore, in reactions with HTO as a precursor, regular hydrogen would be preferentially used (instead of tritium) due to its lower atomic mass. However, as pointed out by the AGIR (HPA, 2007), any effects due to isotopic differences would be accounted for in the determination of RBE values.

3.4 Conclusion on Adverse Health Effects

Laboratory studies have demonstrated that tritium induces lethality, teratogenicity, genetic (chromosome aberrations) and reproductive effects. Tritium has also been shown to induce and promote cancer in mice under experimental conditions. Table 3.1 summarizes the studies reviewed in this report, although one should be careful when comparing the endpoints and the different dose regimes (injection or ingestion), especially with respect to the mouse oocyte. Generally, doses above 0.5 GBq and radiation doses of 0.5 Gy are needed to induce an adverse health effect. The exception to this, as discussed earlier, is the mouse reproductive system, whose oocytes are about 100 times more radiosensitive than that of humans.

Table 3.1: Overview of Studies Showing Lowest Concentration or Administered Dose of Tritum to Produce an Adverse Effect

Study	Means of Exposure	Test Animals	Parameter	Lowest Concentration or Administered Dose to Show Effect	Dose (When Available)
Lethality					
Brues *et al* (1952)	Single injection of HTO	Mice	$LD_{50/30}$	0.37 GBq/g body weight (BW) (~1.5 GBq total dose)	N/A
Yokoro *et al* (1986)	Single injection of HTO	Mice	Lowest dose	0.37 GBq	~5 Gy
Yokoro *et al* (1986)	Single injection of HTO	Mice	$LD_{50/30}$	0.56–0.93 GBq	~8–13 Gy
Furchner (1957)	Single injection of HTO	Mice	$LD_{50/30}$	0.035 GBq/g (~1.3 GBq total dose)	N/A
Yamamoto *et al* (1990)	Ingestion of HTO	Mice	Lowest dose	1.37 GBq	11.1 Gy
Teratogenic Effects					
Zamenhof and Van Marthans (1979)	Ingestion of HTO	Mice	No observed effects in mothers, temporary effects in offspring	111 MBq/L	N/A
Laskey *et al* (1973)	Ingestion of HTO	Mice	Lowest dose Reduced brain weight	3.7 MBq/L	0.00003 Gy/d
Bursian *et al* (1975)	Ingestion of HTO	Mice	Reduced brain weight and neural hormones	370 MBq/L	0.66 Gy
Jones *et al* (1980)	Ingestion of HTO	Squirrel monkeys	Oocyte reduction, no other noted effects	111 MBq/L	N/A

Study	Means of Exposure	Test Animals	Parameter	Lowest Concentration or Administered Dose to Show Effect	Dose (When Available)
Reproductive Effects					
Satow *et al* (1989a,b)	Injection of HTO	Mice	Oocyte reduction	0.17 MBq/g BW	0.035 Gy
Lambert (1969)	Injection of ^{3}HTdR	Mice	Reduction of spermatogonia	185 kBq/g BW	0.084 Gy (to cell nucleus)
Lambert (1969)	Injection of HTO	Mice	Reduction of spermatogonia	2.22 MBq/g BW	0.049 Gy (to cell nucleus)
Carcinogenicity					
Yamamoto *et al* (1995)	Ingestion of HTO	Mice	Thymic lymphoma	1.85 GBq/L	0.048 Gy/d
Yamamoto *et al* (1995)	Ingestion of HTO	Mice	Solid tumours	0.925 GBq/L	0.024 Gy/d
Yamamoto *et al* (1998)	Ingestion of HTO	Mice	Thymic lymphoma	0.463 GBq/L	0.012 Gy/d
Gragtmans e*t al* (1984)	Injection of HTO	Rats	Early onset of mammary tumour	0.45 MBq/g BW	0.46 Gy
Johnson *et al* (1995)	Injection of HTO	Mice	Myeloid leukaemia	90 MBq	0.85 Gy
Seyama e*t al* (1991)	Injection of HTO	Mice	Tumours	140 MBq	1.97 Gy
Mushkacheva *et al* (1992)	Ingestion of HTO	Mice	DNA damage	37 kBq/g/d	1.2 Gy

Because it is ionizing radiation, the tritium beta particle would also be expected to induce hereditary and reproductive effects. This is in line with an equivalent dose of gamma or x-ray radiation, although no studies were found to support this hypothesis. Similarly, non-cancer effects such as cardiovascular disease could also be expected as a result of radiation exposures to doses exceeding 0.5 Gy. Not surprisingly, the doses resulting from the amount of tritium needed to cause these effects are essentially the same as doses of other types of ionizing

radiation (gamma and x-ray) when the RBE and dose protraction are taken into account. Current risk estimates for tritium therefore appear to be appropriate.

In general, the greater biological effectiveness of OBT relative to HTO appears to be related to longer retention times, rather than to differences in RBE. DNA precursors are the exception, where preferential irradiation of the nucleus can give higher RBE values, expressed in terms of average cell dose. However, OBT concentrations in the environment are generally low and the compounds that pose the greatest risk (such as ^{3}HTdR) are not expected to approach concentrations anywhere near those that pose a significant risk.

Non-radiological effects from tritium such as transmutation and isotopic effects are likely, but if they do occur, it would not be possible to distinguish their effects from those of radiation. Therefore, they are taken into account in risk estimates and do not require special consideration.

Recap: Section 3

- To date, no human studies have demonstrated tritium-induced cancer.
- Laboratory studies using animals have demonstrated that tritium can interfere with the development of an embryo or foetus, and induce genetic and reproductive effects and cell death, if delivered at doses that are millions of times higher than what members of the public are exposed to.
- Tritium has been shown to induce and promote cancer in mice under some experimental conditions but only at extremely high doses (i.e., in excess of 500 mSv).
- In Canada, doses to members of the public from tritium releases from nuclear facilities are much lower than the annual public dose limit of 1 mSv.
- Doses to workers in tritium handling facilities average less than 1 mSv per year.
- Given the extremely low doses to members of the public and workers from tritium emissions, adverse health effects are highly unlikely.

4 EPIDEMIOLOGY

4.1 Introduction

Epidemiological studies based on good-quality radiation exposure data are the best source of evidence for attributing human health risks to radiation exposure, because they assess the actual health outcome to humans from this exposure. Epidemiological studies of the Japanese atomic (A) bomb survivors (Preston *et al*, 2003; 2004; 2007), patients treated with radiation (Boice *et al*, 1985; 1988; Weiss *et al*, 1994; 1995; Howe, 1995; Howe and McLaughlin, 1996; Little *et al*, 1999; Little and Boice, 1999) and radiation exposed workers (Lubin *et al*, 1995; Cardis *et al*, 1995; Cardis *et al*, 2005; 2007), have been assessed to estimate radiation risk coefficients (ICRP, *1991*; US NRC, 2006; UNSCEAR, 2000; 2008). Unfortunately there is little data specific to tritium. In epidemiological studies where tritium exposures exist, workers were also exposed to other radiations, particularly external gamma irradiation. Tritium specific exposures are often lacking from these assessments.

The risk to human health from internal emitters, especially tritium, has recently become a topic of considerable interest. In the following sections, we review the more important epidemiological studies and authoritative comprehensive reviews of the scientific literature to assess the human health risks from tritium exposure. Studies were identified by a comprehensive literature search, review of references, government publications and recommendations from researchers active in the field. There is considerable overlap between this discussion, that of the UK HPA Advisory Group on Ionizing radiation (HPA, 2007) and the analysis of Little and Wakeford (2008), as a result of the timeframe in which they were undertaken. This report includes a few very recent publications, provides more in depth analysis of the Canadian studies, and adds a Canadian perspective. The review assesses several studies: some where it is possible to draw inferences about tritium risk based on current analysis, some where estimates of risks from tritium may be possible in future analyses should tritium dose assessments become available, and some that are not capable of providing useful information on risks from tritium. Studies include cohort and case-control studies of radiation workers with occupational exposures to tritium, case-control studies of *in utero* exposure and offspring of radiation workers, and ecological studies of environmental releases and people living near nuclear facilities.

4.1.1 Types of Epidemiological Studies

The following is a brief description of the different types of epidemiological studies. It is necessary to understand basic epidemiology and the purposes, strengths and limitations of the various types of epidemiological studies to appreciate the information provided by each study type.

Epidemiology is the study of the distribution and causes of diseases in specified human populations and the application of this study to control disease (Porta, 2008; UNSCEAR, 2008). It is based on observation, not experiments, so the degree of bias will vary. A well-designed study will try to minimize potential biases. There are three main types of epidemiological studies: cohort studies, case-control studies, and ecological correlation (descriptive) studies.

Particular attention is given to the soundness of study design and the statistical power of any such study to reveal excess, radiation associated cancer. Discussion of statistical power, potential for systematic error and other sources of uncertainty, including those doses received, are a focus of this work.

Cohort studies are the strongest type of epidemiological study. These studies start with a defined group of individuals (the cohort) who are free of the disease under consideration, but who vary in exposure to a supposed noxious factor (such as occupational tritium exposure). Detailed information is gathered on each individual's exposure (for example, date of first and last exposure, time since exposure, annual and cumulative exposure, dose rate). Each member of the cohort is followed over time to determine differences in the rate at which disease (for example, cause of death, cancer diagnosis) develops in relation to his/her exposure to the noxious factor (Porta, 2008; UNSCEAR, 2008). Individuals with different exposures (or levels of exposure) are compared to assess differences in their probability (or risk) of developing or dying from a given disease (Porta, 2008; UNSCEAR, 2008). Cohort studies can produce useful information on the incidence and death rates of disease. They can also assess the risk (or probability) of developing a disease as a result of the exposure of interest (that is, assess whether tritium exposure was causally related to disease). They are efficient in studying rare exposures (such as occupational tritium exposure) and are not as prone to bias as case-control studies. However, they are very costly and require a large number of subjects and a long follow-up period. There may be problems in attrition of cohort members, and disease ascertainment, and changes in criteria and methods over time (such as requirements for reporting occupational tritium exposures and/or changes in dosimetry over time).

Case-control studies, unlike cohort studies, tend to focus on a single disease. People recently diagnosed as having a disease (cases) are compared with people who do not have the disease (controls). The purpose is to determine if the two groups differ in the proportion of persons who have been exposed to a specific factor or factors, with the aim of establishing an etiological (causal) relationship between the disease and factor. It compares cases and controls with regard to the presence of some element in their past. Data on individuals (the "cases") with a recently diagnosed specified disease (for example, childhood leukaemia) are assembled and matched with data on a suitable set of "control" (comparison/reference) individuals. The control individuals are otherwise similar to the cases (for example, the same age or sex, the same opportunity of having the exposure) but do not have the specified disease (Porta, 2008; UNSCEAR, 2008). Detailed information on exposures (for example, residence at birth, residence at death, parent's occupation, parent's occupational radiation exposure; number of years living in a home, number of hours at home per day) and other information (for example, smoking history, diet, exercise, genetic factors, other occupational exposures) are collected on both the cases and controls. The relationship between the exposure and the disease is examined by comparing the cases (diseased) and controls (non-diseased) with regard to the distribution of a number of exposures between the two groups (Porta, 2008; UNSCEAR, 2008). The advantage of a case-control study is that detailed histories of exposure and other information can be collected relatively easily, they are relatively inexpensive to carry out, the number of subjects can be small (especially for rare diseases), results can be obtained relatively quickly and they can identify more than one risk factor. However, case-control studies are prone to bias (such as

selection of appropriate controls, recall bias of past exposures), information from the past may be incomplete and there can be problems in selecting an appropriate control group and matching on variables (Porta, 2008; UNSCEAR, 2008). Thus, cohort studies are regarded as more reliable than case-control studies.

Descriptive ecological (correlation) studies compare the occurrence of a specific disease (observed) within a defined population, time and geographical area to the (expected) occurrence of the disease based on a stable reference population (for example, the general population of Ontario, or Canada). These studies analyze populations or groups of people, rather than individuals. An association observed between variables on an aggregate level does not mean the same association will exist at the individual level. This is the weakest type of epidemiological study since it operates at a group level, not an individual level, and data is averaged over groups (Porta, 2008; UNSCEAR, 2008). Mortality and morbidity statistics, reflecting the frequency of occurrence of disease in a population, are often routinely collected so ecological studies provide a readily available indicator of a disease's frequency in a population. They are useful monitoring tools for epidemiologists to identify high and low rates of disease in a population, which may warrant further study. They can identify trends over time or within groups. They are relatively simple, easy and inexpensive to conduct in comparison with case-control and cohort studies. However, when making conclusions, it should be made very clear that one cannot make conclusions/inferences/causal statements on the etiological factor (this is, if tritium was the cause of an increase or decrease in disease) in relation to the disease incidence/mortality because these studies do not examine individual exposures. Absolutely no conclusions can be drawn about the possible causal factors that could be associated with a disease. Information on exposures to individuals is not known, and no consideration is given to the multiple risk factors of disease (for example, diet, exercise, tobacco, alcohol or obesity) (Porta, 2008; UNSCEAR, 2008). On occasion, assignment of cumulative exposures is made to groups; however, many assumptions still exist and individual exposures are still unknown. This becomes especially important when a causal factor (such as tobacco smoking) is known to be strongly associated with the disease (such as heart disease, lung cancer). Mortality figures do not reflect the frequency of illnesses that are successfully treated, nor do morbidity figures accurately reflect the prevalence of illnesses that are not diagnosed by a medical professional or are not severe enough to require treatment or hospitalization. Errors in the assignment of place of residence are known to occur and are often not specific, particularly in rural communities. Population mobility and daily activities also affects the assignment of environmental exposures. Finally, the precision of the statistics is often limited because of the small numbers of observed and expected cases or deaths in small populations (Porta, 2008; UNSCEAR, 2008). This makes it extremely difficult to interpret results.

4.2 Studies of Radiation Workers

Several cohort and case-control studies of radiation workers with occupational exposures to tritium and other types of radiation have been conducted and are summarized below.

4.2.1 United Kingdom Atomic Energy Authority Workers

Beral *et al* (1985) studied mortality from low-level ionizing radiation in 39,546 United Kingdom Atomic Energy Authority (UKAEA) workers (Winfrith, Harwell, Culham and Dounreay) from 1946 to 1979. About 52% of the workers were monitored for radiation exposure. Yearly summary information from personal dosimeters was recorded for total whole-body doses. Information on internal sources, including tritium, was limited to noting the years in which subjects were monitored for possible contamination. Tritium doses were not evaluated. The mean dose for employees with a radiation record was 32.4 mSv. Doses attributed to tritium contamination were small. Overall, mortality rates among radiation workers (ages 15 to 74) were below the national mortality rates of England and Wales. The standardized mortality ratio (SMR) for all causes of death and all cancers were 0.76 (95% CI: 0.72–0.79; 2-sided $p<0.001$) and 0.79 (95% CI: 0.74–0.85; 2 sided $p<0.01$), respectively. There was a significant elevation in prostate cancer mortality compared to national rates in the cohort of 1,416 workers monitored for possible tritium exposure (SMR=8.89) (see Table 4.1). However, this was based on only 6 deaths. There was a statistically significant (2-sided $p<0.001$) trend of increasing prostate cancer mortality with film badge dose in the full cohort (tritium and non-tritium workers). Mortality was also high for prostate cancer in men with a single dosimeter reading exceeding 10 mSv (SMR=5.94) and those monitored for other unspecified radionuclides (SMR=2.54). There was considerable overlap in these exposure categories. The highest mortality ratio for prostate cancer was in younger men and was concentrated in a small group of workers who were monitored for possible exposure to tritium and had cumulative dosimeter readings exceeding 50 mSv (SMR=12.77). Because multiple exposures were common, and other relevant information was not available, the reason (such as the type of radiation) for the increased prostate cancer could not be determined. There was no statistically significant elevation in SMRs for nine other endpoints.

Table 4.1: Summary of the UKAEA Cohort and Prostate Cancer Standardized Mortality Ratios (1946–79), Beral *et al* (1985)

Category of Workers	Standardized Mortality Ratio	95% Confidence Interval	2-Sided p-Value
Monitored for possible tritium exposure	8.89	3.29–19.49	$p<0.001$
Single dosimeter reading exceeding 10 mSv	5.94	1.63–15.29	$p<0.05$
Monitored for other unspecified radionuclides	2.54	1.16–4.82	$p<0.05$
Monitored for possible tritium exposure, and had cumulative dosimeter readings exceeding 50 mSv	12.77	2.72–27.79	$p<0.001$

Fraser *et al* (1993) conducted a further mortality analysis of the UKAEA cohort with follow-up until 1986. Cancer mortality, based on 1,506 deaths from 1946 to 1986, was 20% below the national average. Cancer incidence, based on 1,699 registrations from 1971 to 1984 was,

12% below the national average. However, the SMR for prostate cancer in men monitored for tritium exposure was 2.82 (95% CI: 1.13-5.80, p=0.03). Prostate cancer mortality showed a statistically significant association with external radiation exposure, largely confined to men who were also monitored for internal contamination by radionuclides other than plutonium. Prostate cancer mortality was highest in radiation workers at Winfrith.

A case-control study by Rooney *et al* (1993) involved the follow-up of UKAEA workers for prostate cancer from 1946 to 1986. Data for 136 cases (deaths or diagnosis) of prostate cancer and 404 controls (comprised of 372 individuals, of whom 28 were matched to more than 1 case) were collected. Work histories of each case or control were examined in detail to assess possible internal contamination from a number of radionuclides (Chromium-51, Iron-59, Cobalt-60 or Zinc-65), including tritium, that were suggested by Rooney to be potentially associated with elevated risk. Potential exposure for each radionuclide was based on a four-point scale (none, possible, probable but low level, probable and relatively high level) from a health physicist's evaluation of each worker's work and exposure history (workplace, type of work done). The risk of prostate cancer was significantly increased in men who were internally contaminated with or who worked in buildings potentially contaminated by tritium. The relative risk (RR) of prostate cancer was 14.26 (95% CI: 3.09–133.16, $p<0.01$) with documented internal contamination by tritium. There was an increasing trend (2-sided $p<0.05$) with degree of potential contamination with tritium and with duration of work (2-sided $p<0.01$) in buildings likely contaminated with tritium. The risk of prostate cancer was most closely associated with work in reactor environments, particularly heavy-water-moderated reactors (RR=2.13; 95% CI: 1.0–4.52). The risk increased with duration of work in heavy-water reactors (chi-squared (χ_1^2) test for trend=8.94; p=0.003).

The main problems with this study are multiple exposures to both internal and external sources of radiation in individuals and the lack of adequate tritium dosimetry. Exposures to the radionuclides of interest and cumulative external dose were correlated, and the association between prostate cancer risk and external dose was limited to those subjects who were probably contaminated with the radionuclides. It was not possible to discrimate effects of one particular radionuclide from those of another. It is problematic to derive risk estimates for tritium from these figures, as exemplified by the inconsistency of these results with those of a later study performed by Carpenter *et al* (1998). In the second study, follow-up ended 6 years earlier for the UKAEA workers and also included Atomic Weapons Establishment (AWE) and Sellafield workers.

Atkinson *et al* (2004) provided an updated analysis of the UKAEA cohort, adding workers from Risley and Culcheth establishments, those recruited between 1980 and 1997 and extending mortality follow-up to 1997. The final study population totalled 51,367, of whom 51% were radiation workers. Information on internal radiation was related only as to whether monitoring took place, and no internal doses were evaluated. The mean annual external dose was 1.57 mSv among the new individuals, versus 4.26 mSv in the original cohort (1946 to 1979). Among tritium-monitored workers no SMRs were significantly high and some were particularly low. The SMR for all causes of death was 0.69 (95% CI: 0.62–0.76) and all cancers were 0.71 (95% CI: 0.59–0.85). These mortality rates were much lower than mortality rates of the general population of England and Wales, non-radiation workers, and all radiation workers. The rate

ratio was significantly greater than one for prostate cancer (RR of 1.8, 95% CI: 1.0–3.1), but the trend with dose was not significant (positive trend χ^2=0.36, 2-sided p=0.55). The rate ratio was only significantly increased for the time period up to and including 1979 (RR of 5.8, 95% CI: 2.2–15.7), which was the original study time period of Beral *et al* (1985), but not for the years post-1979 (RR of 1.2, 95% CI: 0.6–2.4).

Atkinson *et al* (2007) analysed the same extended UKAEA cohort considered by Atkinson *et al* (2004), with particular reference to prostate cancer mortality. Once again, the information on tritium related only to whether monitoring was carried out, and tritium doses were not evaluated, nor were doses from any other internally deposited radionuclide. An additional 90 prostate cancer deaths occurred in the period from 1980 to 1997. Overall, there was no statistically significant excess prostate cancer mortality either in the earlier 1946–79 cohort (27 deaths compared to 23.46 expected; SMR=1.15, 95% CI: 0.76–1.67) or the later 1980–97 cohort (90 deaths compared to 116.37 expected; SMR=0.77, 95% CI: 0.62–0.95). Table 4.2 indicates that workers monitored for tritium showed a highly statistically significant excess of prostate cancer mortality in the earlier 1946–79 cohort (6 deaths compared to 0.77 expected; SMR=7.81), confirming the earlier results of Beral *et al* (1985). However, an elevated risk was not found in the later 1980 to 1997 cohort (9 deaths compared to 10.16 expected; SMR=0.89). The study confirmed previous indications of a statistically significant increasing trend (p<0.001) of prostate cancer mortality with cumulative external radiation dose among the radiation workforce overall. However, there was no radiation-related excess among the 1980–97 cohort (p=0.920), and there were no trends of prostate cancer among those monitored for tritium exposure for either sub-cohort (p=0.264 for 1946–79 workers, p=0.862 for 1980–97 workers).

Table 4.2: Summary of the UKAEA Cohort and Prostate Cancer SMRs Standardized Mortality ratios (1946–97), Atkinson *et al* (2007)

Category of Workers	Standardized Mortality Ratio*	95% Confidence Interval	2-Sided p-Value
Monitored for tritium exposure from 1946–79	7.81	2.85–17.00	p<0.001
Monitored for tritium exposure from 1980–97	0.89	0.40–1.68	p=0.920

** Adjusted for age, sex and calendar year*

Atkinson *et al* (2007) discussed the reasons for the inconsistent results obtained in the various studies of UKAEA workers. They concluded that the original observation of a raised risk was most likely a chance finding based on the large number of diseases being analysed. In fact, only the trend for prostate cancer was significant and this association with radiation dose was not an expected outcome. This is supported by the lack of evidence of an increased risk of prostate cancer elsewhere in the nuclear industry; positive results are intermittent and inconsistent (BEIR VII, 2006), and an increased risk of prostate cancer has not been found in medical settings or among atomic bomb survivors. UNSCEAR (2008) concludes that occupational

workers, medical patients and atomic bomb survivors provide little indication that external or internal radiation exposure increases the risk of prostate cancer. In the absence of tritium-specific doses, no inference can be made about the risk from tritium in these studies. In fact, any connection between tritium exposure and these effects is tenuous at best.

4.2.2 Atomic Weapons Establishment Workers

The study of Beral *et al* (1988) involved mortality follow-up of 22,552 Atomic Weapons Establishment (AWE) workers. About 42% of these workers were monitored for exposure to radiation from 1951 to 1982. For tritium, yearly doses were assessed and added to external (film-badge) dose for purposes of analysis. Little information was given on the magnitude of tritium doses to this group (nor for doses from any other internally deposited radionuclide). The exposures were small compared with external radiation doses with fewer than 2% of workers having a tritium dose of 10 mSv or more recorded. Only 7% (1,562) of workers were ever monitored for tritium intake.

Based on 3,115 deaths overall comparisons of mortality for all cancers and all other causes of death for workers with exposure to tritium in relation to others with a radiation record revealed no notable results. This persisted even after lagging exposures to account for differences in latency periods between exposure and disease (0, 5, 10, 15 years). Among 20 causes of death considered, only brain and central nervous system cancer mortality showed a statistically significant excess (2-sided $p<0.01$) among tritium-monitored workers relative to other radiation workers. This finding was based on a single death. There was no statistically significant trend in mortality with external dose in the full cohort and non-statistically significant excess in prostate cancer mortality in the tritium-monitored group, based on 3 prostate cancer deaths. There was no significant trend with external dose for prostate cancer in an internal analysis of the full cohort (in which regression of risk relies only on comparisons of risks between different dose groups), although there was a statistically significant (2-sided $p<0.01$) increasing trend with dose in SMR.

Given that the results related to tritium-monitored workers are based on very few deaths and the absence of analysis separately accounting for tritium-specific doses, it is difficult to draw any inference about risk from tritium in this study. The apparently significant results in relation to prostate and brain cancer should be considered against Carpenter's (1998) negative results for these cancers in the same workforce together with various other UK radiation workforces.

Johnson *et al* (1999) conducted further analyses of the AWE workforce (N=22,543), with mortality follow-up to the end of 1996. Dose data previously used by Carpenter *et al* (1998) included annual external and tritium doses and flags to indicate monitoring for other internal exposure until the end of 1985. This analysis was based on 6,516 total deaths. For some of the trend analyses, the doses were lagged by 11 years to remove potential bias introduced by the truncation of dose data. For all causes of death and all cancers, the workforce was significantly healthier than the general population of England and Wales as indicated by SMRs significantly less than 1.0 reported for 13 separate causes of death (2-sided, $p<0.01$). Among radiation workers monitored for internal contamination, presumably including those workers exposed

to tritium, only kidney cancer mortality was significantly elevated compared with national mortality rates (SMR=1.88, observed/expected=16/8.53, p=0.0161). There were statistically significant increasing trends of mortality for multiple myeloma (p=0.0002, 7 deaths), bladder cancer (p=0.0134, 20 deaths) and all diseases of the circulatory system (p=0.0455, 1147 deaths) with cumulative (film-badge and tritium) dose when a lag of 0 years was used. There were also statistically significant increasing trends of mortality for multiple myeloma (p=0.0132, 7 deaths), bladder cancer (p=0.0016, 19 deaths) and bronchus and lung cancer (p=0.0322, 183 deaths) with cumulative (film-badge) dose when a lag of 11 years was used.

It is difficult to infer very much about risk from tritium from this study, because they did not include a separate analysis of risk in relation to tritium dose.

4.2.3 Three Groups of UK Classified Workers

The study by Carpenter *et al* (1998) involved follow-up of three groups of UK classified radiation workers: those employed at the UKAEA establishments at Harwell (including Culham and London), Dounreay or Winfrith before 1980, those employed at the AWE before 1983 and a group that worked at Sellafield before 1976. A total of 40,761 monitored workers were studied, of whom approximately 10% (4,111) were monitored for exposure to tritium (among other radionuclides). The information on tritium, however, related only to whether monitoring had been carried out; tritium doses were not evaluated (nor were doses from any other internally deposited radionuclide). All analyses were in terms of cumulative external (film-badge) dose. Overall, mortality rates among radiation workers not monitored for radionuclides were 20% lower than those expected on the basis of national rates. SMRs for all causes of death, all cancers and all causes of death other than cancer were significantly below 1.0 for workers monitored for tritium (2-sided, $p<0.05$), indicating lower mortality rates than the general population. There were no specific cancers for which SMRs were significantly high in these workers. Significantly low SMRs were seen for lung cancer among workers monitored for tritium. A comparison of tritium-monitored workers with radiation workers not monitored for internally deposited radionuclides revealed that the risk for all causes of death was 0.92 (95% CI: 0.83–1.01) and for causes other than cancer was 0.88 (95% CI: 0.78–0.98). Thus, there was a statistically significant decrease in risk among tritium monitored workers. The only cancer site to exhibit an excess mortality among tritium-monitored workers was testicular cancer, for which the RR was 8.37 (95% CI: 1.48–43.14). This was based on 3 deaths and likely arose by chance. There was a statistically significant decrease in risk for cancer of the buccal cavity and pharynx (RR=0.00, 95% CI: 0.00–0.90). For tritium-monitored workers, there was little evidence that RRs varied according to the time period since the first monitoring. Table 4.3 shows that when examining RRs by dose group, there is little evidence of an increased risk associated with tritium exposure relative to radiation workers not monitored for any radionuclide. The only statistically significantly RR was for bronchus and lung cancer among those with < 10 mSv cumulative external dose, for which the RR was 1.86 (95% CI: 1.01–3.17). However, the risk was not statistically significant among those with exposures above 10 mSv. In the absence of tritium specific dosimetric data for internal exposures, inference cannot be made about the risk from tritium.

Table 4.3: Rate Ratios[a] (and Numbers of Deaths) Among Workers Monitored for Tritium in Three United Kingdom Radiation Workforces (from Table 6, Carpenter *et al*, 1998)

Cause of Death	Cumulative External Whole-Body Dose (mSv)		
	<10 mSv	>10 mSv	Total
All malignant neoplasms (ICD9[c] 140-209)	1.07 (32)	1.01 (133)	1.02 (165)
Bronchus and lung (ICD9[c] 162)	1.86 (15)[b]	1.05 (42)	1.18 (57)
Prostate (ICD9[c] 185)	0.89 (2)	1.39 (12)	1.33 (14)

[a] *Relative to workers monitored for exposure to external radiation, but not monitored for any radionuclide, adjusted for age, sex, calendar period, social class and establishment*

[b] *2-sided p<0.05: 95% CI 1.01–3.17*

[c] *Underlying cause of death (as stated on the death certificate) coded according to the International Classification of Disease (ICD) 9th Revision (WHO, 1977)*

4.2.4 British Nuclear Fuel Limited Capenhurst

The British Nuclear Fuel Limited (BNFL) Capenhurst site was established in the early 1950s primarily to enrich uranium, initially for defence purposes. A tritium facility was also operated from 1965 to 1987 for defence purposes. When the tritium plant ceased operation, it was kept under care and maintenance until 1993 and decommissioning was completed in 1998. Jackson *et al* (1997) reconstructed the discharges and environmental doses (doses to the public) from the former tritium facility at Capenhurst.

McGeoghegan and Binks (2000) analysed the mortality and cancer morbidity experience of 12,540 workers employed at the Capenhurst uranium enrichment facility from 1946 to 1995. Mortality was available from 1946 to 1995 and cancer morbidity from 1971 to 1991. It is not clear how many of the Capenhurst workers assessed were exposed to tritium. Annual external whole-body radiation dose data from Capenhurst or other sites (transfer sites) were included in the analysis. Importantly, doses from internally deposited radionuclides, such as tritium, were excluded.

As with most radiation workforces, mortality was generally below national and regional rates of England and Wales. Most SMRs were less than 1.0, and several were statistically significantly less than 1.0 (for example, all causes of death, all cancers, circulatory disease, respiratory disease, digestive disease, lung cancer, bladder cancer, leukaemia excluding chronic lymphocytic leukaemia (CLL), cancer of the bone, skin and breast) (2-sided, $p<0.05$). Only pleural cancer mortality had an elevated SMR (11 observed vs. 4.66 expected, SMR=2.36, 2-sided $p<0.05$, RR=2.38); however, it did not have an elevated standardized incidence ratio (SIR), and there were no statistically significant positive mortality or cancer morbidity trends with cumulative external radiation. The only statistically significant positive trend (1-sided $p<0.05$) of cancer morbidity with cumulative external dose was for bladder cancer (out of 16 cancer sites examined), based on 14 male cases, when the dose was lagged by 20 years. However, no

association between bladder cancer mortality and external dose was found. There was no association between external dose and leukaemia; mortality and morbidity due to leukaemia were consistent with the general national population. There was no evidence of an association between prostate cancer and cumulative external dose.

In the absence of tritium-specific doses inference cannot be made about tritium risk from this study. As these workers (or their co-workers at the tritium facility) may have considerable tritium exposures, if tritium doses become available in the future, this cohort could be informative.

4.2.5 Chapelcross Nuclear Reactor Workers

McGeoghegan and Binks (2001) assessed the mortality and cancer morbidity experience of 2,628 workers of British Nuclear Fuels Limited (BNFL) and the UKAEA workers who had ever been employed from 1955 to 1995, at the Chapelcross plant, where four Magnox reactors were used to produce tritium for defence purposes starting in 1980. Dosimetry data were collected using film badges. Annual external whole-body radiation dose data from Chapelcross or at other sites (transfer sites) were used. Doses from internally deposited radionuclides, such as tritium, were again excluded. It is not clear how many of the workers were exposed to tritium as of 1980. Mortality data was available from 1955 to 1995 and cancer registration from 1971 to 1991. As with most radiation workforces, mortality rates were generally below that expected from national rates.

Most SMRs were less than 1.0, several statistically significantly so (for example, all causes of death, all cancers, lung cancer, diseases of the respiratory system, endocrine and nutritional diseases). The only observation of an elevated SMR related to benign and unspecified neoplasms (5 observed vs. 1.81 expected, SMR=3.31, 2-sided $p<0.05$). Likewise, most cancer standardized registration rates (SRR) were less than 1.0. The only statistically significant positive trend of cancer mortality with cumulative external dose was for prostate cancer, based on 8 deaths. However, none of the 8 deaths were monitored for tritium (or Chromium-51, Iron-59, Cobalt-60 or Zinc-65, the radionuclides suggested by the study of Rooney *et al* (1993) to be associated with elevated risk). The latency period for solid cancer is about 10 to 20 years. When doses were lagged by 0, 2, and 10 years, the simulated 1-sided p-values were 0.023, 0.023, and 0.036, respectively (adjusted for age, sex, calendar year, industrial status, worker status and time since first exposure). Thus, the significance of the trend of prostate cancer mortality with increasing dose was progressively decreased with increasing lag time. However, the association was unlikely to be causal. The finding has little biological plausibility, as the strength of the association weakened as the dose lagging increased. It was strongest when the dose was not lagged and disappeared when the dose was lagged 20 years.

For non-cancer causes, there was also a statistically significant increasing trend for bronchitis deaths, based on 6 deaths (1-sided p=0.018, 0.018, 0.002, 0.0004 and 0.088 when lagged 0, 2, 10, 15, and 20 years respectively) and adjusted for age, sex, calendar year, industrial status, worker status and time since first exposure. There was a suggestive increasing trend of prostate cancer incidence with cumulative external dose, based on 12 cases (1-sided p=0.086 for 10-year, adjusted for age, sex, calendar year, industrial status, worker status and time since first exposure). None of these workers were monitored for tritium, which suggests there had been no exposure.

Only two of the workers with prostate cancer worked at Chapelcross during the production of tritium, thus, the excess risk of prostate cancer was not due to tritium exposure.

4.2.6 Sellafield Nuclear Workers

Mortality and morbidity studies of Sellafield workers previously focused on external doses (Smith and Douglas, 1986; Douglas *et al*, 1994). However, internal doses from plutonium are of greatest concern, since more Sellafield workers are exposed to plutonium than any other radionuclide. There are tritium-exposed workers at the Sellafield site, although they were never separately assessed, nor are there analyses in relation to tritium dose (Omar *et al*, 1999). The highest tritium exposures occurred in the late 1950s and early 1960s when tritium was produced by irradiation of lithium rods in reactors and extracted from these rods in a specifically designed plant.

Omar *et al* (1999) conducted the most recent analysis of the whole workforce, including 14,319 workers first employed between 1947 and 1975 with mortality followed-up over the period 1947 to 1992, and cancer incidence examined from 1971 to 1986, in relation to internal exposures to plutonium and to external radiation. External radiation doses were estimated from film badge dosimeters from 1947 to 1990, and internal assessments of exposure to plutonium were made through monitoring urine samples starting in 1951. Doses acquired in other employment were included if available. In general, the mortality rate for all causes of death and all cancers was close to that of the general population of England and Wales (SMR=0.98 and 0.95 respectively). The only cancers with statistically significantly elevated SMRs among the total workforce were for pleural cancer (14 observed vs. 4.0 expected, SMR=3.51, 1-sided $p<0.001$) and thyroid cancer (6 observed vs. 2.2 expected, SMR=2.78, 1-sided $p<0.05$). Diseases of the circulatory system (1,989 observed vs. 1,858.2 expected, SMR=1.07, 1-sided $p<0.01$) were significantly elevated, owing to the excess deaths from ischemic heart disease (1,354 observed vs. 1,217.67 expected, SMR=1.11, 1-sided $p<0.001$). Symptoms, signs and ill-defined conditions (13 observed vs. 6.5 expected, SMR=2.01, 1-sided $p<0.05$) were also elevated (Omar *et al*, 1999). There was no significant excess in cancer registration rates compared to rates for England and Wales. Among all radiation workers, the only statistically significant increasing trend with cumulative external radiation dose and mortality was for non-CLL leukaemia (1-sided $p=0.015$ for 2-year lag), based on 13 deaths, and for leukaemia (1-sided $p=0.05$ for 2-year lag), based on 16 deaths. This was likely a real effect of radiation exposure. There was a statistically significant increasing trend for multiple myeloma mortality, but only when a 20-year lag was used (1-sided $p=0.017$ for 20-year lag), based on 8 deaths. This suggests possible effects after long induction times.

McGeoghegan *et al* (2003) analysed mortality (1946–98) and cancer morbidity (1971–94) experience of the 6,376 female workers who were ever employed at the BNFL plant at Sellafield between 1946 and 1998. External radiation doses were estimated from film badge dosimeters and internal assessments of exposure to plutonium were made through monitoring urine samples. Doses acquired at other work places were included if available. Mortality rates were generally at about national rates; the SMR for all causes of death and all cancers was 1.02 (671 observed deaths vs. 659.5 expected) and 0.97 (210 observed deaths vs. 217.2 expected), respectively. The only causes of death with statistically significantly elevated SMRs were bone cancer (3 observed

vs. 0.5 expected, SMR=5.54, 2-sided $p<0.05$) and aplastic anaemia (4 observed vs. 0.4 expected, SMR=11.35, 2-sided $p<0.001$), both of which were only among non-radiation workers. Diseases of the circulatory system were in excess (291 observed vs. 258.1 expected, SMR=1.13, 2-sided $p<0.05$), owing largely to ischaemic heart disease (150 observed vs. 126.6 expected, SMR=1.18, 2-sided $p<0.05$). Incidence for all cancers was less than that of the general female population of England and Wales (240 observed vs. 297.3 expected, SRR =0.81, 2-sided $p<0.001$); most cancer SRR were less than 1.0. No statistically significant trends were noted between mortality or cancer incidence and cumulative external whole-body radiation dose overall, or for any of the individual disease groupings examined.

Although tritium-specific doses have been estimated for the Sellafield workforce, they were not taken into account in the analyses. Thus no inference can be made about the risk from tritium in these studies, although this cohort should be regarded as potentially informative.

4.2.7 UK National Registry for Radiation Workers: Mortality and Cancer Incidence Following Occupational Radiation Exposure

The UK Health Protection Agency (HPA) started the National Registry for Radiation Workers (NRRW) in 1976 to obtain data relevant to protracted or low-dose radiation exposure. Two earlier NRRW analyses (Kendall *et al*, 1992; Muirhead *et al*, 1999a, b) found a strong healthy worker effect. Cancer mortality, in relation to external radiation dose, was consistent both with existing radiation risk estimates and — for the most part — with the absence of an association. However, there was slight evidence in the second analysis (NRRW-2) of an increasing trend with dose in leukaemia (excluding CLL) mortality.

Muirhead *et al* (2009) recently updated the mortality analysis of the NRRW-2 study, including an enlarged cohort of 175,541 workers, with longer follow-up (to 2001) and for the first time, cancer incidence data. Most workers were those who undertook radiation work on or after 1 January 1976. However, earlier radiation workers were included (back to 1 January 1955) in most instances, namely: for most employers, persons who started work between 1991 and 1999 (after the cut off for NRRW-2); workers who stopped working at BNFL Capenhurst and Springfields before 1976; Ministry of Defence radiation workers who ceased employment before 1977, and workers at British Energy Generation/Magnox Electrics Dungeness A and B power stations from 1965 to 1990. The analysis focused on external dose. Most of the doses were associated with x-rays and gamma rays, together and, to a lesser extent, with beta particles and neutrons. Estimates of doses from internal emitters were not generally available, but workers monitored for potential exposure were identified. The SMRs (unadjusted for social class) for all causes and all malignant neoplasms were 0.81 (95% CI: 0.50–0.82) and 0.84 (95% CI: 0.82–0.86), respectively, demonstrating a healthy worker effect. Within the cohort, mortality and cancer incidence from both leukaemia (excluding CLL) and the grouping of all malignant neoplasms (excluding leukaemia increased to a statistically significant extent with increasing radiation dose. Table 4.4 illustrates that the estimates of the trend in risk with dose were similar to those of the Japanese atomic bomb survivors, with 90% confidence intervals that excluded both risk more than 2-3 times greater than the atomic bomb values and no raised risk.

Although no tritium specific doses were available, there was little impact on results when the data was stratified according to whether a worker was ever internally monitored. The analysis provided precise estimates of mortality and cancer risks following occupational radiation exposure and strengthened the evidence for raised risks from these exposures. The cancer risk estimates were consistent with values used to set radiation protection standards.

Table 4.4: Comparison of Estimates of Excess Relative Risk per Sv (and 90% Confidence Intervals) for Cancer in the NRRW and the Japanese Atomic Bomb Survivors (from Table 3, Muirhead *et al*, 2009)

	Leukaemia, Excluding Chronic Lymphocytic Leukaemia	All Malignant Neoplasms, Excluding Leukaemia	All Malignant Neoplasms, Excluding Leukaemia, Lung and Pleura Cancer
3rd NRRW analysis			
Mortality	1.712 (0.06–4.29)	0.275 (0.02–0.56)	0.323 (0.02–0.67)
Incidence	1.782 (0.17–4.36)	0.266 (0.04–0.51)	0.305 (0.05–0.58)
2nd NRRW analysis (Muirhead *et al*, 1999a, b)			
Mortality	2.55 (-0.03–7.16)	0.09 (-0.28–0.52)	0.17 (-0.26–0.70)[a]
Japanese Atomic bomb (A-bomb) survivors			
BEIR VII (NCR, 2006): Mortality	1.4 (0.1–3.4)[b]	0.26 (0.15–0.41)[c]	-
BEIR VII (NRC, 2006): Incidence	-	0.43[d]	-

[a] *Based on data for all malignant neoplasms excluding leukaemia and lung cancer.*

[b] *Based on the low-dose component of a linear-quadratic dose-response model fitted to A-bomb data on mortality during 1950–2000.*

[c] *Based on fitting a linear dose-response model to A-bomb data on solid cancer mortality during 1950-2000.*

[d] *Based on fitting a linear dose-response model to A-bomb data on the incidence of all solid cancers other than thyroid and non-melanoma skin cancers during 1958–98. The ERR estimate cited applies to men exposed at ages of 30 years or more, at an attained age of 50 years.*

4.2.8 United States: Savannah River Site Workers and Other US Nuclear Workers

Cragle *et al* (1988) assessed mortality in a cohort of 9,860 white male workers at the Savannah Rive Site (SRS) from 1952 to 1980. Approximately 15% of workers' total occupational dose was from internally deposited radionuclides. Unfortunately, dosimetric information specific to

tritium or any other radionuclide was not available for the analysis. According to plant sources, approximately 5,000 present and former workers had experienced occupational exposure to tritium, about 800 employees received >0.5 mSv from tritium and 1 worker exceeded the plant administrative guide of 30 mSv/year from this radionuclide. There were few indications of excess mortality in this cohort with lower SMRs for all causes of death and all cancers compared with the U.S white male population (two sided, $p<0.05$), as well as many cause-specific categories. One could not assess radiation risk in this study without individual dosimetry data.

Cragle *et al* (1998) extended follow-up and analysis of this cohort to 1986, but results were not published in the peer-reviewed literature. Tritium effective dose equivalent and neutron dose equivalent were available from radiation monitoring files, but analysis was performed only in relation to cumulative external dose. Only results for leukaemia (excluding CLL) indicated a statistically significant increasing trend in mortality with increasing radiation dose (2-sided $p<0.05$). This trend was significant for the 10-year lag and the 2-year lag. There were no statistically significant trends for prostate cancer (2-sided $p=0.77$) or 12 other endpoints considered. Modelling of prostate cancers was not attempted since 85% of the workers who died with prostate cancer had a total cumulative dose of less than 20 mSv.

Schubauer-Berrigan *et al* (2007) conducted a nested case-control study of leukaemia among workers at four U.S. nuclear facilities (Hanford, Oak Ridge National Laboratories, SRS and Los Alamos National Laboratories) and the Portsmouth Naval Shipyard, to assess leukaemia and non-CLL leukaemia mortality risk from ionizing radiation using worksite doses and adjusting for confounding factors (race, hire year, smoking, sex, and benzene exposure). There were 206 non-CLL leukaemia cases and 823 age-matched controls. The primary exposure evaluated was bone marrow dose from photons, tritium, neutrons and plutonium. Photons and tritium comprised 91–95% of the total bone marrow dose for study subjects. Mortality follow-up was extended through 1994 or 1996, depending on the cohort of workers. Using a 2-year lag (suggesting short latencies) there was an unadjusted excess odds ratio (EOR) of 5.96 Sv^{-1} (95% CI: 0.32–16.5). After adjustment for sex and benzene exposure (the only apparent confounders) the EOR was 2.60 Sv^{-1} (95% CI: <–1.03–10.3) indicating that sex and benzene exposures were important confounders contributing to the overall risk. The unadjusted EOR for the SRS workers, likely to be among the most heavily exposed to tritium among these five workforces, was 30.6 per Sv (95% CI: 4.77– >130).

Richardson and Wing (2007) assessed associations between ionizing radiation exposures and all leukaemia, non-CLL leukaemia and myeloid leukaemia in US nuclear weapons workers at the SRS principally exposed to gamma radiation and tritium. A mortality follow-up of 18,886 workers hired between 1950 and 1986 was conducted until 2002. A nested case-control design within the cohort was employed. Radiation doses from external sources (photons and neutrons) and internal doses from tritium intakes were derived from dosimetry records at SRS from 1950 to 1999. A total of 84 leukaemia cases were observed, of which 62 were from leukaemia excluding CLL, and 40 from myeloid leukaemia. A positive non-significant association between leukaemia mortality and radiation was observed after assuming a 3-year lag. The excess relative risk (ERR) for all leukaemia mortality was 4.1 per Sv (90% CI: -0.1–11.6), for non-CLL leukaemia was 7.7 per Sv (90% CI: 1.4–19.8), and for myeloid leukaemia was

12.3 per Sv (90% CI: 2.1–35.4). Restricting analysis to male workers resulted in a modest increase in the magnitude of association and goodness of fit for each leukaemia category.

A substantial increase in observed relative rates with increasing dose is seen for all leukaemias, even at cumulative doses <50 mSv. This study provides evidence of positive associations between leukaemia mortality and low-level occupational exposure to ionization radiation at the SRS, consistent with the patterns of populations exposed at higher doses. However, no tritium-specific risk estimates were provided.

4.2.9 Canada: Atomic Energy of Canada Limited and Other Canadian Nuclear Workers

The first Canadian analyses of mortality among nuclear energy workers included two reports on 8,977 male permanent employees of Atomic Energy of Canada Limited (AECL), employed up to 1980 (Howe *et al*, 1987; Gribbin *et al*, 1993). A slight difference in follow-up times (1956 to 1981 vs. 1956 to 1985, respectively) and minor improvements in dose information had no bearing on the final results, which were essentially the same. Although nuclear work was carried out in the facility starting in 1947, a fire in 1956 destroyed paper records of doses in the preceding years. For those workers continuing to work at AECL after 1956 it was possible to reconstruct the doses, but those who left employment had to be excluded from the study. The study focused on whole-body equivalent doses from exposure to external gamma radiation from 1956 onward. The mean cumulative whole-body dose was 15.0 mSv and 63 study subjects with cumulative doses in excess of 500 mSv were retained in the analysis. AECL workers had recorded internal exposures for tritium. The cohort had a total of 157,100 person-years at risk and 17.5 mean years of follow-up. Overall, there was a healthy worker effect. For all causes of death, the SMR was 0.77 (95% CI: 0.72–0.83) and for all cancers the SMR was 0.87 (95% CI: 0.76–0.99). None of the cancers had SMRs that were significantly greater than 1.0. Of interest was the deficit in deaths from both all leukaemia and non-CLL leukaemia, although these were not statistically significant. The risks of other cancers previously reported to be associated with radiation exposures in some nuclear worker studies — such as bladder cancer, prostate cancer, and multiple myeloma — was not substantially increased in the AECL cohort, with SMR=1.21 (95% CI: 0.71–1.13), SMR=0.15 (95% CI: 0.00–0.85), SMR=0.56 (95% CI: 0.07–2.04), respectively. In fact, there was a statistically significant decreased risk of bladder cancer (p=0.02, two-sided). There was no meaningful evidence of excess mortality for cancer as a whole for individual cancer sites in AECL workers compared to the general population. Mortality rates and radiation doses were examined using Poisson regression techniques, stratified by age, calendar year at risk and time since first employment at AECL, with a relative risk model linear in dose being fitted to the data. Leukaemia was lagged by 2 years and all other causes of death were lagged by 10 years. Table 4.5 illustrates that for all cancers the ERR, based on 227 deaths was non-significant: 0.36 per Sv. Only non-CLL leukaemia (p=0.058), based on only 4 deaths and extremely wide confidence intervals (90%), showed a positive relationship between dose and risk with an ERR of 19.0 per Sv. A large part of the ERR for all cancers was due to the contribution from leukaemia; when these were excluded, the ERR fell to a non-significant increase in risk for solid cancers of 0.049 per Sv. Thus, the AECL cohort provides no substantive evidence of a positive relationship between dose and cancer risk as a whole.

Table 4.5: Summary of Cancer Mortality Excess Relative Risk Results (1956–85) (from Gribbin *et al*, 1993)

Disease	Number of Observed Deaths	Excess Relative Risk per Sv	90% Confidence Intervals
All cancers	227	0.36	-0.46–2.45
Non-CLL leukaemia	4	19.0	0.14–113
Cancers (excluding leukaemia)	221	0.049	-0.68–2.17

Although tritium exposures were not assessed in this study, AECL workers did have recorded tritium doses, which may be contributing to a portion of the total effect seen in this study. The total effect from occupational radiation exposure, based on 30 years of mortality follow-up, was negligible; the risk from tritium is also likely small. It might be possible to investigate tritium risk in future follow-up of these workers.

Since its creation in 1951, the National Dose Registry (NDR) has contained radiation exposure data records for virtually all monitored radiation workers in Canada. Exposure records cover over 500,000 workers from about 24,000 organizations that provide the data to the NDR. The NDR's information is thought to contain radiation information that was essentially identical to that kept in CNSC-licensed facilities.

Two parallel studies based on the NDR were published by Ashmore *et al* (1998) and Sont *et al* (2001), which included not only occupationally exposed nuclear power industry workers (from AECL, Hydro-Québec, New Brunswick Power Corporation and Ontario Hydro), but also workers from other fields, such as the medical and dental industries. Compared to the cancer mortality risk estimates (ERR=0.36 per Sv) reported by Gribbin *et al* (1993) that were based on AECL workers only, Ashmore *et al* (1998) reported unusually high estimates of cancer mortality among male workers (ERR=3.0 per Sv; 90% CI: 1.1–4.9). Sont *et al* (2001) reported unusually high estimates for solid cancer incidence (ERR=2.5 per Sv; 90% CI: 1.1–4.2). Mean cumulative exposures among males were low, 10.6 mSv and 11.5 mSv respectively, compared to 15.0 mSv for the AECL nuclear workers from Gribbin *et al* (1993). The tritium dose equivalents were included in the whole-body dose estimates. Many non-cancer causes of death (including infectious and parasitic diseases, and accidents) were also correlated with dose.

In an invited commentary of studies of workers exposed to low doses of radiation, Gilbert (2001) suggested these unusual high estimates of cancer mortality and solid cancer incidence reported by Ashmore *et al* (1998) and Sont *et al* (2001) could be the result of a bias in the NDR. No inference can be made about tritium in these studies.

The study by Zablotska *et al* (2004) involved mortality follow-up of 45,468 Canadian nuclear power industry workers registered in the Canadian NDR and monitored for more than one year for chronic low-dose whole-body ionizing radiation exposures from 1957 to 1994 (mean duration of monitoring is 7.4 years). Records included those employed by the three nuclear power companies (Ontario Power Generation (OPG) which was previously Ontario Hydro [OH], New Brunswick Power Corporation, and Hydro-Québec) and AECL, which conducts research in areas related to nuclear power generation. Workers with less than one year of monitoring and those employed at AECL before 1956 (since a 1956 fire destroyed prior dose records) and those with cumulative doses of 500 mSv or more were excluded.

Exposures to neutrons and alpha particle emitters were extremely low in the cohort so they were not analyzed separately from gamma radiation. All external doses were penetrating (whole-body) doses expressed as equivalent doses given in millisieverts. Annual summary doses for whole-body external and internal radiation exposure were collected for each monitored individual. Neutron exposures were included in the external whole-body dose. Quality factors for x-rays, gamma rays and beta particles were assumed to equal 1.0, and for neutrons were taken as 10.0. Internal doses for nuclear workers in Canada were primarily from tritium, which is present in heavy-water moderated CANDU reactors. Tritium doses were assessed by routine urinalysis of workers, converted to equivalent doses (mSv), and added to external (film-badge) doses for the whole-body dose estimates used in this study. Other internal doses were minimal. The mean cumulative equivalent dose was 13.5 mSv, and probably reflected the inclusion of female workers known to have lower radiation doses and among those workers recorded as having non-zero doses the mean was 19.7 mSv. Fact and cause of death were obtained from the Canadian Mortality Database (CMDB) back to 1950 for all Canadians and residents who died while in the United States. 1,599 deaths occurred between 1957 and the end of 1994.

The SMR analysis of Zablotska's study was consistent with a healthy worker effect. For all causes of death there were 1,599 observed vs. 2,538 expected deaths (SMR=0.63, 95% CI: 0.60–0.66). For all cancers there were 531 observed vs. 721 expected deaths (SMR=0.74, 95% CI: 0.68–0.80).

Overall, there was no indication of any unexpected pattern in the cohort mortality compared with that of the general population. Socioeconomic status (SES) information was missing for 43 percent of the cohort, primarily for workers employed at AECL and OPG. However, SES was not a significant confounder of the association between ionizing radiation and risk of solid cancers or leukaemia. Therefore, the study presented an estimate of ERR for all cancers excluding leukaemia based on all workers.

In the internal analysis (an analysis that makes comparisons between workers only), there was a large and generally borderline statistically significant trend with dose for many diseases, both malignant and non-malignant, as shown in Table 4.6, although the confidence intervals were wide.

Table 4.6: Summary of Cancer Mortality Excess Relative Risk Results (from Zablotska *et al*, 2004)

Disease	Number of Observed Deaths	Excess Relative Risk per Sv	95% Confidence Intervals	2-Sided p-Values
All non-CLL leukaemia[a]	18	52.5	0.205–291	p=0.048
All leukaemia[a]	22	18.9	<-2.08–138	p=0.25
All solid cancers[b]	474	2.80	-0.038–7.13	p=0.054
Rectal cancer[b]	16	34.1	1.41–165	p=0.029
Lung cancer[b]	183	4.34	-0.193–12.7	p=0.066
Non-Hodgkin's lymphoma[b]	19	-2.03	<-2.08–38.0	p=0.74
Multiple myeloma[b]	10	-2.04[c]	<-2.08–18.3	p=0.41
Pancreatic cancer[b]	22	-2.03	<-2.08–34.4	p=0.59
Brain and other central nervous system cancer[b]	25	-2.04	<-2.08–8.99	p=0.34

Background rate stratified by sex, age, calendar year, SES and duration of monitoring
[a] *Doses lagged by 2 years*
[b] *Doses lagged by 10 years*
[c] *Negative trend*

Analysis of the dose estimates when tritium was first excluded and then included in the whole-body dose yielded ERR values of 2.67 per Sv and 2.80 per Sv, respectively, for all solid cancers. Likewise, for all leukaemias, when tritium was first excluded and then included the ERR values were 16.3 per Sv and 18.9 per Sv (confidence intervals not provided). Thus, results did not depend materially on whether tritium was included in the whole-body dose, and the tritium risk was likely to be small.

Hazelton *et al* (2006) conducted a biologically based analysis (two–stage clonal expansion model TSCE) of lung cancer incidence in a large Canadian cohort (N=191,042) with individual annual dosimetry for low-dose occupational exposure to gamma and tritium radiation. Radiation exposures between 1951 and 1988 were obtained from the Canadian NDR, and cancer incidence between 1969 and 1988 was obtained through linkage to the Canadian Cancer Data Base. Miners were excluded because their gamma radiation exposure data only became available after 1980. Past uranium miners had high rates of lung cancer as a result of high radon progeny exposure (UNSCEAR, 2008) so should be excluded. Annual exposure information was based on personal badge dosimetry and included cumulative annual values with whole-body and skin exposures to gamma radiation and tritium. Tritium dose equivalents made up 9.0% of the collective dose, so the whole-body tritium exposures were generally small in comparison

with gamma exposures. The mean cumulative exposure for males (N=60,677) and females (N=44,238) with non-zero cumulative exposure of whole-body gamma and tritium radiation was 18.2 mSv and 3.8 mSv, respectively. Males had a significant dose-response, with 33 of 322 lung cancer cases attributable to radiation. Lung cancer incidence among the 95,430 males was strongly associated with whole-body gamma radiation. The dose-response for tritium considered separately was marginally significant. In a restricted analysis of males without neutron exposure (N=69,826) the tritium dose-response was not statistically significant, which suggests that any observed tritium risk was confounded by the observed risk associated with the neutron exposure. The very small contribution of tritium to workers' low-dose cumulative exposures, the small numbers of lung cancer cases (which are associated with statistical uncertainty) and tritium's marginal to non-significant dose-response relationship with lung cancer, limits the interpretability of these findings.

4.2.10 The International Agency for Research on Cancer Multi-Country Worker Studies

In 1995, the World Health Organization's International Agency for Research on Cancer (IARC) conducted the first international study of nuclear industry workers to assess external sources of ionizing radiation (Cardis *et al*, 1995). Data were pooled from three US sites, (Gilbert *et al*, 1993), the UK workforces (Carpenter *et al*, 1994) and the Canadian Atomic Energy of Canada Limited (AECL) (Gribbin *et al*, 1993). This provided a more precise assessment of the carcinogenic effects on nuclear power industry workers.

The ERR for all cancers (excluding leukaemia) was -0.07 per Sv (90% CI: -0.04–0.30), with a ten-year dose lag. For leukaemia (excluding CLL) the ERR was 2.18 per Sv (90% CI: 0.1–5.7) with dose lagged two years. These estimates were consistent with the three countries' findings and were lower than, but comparable to the studies of the atomic bomb survivors.

Internal emitters, such as tritium, were not assessed; however, it is likely that workers received internal doses. Note that both Gribbin *et al* (1993) and Cardis *et al* (1995) used radiation dose information from the AECL facility directly and not from the Canadian NDR as commented by Gilbert (2001).

Most recently, Cardis *et al* (2005; 2007) incorporated the cohort of Canadian nuclear workers by Zablotska *et al* (2004) in a large pooled analysis of nearly 600,000 radiation workers from 15 countries. This study focused on workers who had been monitored for external radiation exposure, and whose doses resulted predominantly from high energy photon radiation. This included all workers who had been monitored for at least one year for external photon (x and gamma) radiation exposure through the use of personal dosimeters. Workers with potential substantial doses (≥ 10% of their whole-body doses) from other radiation types (39, 730 workers with internal contamination (i.e., tritium) and 19,041 workers with neutron exposures) were excluded. Since workers with internal contamination by tritium of ≥ 10% of their whole-body dose were excluded, no information on tritium can be derived from this study.

Table 4.7: Summary of Cancer Mortality Excess Relative Risk Results (from Cardis *et al*, 2005; 2007)

Disease	Excess Relative Risk per Sv	95% Confidence Intervals
All cancers excluding leukaemia	0.97	(0.14–1.97)[a]; (0.27–1.80)[b]
Solid cancers	0.87	(0.03–1.88)[a]; (0.16–1.71)[b]
Solid cancers (excluding Canada)	0.58	(-0.22–1.55)[a]; (-0.10–1.39)[b]
Leukaemia excluding CLL	1.93	(<0–8.47)[a]; (<0–7.14)[b]
Canada Only	**Excess Relative Risk per Sv**	**90% Confidence Intervals**
Solid cancers (excluding OH)*	6.65	2.56–13.00
Solid cancers (including OH)	3.60	1.03–7.27

[a] *90% CI based on Cardis* et al *(2005) report*
[b] *90% CI based on Cardis* et al *(2007) report*
* *OH: Ontario Hydro*

The significantly different Canadian risk estimates between the Zablotska *et al* (2004) and Cardis *et al* (2005; 2007) findings, when Ontario Hydro was excluded, as indicated in Tables 4.6 and 4.7, has raised considerable scientific interest in that the reasons for such differences from studies based on essentially the same data sources are unclear (UNSCEAR, 2008). The CNSC is conducting a detailed analysis to understand the differences in risk estimates obtained by the Canadian analysis (Zablotska *et al*, 2004) and the IARC 15 country analysis (Cardis *et al*, 2005; 2007).

A review of historic dose records by Ashmore *et al* (2007) has raised possible concerns about the completeness of early AECL records in the NDR that may have biased the Canadian ERR in the IARC 15-country analysis. The CNSC is thus conducting a reanalysis of the Canadian worker cohort, with a particular attention to the historic AECL records. Until the AECL data of the Canadian cohort are better understood and validated, the Canadian facilities, excluding AECL, provide the best Canadian ERR estimate. The revised and validated Canadian cohort will be reanalyzed to assess mortality among Canadian nuclear power industry workers, with specific attention to tritium exposure. This will be a potentially important cohort to assess the health impacts of occupational tritium exposures.

Summary

No direct inference can be drawn about the risk from tritium from published studies of UKAEA, AWE and Sellafield, Capenhurst or Chapelcross workers because of the absence of tritium-specific dosimetry. Capenhurst workers may have received considerable tritium exposures, and if tritium dosimetry became available, this cohort could be potentially informative. It is also difficult to infer much about tritium risks from the Canadian and American studies.

Although tritium doses were assessed and used, there was little analysis specific to the effects of tritium exposures.

Once the issue with the historic dose records at AECL (and therefore the NDR) is resolved, the Canadian nuclear workers cohort may provide a useful source of information to assess tritium risk. It should be stressed that there are substantial uncertainties in the risk estimates derived from the IARC 15-country analysis (UNSCEAR, 2008). However, there was no known bias in the AECL records used in the IARC 3-country (UK, US, Canada) analysis by Cardis *et al* (1995) and the earlier Canadian cancer mortality study by Howe *et al* (1987) and Gribbin *et al* (1993) because AECL company records were used directly. The risk estimates for these studies indicate very low risk, if any, for leukaemia and solid cancers among nuclear power workers with occupational radiation exposures, including tritium. The four U.S. studies showed positive associations between leukaemia mortality and low-level occupational exposure to ionizing radiation. Again, it is difficult to infer much about tritium risks from these studies. Although tritium doses were assessed and used, there was no analysis specific to the effects of tritium exposures. However, tritium exposures are relatively high among the SRS workers so this workforce could potentially be informative about tritium risks.

4.3 Case-Control Studies of *In Utero* Exposure and of Offspring of Radiation Workers

4.3.1 Case-Control and Cohort Studies of Childhood Leukaemia Around British Nuclear Plants

In 1990, Gardner *et al* (1990) conducted a case-control study of leukaemia and lymphoma among young people near Sellafield nuclear plant in West Cumbria to determine if the observed excess of these cancers was related to behavioural or lifestyle variables and to radiation received during fathers' employment at Sellafield. There were tritium exposed workers at Sellafield although there are no analyses specific to tritium dose (Omar *et al*, 1999). Gardner *et al* (1990) used only external doses. Cases included 52 cases of leukaemia, 22 of non-Hodgkin's lymphoma (NHL), and 23 of Hodgkin's disease in people born in the area and diagnosed under the age of 25 between 1950 and 1985. Controls (1,001), matched for sex and date of birth, were taken from the same birth registers as the cases. Through questionnaires and other methods, the main outcome measures were paternal occupation, paternal pre-conception radiation dose, maternal abdominal x-rays during pregnancy, maternal viral infections during pregnancy, family eating, children's play habits, paternal and maternal ages, and proximity to Sellafield. Comparisons were carried out using data from birth and medical records, from questionnaires to parents, and from employment and radiation records held by British Nuclear Fuels Limited.

The relative risks for leukaemia and NHL were higher in children born near Sellafield and in children of fathers employed at the plant, particularly those with high radiation doses before their child's conception. The relative risks compared with the controls were 0.17 (95% CI: 0.05–0.53) for being born further than 5 km away from Sellafield, 2.44 (95% CI: 1.04–5.71) for children of fathers employed at Sellafield at their conception, and 6.42 (95% CI: 1.57–26.3) for children of fathers receiving a total pre-conception ionizing radiation dose of 100 mSv or more. None of the other factors could explain these relationships. The study concluded that the raised incidence of leukaemia and NHL among children living near Sellafield was associated

with parental employment and recorded external dose of whole-body radiation at the plant prior to conception of the child (parental pre-conception irradiation effect). These results suggested an effect of ionizing radiation on fathers (that may be leukaemogenic in their offspring), although other, less likely explanations are possible.

The UK Department of Health and the Health and Safety Executive (HSE, 1993) carried out an investigation into occupational factors arising at Sellafield to see if any could explain or clarify the association reported by Gardner *et al* (1990). The investigation was divided into three parts. A case-only study examined the occupational histories of the 11 case fathers only. A radiation dose study compared the radiation dose histories (1950–85) of the 11 case fathers with all other male Sellafield radiation workers of the same age when the children were conceived, to determine if radiation doses of case fathers were unusual. Nothing emerged from these two studies to take action to further protect the health and safety of Sellafield employees or radiation workers in general, although the radiation dose study provided some weak support for the association between pre-conception radiation dose to fathers and the risk of leukaemia and NHL in their children.

A case-control study was the main epidemiological study and included all cases of childhood cancer (age 0–25 years) born in West Cumbria whose fathers had worked at Sellafield prior to the diagnosis. In all, 16 cases of leukaemia and NHL, and 16 cases of other cancers were identified between January 1950 and September 1989. The study investigated the effects of exposure to internal and external radiation, occupational history, exposure to chemicals and involvement in radiological or other incidents. The investigation also assessed if available data supported the Kinlen theory (Kinlen, 1988) that population mixing results in an infectious basis for childhood leukaemia.

The case-control study's main conclusion was that a clear distinction existed between the risk of leukaemia and NHL for the children of Sellafield workers living in Seascale when their children were born versus with those living elsewhere. The association was confined to workers who started work at the plant before 1965 and who lived in Seascale when their children were born.

The rate of leukaemia and NHL was about 14 times the national average for the Seascale children born to Sellafield fathers, and about twice the national average for the children of Sellafield fathers' resident elsewhere. Thirteen out of sixteen leukaemia and NHL case children were born to fathers who started work at Sellafield before 1965. The excess in these cases was almost entirely in children whose fathers started work from 1950 to 1964, with the observed/expected ratios being 10/2.25 for lymphatic leukaemia and NHL, and 13/3.56 when considering all leukaemia and NHL. If there was a workplace-related cause, it had either ceased or been substantially reduced since the mid-1960s.

Overall, the evidence that cumulative paternal pre-conception external radiation exposure alone was linked to an increased risk of leukaemia and NHL in children was weak. Likewise, there was no association between other forms of cancer and the father's exposure to radiation. For the study population as a whole, there was no statistically significant evidence for the relationship between radiation dose received during the 12 week pre-conception period and any of the cancer types examined.

For the Seascale cases, there was a strong association with fathers' cumulative pre-conception radiation doses, and a weaker association in the 12-week period before conception. It is possible these cases can be explained by a combination of causes, including population mixing (Kinlen, 1988) since there was a high degree of population mixing in Seascale — especially before 1965 — which may have been important. For the other factors examined (fathers' pre-conception internal radiation doses and potential neutron and alpha exposures; exposures to various chemicals; involvement in radiological incidents) it was concluded that they were not significant.

Two factors, which did produce significant associations independently of external radiation and residence in Seascale, were potential exposure to tritium and trichloroethylene. The association for LLNH and LNHL for the potential for exposures to tritium (ever or never exposed) is shown in Table 4.8 and 4.9, respectively. There is a strong positive relationship for the continuous measure ($p<0.00001$) and for both grouped measures with a positive trend in risk for the 3 group analyses. Table 4.10 shows a joint analysis of LNHL cases by potential exposure to tritium and trichloroethylene (highest groups/others). All of the cases with potential tritium exposure lie in the highest trichloroethylene exposure group. The associations of these two exposures cannot therefore be statistically separated with any certainty. One cannot infer tritium specific risks from this study.

Table 4.8: Lymphatic Leukaemia and Non-Hodgkin's Lymphoma (LLNH): Observed and Expected Numbers With Relative Risks by Father's Assessed Exposure to Tritium Prior to Child's Conception (from Table 24, HSE, 1993)

Grouped analysis p for trend = 0.0018	Controls	Cases	Expected	Observed/ Expected	Odds Ratio	95% Confidence Interval
Unexposed	87	5	2.13	2.35		
Exposed–low half*	8	2	0.13	14.97	8.29	1.26–54.7
Exposed–top half*	7	3	0.15	20.29	15.9	2.52–100.6
Grouped analysis (2 groups) p=0.0059	**Controls**	**Cases**	**Expected**	**Observed/ Expected**	**Odds Ratio**	**95% Confidence Interval**
Unexposed	87	5	2.13	2.35		
Exposed (>0)	15	5	0.37	13.54	7.77	1.91–31.5

**Median weighted days exposed: 136.4 days*

- *Exposed–low half: weighted days < 136.4 days*
- *Exposed–top half: weighted days > 136.4 days*

This table contains extracts from Table a-20 in Appendix 3 of HSE.

Table 4.9: All leukaemias and Non-Hodgkin's Lymphoma (LNHL): Observed and Expected Numbers With Relative Risks by Father's Assessed Exposure to Tritium Prior to Child's Conception (from Table 25, HSE, 1993)

Grouped Analysis p for Trend = 0.0026	Controls	Cases	Expected	Observed/ Expected	Odds Ratio	95% Confidence Interval
Unexposed	128	11	4.15	2.65		
Exposed–low half*	11	2	0.27	7.40	3.17	0.57–17.63
Exposed–top half*	11	3	0.28	10.77	5.61	1.18–26.66
Grouped analysis (2 groups) p=0.0014	**Controls**	**Cases**	**Expected**	**Observed/ Expected**	**Odds Ratio**	**95% Confidence Interval**
Unexposed	128	10	4.15	2.41		
Exposed (>0)	25	6	0.67	8.93	4.71	1.46–15.13

**Median weighted days exposed: 136.4 days*

- *Exposed–low half: weighted days < 136.4 days*
- *Exposed–top half: weighted days > 136.4 days*

This table contains extracts from Table A-570 in Appendix 3 of HSE (see TRI 2 and TEN 2).

Table 4.10: All Leukaemias and NHL (LNHL): Observed and Expected Cases by Potential Exposures to Tritium and Trichloroethylene (from Table 28, HSE, 1993)

Trichloroethylene Exposure	Tritium Exposure		
	No Observed/ Expected	Possible Observed/ Expected	Unknown Observed/ Expected
Unexposed and exposed–low-half	2/1.19	0/0.12	0/0.14
Exposed–top half	2/0.44	6/0.37	0/0.31
Unknown	6/2.52	0/0.18	0/0.52
This table contains extracts from Table A-47 in Appendix 3 of HSE.			

Dickinson and Parker (2002) conducted a cohort study of live births from 1950 to 1991 in Cumbria to investigate if the following existed:

(i) an excess risk of leukaemia/non-Hodgkin's lymphoma (NHL) among children of male radiation workers at Sellafield nuclear installation

(ii) a dose-response relationship between fathers' pre-conception irradiation and their children's risk of these cancers
(iii) whether any observed association could be explained by demographic factors

Children were followed until they were 25 years old or until the end of 1991. The risk of these cancers among all 9,859 children of male radiation workers was compared to that of all 256,851 children of non-Sellafield fathers. Total external radiation doses were estimated based on film badge monitoring, up to the time of conception. Urinalysis data was used to identify workers monitored for internal radiation before their children were conceived. However, analysis was restricted to internal plutonium, fission products and natural uranium since there were few births and only one leukaemia/NHL case with pre-conception internal doses to polonium, fission products, enriched uranium or tritium.

Children of radiation workers had a higher risk of leukaemia/NHL than other children (RR=1.9, 95% CI: 1.0–3.1, p =0.05). This risk was driven by children aged 0–7 years born between 1950 and 1968 (RR=3.3, 95% CI: 1.3–7.0, p=0.02). Adjustment for population mixing greatly reduced the excess in Seascale (where population mixing was very high throughout the entire time period), but not elsewhere.

The risk increased significantly with father's total pre-conception external radiation dose (RR_{100mSv} =1.6, 95% CI: 1.0–2.2, p =0.05), with this effect being determined largely by children aged 0–7 years born between 1950 and 1968 (RR_{100mSv} =1.9, 95% CI: 1.1–2.6, p=0.03). Adjustment for population mixing had little effect. Children whose fathers were monitored for natural uranium before conception had a non-significant increased risk of leukaemia/NHL compared to other children of radiation workers, even after adjustment for external radiation (RR=2.9, 95% CI: 0.6–9.8, p =0.15).

There was no significantly increased risk for children whose fathers were monitored for plutonium or fission products before conception. The 13 exposed cases included 10 studied earlier by Gardner *et al* (1990). However, this study was a cohort as opposed to a case-control study, used a wider timeframe and geographical area, and confirmed the statistical association between a father's pre-conception irradiation and a child's cancer risk. This cohort study — with 1,737 subjects with greater than 100 mSv of exposure —had greater statistical power than any other studies of the nuclear industry in Western Europe or North America, as it included 7% and 23% more live births following external/internal doses of 50–99 mSv and more than 100 mSv, respectively. The implications of these findings for current nuclear workforces must be viewed cautiously, since exposures are now very low compared to those during earlier decades.

At the request of the Department of Health and the HSE, the Committee on Medical Aspects of Radiation in the Environment (COMARE) reviewed this subject in its Fourth (COMARE, 1996) and Seventh (COMARE, 2002) Reports. The reports extensively reviewed the most recent epidemiological studies of the offspring of radiation workers in the UK and other countries. They also included the latest laboratory and genetic research related to the possible biological mechanisms that could have explained any observed effects in the offspring of irradiated parents.

COMARE's review reported the following key findings:

- Studies in the UK or in other countries found no evidence of a causal link between workers' exposure to radiation and cancer in their children.
- There was a known "cluster" of childhood cancer in the village of Seascale near Sellafield, where the fathers of children who developed leukaemia or NHL had all received larger-than-average occupational doses. However, no excess was found in the surrounding area where the majority of radiation workers lived. If there had been a link with workers' radiation exposure, similar rates of cancer would have been expected in their children.
- Childhood leukaemia had accounted for just under half the cases of cancer in young people in Seascale in the previous 50 years. This made it increasingly unlikely that a single factor, such as parental exposure to radiation, was the cause.
- Much of the increased cancer rate in Seascale may have been due to some effect associated with population mixing, probably an increased exposure to infectious agents. Although it is possible that this effect might have combined with parental radiation exposure to give a greater risk, it is more likely that the highest paternal doses occurred by chance at the time that the population mixing effect was at its greatest.

COMARE also highlighted that children of radiation workers had a low risk of developing childhood leukaemia, in absolute terms. On the basis of the balance of evidence, COMARE concluded that rates of cancer in the children of male radiation workers in the British nuclear industry were not related to parental radiation exposures. The rates may have been associated with lifestyle factors, work practices or population mixing (although the biological mechanism of the population mixing effect has not yet been established).

Bunch *et al* (2009) examined the National Registry of Childhood Tumours (NRCT) and the National Registry for Radiation Workers. The researchers linked the two sets of records to reassess earlier findings that offspring of female radiation workers exposed to ionizing radiation before conception may have had higher risk of childhood cancer (Draper *et al*, 1997a, b; Sorahan *et al*, 2003). Pooled analyses based on the new and original datasets included 52,612 cases and the same number of matched controls. Relative risks (RRs) for maternal employment as a radiation worker, maternal exposure or not during the relevant pregnancy and pattern of employment relative to conception and diagnosis dates were calculated. Estimates of doses for internal emitters were not available, but workers monitored for potential exposure were identified. RRs of cancer in offspring were estimated separately for female workers monitored for internal radiation exposures or not.

Overall, the new data found no evidence of an increased risk of childhood cancer associated with maternal pre-conception radiation work and thus did not support the earlier findings. When the data was pooled, there was no statistically significant increase in risk for cancer overall or for either diagnostic subgroup (leukaemia and NHL, all cancers excluding leukaemia and NHL). The RR of all childhood cancers combined among the offspring of female radiation workers was 1.90 (95% CI: 0.84–4.58) based on 19 cases and 10 controls. There were no significantly raised risks for the offspring of female workers monitored for internal exposure; the RR of all childhood cancers combined was 1.50 (95% CI: 0.17–18) based on 3 cases and 2 controls.

This evidence was limited because of the small number of cases and controls and the lack of information on exact internal doses.

4.3.2 Congenital Malformations and Occupational Exposure to Low-Level Ionizing Radiation at the Hanford Site

The Hanford Site was built in 1943 to produce plutonium for the weapons program. At its peak production, nine reactors were in operation. In the early 1970s all reactors but one were closed, with the remaining reactor used for the joint production of plutonium and electrical energy. Plant operations have included other functions such as chemical separation, fuel fabrication, radioactive waste storage, and laboratory research. There are limited details of tritium exposure, which does not seem to have been extensive (NIOSH, 2007); however, workers were exposed to tritium at Hanford (if only as a fission product) and measurements were taken. Over 65,000 persons have been employed at the site, with most living in Benton and Franklin counties, Washington State, near the Hanford nuclear site. Males held most jobs involving radiation exposure; therefore, possible effects of maternal exposures are very limited.

Sever *et al* (1988a) conducted a case-control study to investigate the association of parental occupational exposure to long-term low-level external whole-body penetrating ionizing radiation and the risk of congenital malformations in their offspring. There were 672 congenital malformation cases and 977 controls (672 matched based on sex, maternal age within five year groups and, to the extent possible, race and 305 unmatched) from births occurring in the three main hospitals in Benton and Franklin counties from 1957 to 1980. Identifying information for both parents was linked to rosters of workers at the Hanford Site to determine if case and control parents were Hanford employees before the birth of the case or control offspring. Quantitative individual measurement of external whole-body penetrating ionizing radiation exposure of Hanford employees, using personal dosimeters were available for all years of employment through the year of delivery of the offspring. Although the analysis was limited to external whole-body penetrating radiation (gamma), it may also have included some high-LET neutrons. In addition, information on internal radionuclide depositions were obtained, but were not of sufficient frequency or magnitude to affect the analyses. Only a very small percentage (394 employees out of over 65,000) of the total employee population had internal systematic depositions exceeding 1% of their total body burden, as examined through routine bioassays and *in vivo* tests.

Twelve specific malformations were analyzed for evidence of association with parental employment at Hanford and with occupational exposure to ionizing radiation. For all malformations combined, there was no evidence of association with parents being employed at Hanford. Two birth defects showed evidence of a statistically significant association with employment of fathers at Hanford, but not with parental radiation exposure: congenital dislocation of the hip (12 cases, 7.1 expected, one-tailed p value between 0.01 and 0.025) and tracheoesophageal fistula (4 cases, 1.4 expected, one-tailed p value between 0.025 and 0.05). Neural tube defects showed a significant association with parental pre-conception exposure ($p=0.04$) on the basis of two cases in the highest dose category (fathers' cumulative doses about 100 mSv) versus 0.6 cases expected. Eleven other birth defects, including Down syndrome, showed no evidence of such an association. When all malformations were analyzed as a

group, there was no evidence of an association with parent's Hanford employment, but the relation of parental exposure to radiation before conception was in the positive direction (one-tailed p value between 0.05 and 0.10).

The authors concluded their findings were most likely false positives, given the number of statistical tests conducted. In light of the lack of genetic effects in the atomic bomb survivors, it is unlikely that these correlations resulted from parental radiation exposure.

4.3.3 Congenital Anomalies in Offspring of Ontario Hydro Power Workers

McLaughlin *et al* (1992a; 1993) assessed the association between childhood leukaemia and paternal occupational exposure to ionizing radiation before the children were conceived. Cases included children (aged 0–14 years) who died from or were diagnosed with leukaemia and were born to mothers who, at the time of their child's births, resided near an Ontario operating nuclear facility. Cases occurred from 1950 to 1988 and were identified from the Ontario Cancer Registry. Eight controls per case were identified from birth registers, matched by date of birth and mother's residence at time of birth. Controls had to have survived and been free of leukaemia by the time the index case was diagnosed.

There were 112 cases and 890 controls. The pre-conception doses of case and control fathers were obtained via record linkage to the NDR and subsequent analysis of employer records. Dose information included external whole-body dose (mainly gamma, whole-body tritium dose in mSv) and internal exposures to radon and radon progeny. Tritium doses, the most common type of whole-body internal exposure received by Canadian nuclear reactor workers, were measured by urinalysis and converted to equivalent doses in mSv. These doses were very small relative to external exposures, although the exact tritium percentage of the total dose was not available in the paper. Separate analyses were done for whole-body external dose, whole-body tritium dose and total whole-body dose (external + tritium). Covariates included maternal age, birth weight, birth order and sex. The distance between residence at birth and a nuclear facility was categorized as 0–14, 15–29, or ≥30 km.

Workers most exposed to tritium were those employed at the AECL research and development laboratories at Chalk River (opened in 1944), and the Nuclear Power Demonstration Station at Rolphton (1962–87), the Pickering Nuclear Generating Station that opened in 1971, and the Bruce Nuclear Power Development (opened in 1967).

There was no statistically significant association between childhood leukaemia and paternal occupational exposure to ionizing radiation that occurred before a child's conception. Specifically, there was no evidence of an elevated leukaemia risk in relation to any exposure period (lifetime, six months or three months prior to conception) or exposure type (total external whole-body dose of gamma radiation, tritium dose, or radon exposure).

The odds ratio (OR) for any lifetime exposure of the father before conception was 0.87 (95% CI: 0.32–2.34 based on 6 cases and 53 controls). The OR for whole-body exposure of the father during the six-month period before conception was 0.96 (95% CI: 0.34–1.77 based on 5 cases

and 41 controls). There was also no apparent gradient of effect with increasing paternal radiation dose, as indicated in Table 4.11.

Tritium doses ≥0.1 mSv prior to conception were recorded for 14 controls, but not for any cases, giving an OR of 0.00 (95% CI: 0.00–2.39, 2-sided p=0.25).

Table 4.11: Odds Ratios (and 95% CI) for Leukaemia Cases Among Offspring of Workers Monitored for Tritium in Ontario (from Table 8, McLaughlin *et al* 1992a and Table III, McLaughlin *et al*, 1993)

	Cumulative Tritium Dose Before Conception (mSv)	
Statistic	**0 mSv**	**≥0.1 mSv**
Cases	112	0
Controls	876	14
Odds ratio (+95% CI)	1.00	0.00 (0, 2.39)[a]
	Tritium dose 6 months before conception (mSv)	
Statistic	**0 mSv**	**≥0.1 mSv**
Cases	112	0
Controls	880	10
Odds ratio	1.00	0.00[b]
	Tritium dose 3 months before conception (mSv)	
Statistic	**0 mSv**	**≥0.1 mSv**
Cases	112	0
Controls	880	10
Odds ratio	1.00	0.00[b]

[a] *1-sided p=0.25 (Fisher's exact test)*
[b] *1-sided p=0.40 (Fisher's exact test)*

The results did not demonstrate an association between childhood leukaemia and occupational exposures of fathers for either whole-body external radiation or tritium exposure. The case-control design and the existence of the dose and cancer registry made it possible to study the relationship between a rare disease and rare exposure over a 40-year period. However, the study lacked information on other known risk factors for leukaemia, such as infectious and environmental agents. Despite that the study covered a long period of time and referred to a large population, it had sufficient power to detect only large relative risks.

Green *et al* (1997) conducted a case-control study to evaluate the risk of having a child with a congenital anomaly in relation to a parent's occupational exposure to low levels of ionizing radiation in the pre-conception period. Congenital anomalies were identified through the Canadian congenital anomalies registry, a population-based registry for such anomalies diagnosed in the first year of life. Cases were defined as parents of a child born between April

1979 and December 1986, where a congenital anomaly was diagnosed during the first year of the child's life. Each case parent had an individually matched control parent of a child without an anomaly taken from the Ontario birth registry and matched by year of birth, exact maternal age, marital status and birthplace of each parent (Ontario vs. not Ontario). The case-control parents were identified and linked to employment records of Canada's largest electrical company, Ontario Hydro (now Ontario Power Generation), and the appropriate pre-conception doses were determined.

In Canada, all nuclear energy workers are monitored for radiation exposure, and the doses are reported to the NDR. Radiation doses received prior to working at Ontario Hydro were collected and added to the Ontario Hydro doses. Detailed dose information is kept for external whole-body dose (using film badge and thermoluminescent dosimeter), external skin dose, and internal dose (primarily from tritium measured through urinalysis), which are the most common exposures associated with nuclear power generation. Tritium doses were assessed for this group, although analyses were only of those case-control parents having a recorded tritium dose 60 days before conception, which corresponds to the period of human spermatogenesis. As such, there was limited quantitative information in relation to tritium dose. A total of 763 case-control pairs of fathers and 165 case-control pairs of mothers were identified in which at least one parent worked at Ontario Hydro.

Findings showed that:

- Only three case-mothers had a non-zero dose so it was not possible to evaluate the effect of ionizing radiation in mothers.
- Of 74 case-fathers with cumulative tritium doses before conception, the mean dose was 16.9 mSv (standard deviation=27.2), ranging from 0.02 mSv to 107.2 mSv. Among the 51 case-fathers exposed to tritium within 60 days before conception, the mean dose was 0.4 mSv (standard deviation=0.5), ranging from 0.01 mSv to 2.8 mSv.
- Analysis of all anomalies combined showed no evidence of a relationship between parents' employment at Ontario Hydro and a child with a congenital anomaly. Exposures of fathers before conception were not associated with increased risk of anomalies in their offspring.
- The OR for cumulative whole-body dose before conception and whole-body dose 6 months before conception was 0.72 (95% CI: 0.55–0.95) and 0.90 (95% CI: 0.60–1.27), respectively. There was also little evidence of a raised risk associated with tritium exposure.
- As indicated in Table 4.12, the OR for non-zero tritium exposure 60 days before conception versus no such dose for all congenital anomalies was 0.99 (95% CI: 0.67–1.47). Similarly, there was no significant increase in risk found between groups of congenital anomalies (such as cleft palate or lip, chromosomal anomalies) and any measure of exposure, although the statistical power in these groups was limited.

Overall, workers exposed before conception to low levels of ionizing radiation did not appear to have an increased risk of a live born child with a congenital anomaly. The absence of a significant increased risk of having a child with congenital anomalies in fathers exposed to radiation within an occupational setting suggested that a public health risk was unlikely. Consistent with higher-dose studies of atomic bomb survivors and cancer patients who subsequently became pregnant, this study was found no evidence for increases in birth defects associated with pre-conception radiation (UNSCEAR, 2001).

Table 4.12: Adjusted Odds Ratios (and 95% Confidence Intervals) for Aetiological Groups of Congenital Anomalies According to Tritium Exposure (Recorded Dose[c] 60 Days Before Conception vs. None) (from Table 2, Green *et al*, 1997)

Aetiological Group	Discordant Pairs*	Odds Ratio (95% Confidence Interval)
Single gene disorders[a]	0/0	–
Chromosomal disorders[a]	3/2	1.46 (0.24–8.80)
Multifactorial disorders[b]	28/28	1.13 (0.66–1.94)
Genetic, unspecified[a]	6/8	0.80 (0.27–2.32)
Unknown disorders[b]	14/15	0.84 (0.40–1.76)
Total[b]	51/53	0.99 (0.67–1.47)

** Case exposed and control not exposed, or case not exposed and control exposed*
[a] *Adjusted for father's age only*
[b] *Adjusted for father's age and history of stillbirths*
[c] *Dose > 0 υ dose = 0 or not exposed*

4.4 Studies of Environmental Releases and People Living in the Vicinity of Nuclear Facilities

4.4.1 Childhood Leukaemia in Communities Around Nuclear Installations in Britain

A possible raised childhood leukaemia risk around nuclear installations in the UK first came to scientific attention in 1983 when a television program (Yorkshire Television, 1983) reported excess of childhood leukaemia around the nuclear fuel reprocessing plant at Sellafield (then Windscale). In response, the Government set up the Black Advisory Group, which reported back in 1984 confirming the presence of an unexpectedly large number of childhood leukaemia cases in the nearby village of Seascale located 3 km from the Sellafield plant. Seven incidence cases were recorded between 1955 and 1984 among those younger than 25 years of age living in Seascale, where less than one case was expected ($p < 0.001$) (Black, 1984). There was no explanation for such excess. As a result, the Black Advisory Group recommended the Government set up a standing committee to monitor such findings. In 1985, the Committee on Medical Aspects of Radiation in the Environment (COMARE) was established to monitor these kinds of findings.

Heasman *et al* (1986) shortly thereafter reported a second cluster of childhood leukaemia in Scotland, near the nuclear processing plant of Dounreay (Caithness). It involved 5 incidence cases observed (O) when 0.5 were expected (E) (O/E=9.8, 95% CI: 3.1– 22.7) over 6 years (1979–84) within a radius of 12.5 km ($p<0.001$).

In 1985, initial findings of a third cluster of an excess of leukaemia incidence within a 10 km radius of the nuclear weapons plant in Aldermaston and Burghfield, West Berkshire was reported (Barton *et al*, 1985). In 1987, Roman *et al* (1987) noted the excess was primarily in children aged 0–4 years (41 cases) observed during a 14-year period among those younger than 15 years

of age (28.6 expected; incidence ratio = 1.4, $p<0.05$), with 29 of them younger than 5 years of age (14.4 expected; incidence ratio = 2.0, $p<0.001$).

Bithell *et al*, 1994 conducted the first systematic analysis using registration data of childhood cancer incidence in relation to proximity to nuclear installations in Britain using the NRCT, the largest database of childhood cancer in the world. The study included children with leukaemia and NHL, under the age of 15 years in England and Wales who were registered from 1966 to 1987 and living within 25 km of 23 nuclear installations and 6 control sites. It confirmed the excess risk found near Sellafield: 24 cases of leukaemia and NHL were observed for an expected 18.5 cases, with an incidence ratio of 1.3 (95% CI: 0.8–1.9). However, the overall results for generating stations were negative. The only significant results for the linear risk score test were for Sellafield ($P = 0.00002$) and Burghfield ($P=0.031$). The circles for Aldermaston and Burghfield overlap; the incidence ratio for each was 1.10. There is no evidence of a general increase of childhood leukaemia or NHL around nuclear installations. Apart from Sellafield, the evidence for distance related risk was very weak.

Sharp *et al* (1996) investigated the incidence of leukaemia and NHL in children living near seven nuclear sites in Scotland to determine if a gradient in risk existed with respect to distance of residence from a nuclear site. The study data set comprised 1,287 cases of leukaemia and NHL diagnosed in children aged less than 15 years in the period 1968–93, validated for accuracy and completeness. A study zone around each nuclear site was established from enumeration districts within 25 km. More cases were observed than expected in the study zones around the Rosyth naval base (O/E 1.02), Chapelcross electricity generating station (O/E 1.08), and Dounreay reprocessing plant (O/E 1.99). The maximum likelihood ratio test reached significance only for Dounreay ($p=0.030$). The linear risk score test did not indicate a trend in risk with distance from any of the seven sites, including Dounreay. In conclusion, there was no evidence of a generally increased risk of childhood leukaemia and NHL around nuclear sites in Scotland, or any evidence of a trend of decreasing risk with distance from any of the sites. There was a significant excess risk in the zone around Dounreay. The persistence of this cluster from 1968 through to 1993 was recently confirmed (9 cases observed over 26 years among those less than 15 years of age ($p=0.03$) by Sharp *et al* (1996). This persistence of the Dounrey cluster was confirmed, although the RR has tended to decrease with time (Sharp *et al*, 1996). Likewise, the excess in Aldermaston and Burghfield persisted when different periods and geographical limits were studied; although the risk was found to be lower (Bithell *et al*, 1994).

COMARE's Fourth Report (COMARE, 1996) examined the incidence of cancer among young people age 0–24 living in the vicinity of Sellafield from 1955 to 1992. This was subdivided into the period examined by the Black Advisory Group (1963 to 1983), the period following (1984 to 1992) and the earlier period (1955 to 1962) to see whether the raised incidence of childhood cancer had persisted. COMARE established that there had been a continuing excess of leukaemia and other cancers in young people aged 0–24 years in Seascale in the period 1984–1992 (O=5, E=0.78, O/E = 6.4) primarily due to an excess of acute lymphoblastic leukaemia (ALL) and NHL. Taken together with the results for the earlier period 1955–62 (for which comparable statistical analysis is not possible) and 1963–1983 (O=6, E=2.18, O/E=2.75), the data showed a continued excess of leukaemia and NHL in Seascale for four decades.

COMARE's Tenth Report (COMARE, 2005) reported on the findings of their study that utilized the NRCT, which included over 32,000 cases of childhood cancer. The study covered the years 1969 to 1993 and included England, Wales and Scotland. It examined the incidence of cancer in children (under 15 years of age) in the vicinity of all major licensed nuclear sites. Specific attention was given to leukaemia and non-Hodgkin's lymphoma (LNHL). A total of 28 nuclear installations were examined, 13 nuclear power generating stations and 15 of various other kinds, including research, commercial and military installations. Results showed no evidence of excess childhood leukaemia or any other cancer in any local 25 km area around any of the nuclear power stations. None of the chosen test statistics was significantly raised, nor was any incidence rate significantly >1. Around non-generating nuclear installations, there were some excesses already noted in the literature (i.e., Sellafield; SIR=25/21.95 =1.14, p=0.018), with only one site being different. COMARE found an excess of leukaemia and NHL near Burghfield, Dounreay and Sellafield. As previously known, Aldermaston, Burghfield and Harwell nuclear installations (because of their close proximity these are discussed together) showed a significantly raised incidence of solid tumours in their vicinity. However, for Rosyth, although the overall incidence of leukaemia and NHL in children living within 25 km of the site was close to the expected value (SIR=1.03), there was evidence of a trend associating risk with distance from the plant. This finding was different from previously published work, so it was important to establish the nature of the differences between the studies before drawing any conclusions. In contrast, no significant trend for the incidence of solid tumours with distance from the site was found. In addition, a study of the small number of cases with myeloid leukaemia under the age of 5 years suggested a slightly increased incidence within 10 km of the four power stations that had at least 1 case; only 1 achieved nominal statistical significance, with 4 observed cases against 1.11 expected (p=0.026).

COMARE's Eleventh Report (COMARE, 2006) showed that childhood leukaemia and many other types of childhood cancers did not occur evenly within the population of Great Britain and these differed more than would be expected from simple random or chance variations. COMARE conducted a thorough examination of the NRCT. The data consisted of 12,415 cases of childhood leukaemia and NHL and 19,908 cases of children with solid tumours registered under the age of 15 in England, Wales and Scotland from 1969 to 1993 inclusive. Clustering had previously been reported for childhood leukaemia but this study was the first evidence of the same phenomenon in other types of childhood cancer. It is not known why childhood cancers tended to cluster like this, although much attention has been given to possible explanations. Infections may have played a role in initiating or promoting the growth of cancer cells, assuming cancer is a multi-stage process. It is also possible that exposure to environmental agents were involved. However, there was no pattern of excess cases of childhood cancer close to the nuclear power generation sites. Although some clusters, which had been previously reported, were observed near other nuclear installations (such as reprocessing plants, research establishments and military sites), this report confirmed that clustering was found in many other places. Therefore, other factors in the environment need to be considered.

Other research (the German KiKK study referred to in section 4.4.4, Kaatsch *et al*, 2008; Spix *et al*, 2008) appeared to conflict with the 2005 in the COMARE Tenth Report, which had presented negative results for childhood leukaemia. The KiKK study found an approximately doubled risk of leukaemia in children under the age of five years who lived within 5 km of

German nuclear power plants between 1980 and 2003. However, this discrepancy could be attributed to the 2 studies' different methodologies, especially those related to the distances from the power plants and the ages of the children. Bithell *et al* (2008) conducted a study of leukaemia in children living near British nuclear power stations, matching the methods of the KiKK study as closely as possible. Using the NRCT data, a Poisson regression model was fitted to best correspond to the conditional logistic regression of the KiKK study. There was no association between childhood cancer and proximity to a nuclear power station in Britain. The results gave no indication of overall excess, nor any indication of a positive trend with proximity. The incidence observed (18 cases within 5 km against 14.58 expected, p=0.21) was not significantly raised. The risk estimate for proximity in the regression fitted was actually negative, though the confidence intervals involved were so wide that the difference from that reported in the KiKK study was only marginally statistically significant (p=0.063). It was concluded that there was no evidence of increased acute leukaemia incidence in children aged five and under living close to nuclear power stations in Britain. An explanation for this discrepancy with the German data remains unclear.

Table 4.13: Observed and Expected Number of Cases of Acute Childhood Leukaemia Within Circles With the Radii Shown (from Table 1, Bithell *et al*, 2008)

Circle Radius (km)	Number of Wards	Observed	Expected	Incidence Ratio	95% Confidence Interval
5	33	18	14.58	1.23	0.73–1.95
10	130	58	63.95	0.91	0.69–1.17
25	768	360	374.90	0.96	0.86–1.06
50	2953	1599	1655.18	0.97	0.92–1.01

4.4.2 Congenital Malformations, Childhood Leukaemia and Mortality in Communities Around Nuclear Sites in the United States

Sever *et al* (1988b) examined the prevalence of congenital malformations among live births and foetal deaths in Benton and Franklin counties (near the Hanford Site) in the state of Washington from 1968 to 1980. Hospital and state vital records were used to identify 454 malformation cases among 23,319 births. The rates of specific malformations ascertained in the bicounty area during the first year of life were compared with combined rates from the Birth Defects Monitoring Program (from Washington, Oregon and Idaho). For the general public residing in the bicounty area, the estimated annual ionizing radiation exposure from the Hanford Site between 1977 and 1982 was 0.0001 mSv–0.0004 mSv. This amount is a small fraction of annual exposure from natural background radiation.

Overall, the congenital malformation prevalence rate for the bicounty was not elevated. The rate of 19.6 per 1,000 births was similar to those reported in other studies. A statistically significant elevated rate of neural tube defects (including spina bifida and anencephaly) was observed in the bicounty area (1.72 per 1,000 births (95% CI: 1.22– 2.34)) compared to 0.99 per 1,000 in the Birth Defects Monitoring Program ($p<0.001$). The excess persisted over the period studied. When rates of neural tube defects were compared with those in a population other than the Birth Defects Monitoring Program, the bicounty area rates were still considered to be elevated. The increased bicounty rate could not be explained by employment of the parents at Hanford; parental occupational exposure (no evidence of a correlation between occupational exposure between 1968 and 1980 and birth neural tube defects); or Hanford emissions (from 1974 to 1980, estimated exposure to the general public were less than 0.05% above the natural background of approximately 1 mSv).

Jablon *et al* (1991) conducted a mortality survey during the 35-year study period (1950–84) in populations living near all nuclear facilities in the United States that began operating before 1982. The 107 study counties with or near a nuclear installation were matched to approximately three "control" counties in the same region (292 control counties in total). Deaths from 15 cancers were obtained from each county's vital statistics, but cancer incidence was available only in Connecticut and Iowa. No information on radiation exposures to individuals was available. Department of Energy (DOE) facilities included Savannah River Site and Mound, both of which were known to have tritium. However, total exposures from the monitored emissions from nuclear facilities in the United States, are typically less than 0.03 mSv per year to the maximally exposed individual, an amount too small to result in detectable harm and are much smaller than the population exposures from natural background radiation (natural background radiation amounts to about 1 mSv per year, excluding lung doses from radon).

Overall, deaths due to leukaemia or other cancers were no more frequent in the study counties than in the control counties. For childhood leukaemia mortality (children under 10 years of age), the RR comparing the study with the control counties before plant startup was 1.08, while after start-up it was 1.03. No facility had a significantly elevated RR. When comparing study counties with control counties after start-up, no facility had a significantly raised RR for deaths of cancer other than leukaemia. For leukaemia mortality at all ages, the RR was 1.02 before and 0.98 after start-up. The deficits were significant ($p<0.05$) for the combined DOE plants and all facilities combined. Cancer incidence data was only available in study counties. For one facility, the standardized registration rate (SRR) for childhood leukaemia was increased significantly after start-up, 1.55 ($p<0.01$); however, the increase also antedated the operation of the facility. The study was limited by the correlation approach and the large size of the geographical areas used (counties). If any excess cancer risk was present in U.S. counties with nuclear facilities, it was too small to be detected with the methods employed.

Richter and Stockwell (1998) studied mortality associated with residential proximity to the Salmon Nuclear Test Site, Mississippi, US, from 1980-1991, following two nuclear test detonations in 1964 and 1966. Radiation monitoring confirmed that the detonations were contained within the salt dome and that all environmental monitoring for tritium showed no increase above background levels in water, soil or air. The highest tritium concentration in

drinking water was 1.8 Bq/L, well below regulatory limits. The tests also "did not result in the release of radioiodine". Since tritium contamination was not detected off site, the analysis assessed the relationship between mortality and the distance of the residence from the test site at the time of death. The statistics used to assess mortality as a function of distance were crude, based on a comparison of the numbers of deaths by distance, using a chi-squared (χ^2) test.

Overall, the age-adjusted mortality rates for all cancers (combined) and for the 34 site-specific cancers for Lamar County were similar to those for Mississippi and other counties within the state. For persons aged 40 years or older at the time of death, the χ^2 test for trend by age-specific category, which indicated the distribution of cancer and non-cancer deaths by distance from the test site were similar. For persons under 40 years old at death, the distribution of deaths by distance was significantly different: a higher percentage of non-cancer deaths occurred closer to the Salmon Test Site, and the highest percentage of cancer deaths occurred more than 20 miles (32 km) from the site. The results were difficult to interpret as being caused by possible radiation releases from the test site. No significant risk of cancer death was found in the area north of the test site.

The analyses concluded that there was no relationship between cancer death and residence near the Salmon Test Site. Tritium was implied to be the main source of radiation exposure although there was no detection of tritium contamination. There was also a 14- to 16-year interval between the tests and start of mortality follow-up; no deaths before 1980 could be examined because there was insufficient registry data on place of death in the registries.

4.4.3 Birth Defects, Childhood Leukaemia, Infant Mortality and Other Health Indicators in Communities Around Canadian Nuclear Facilities

Studies by Clarke *et al* (1989; 1991) and McLaughlin *et al* (1992b) examined mortality and incidence of childhood leukaemia in the vicinity of nuclear facilities in Ontario. Their reports considered leukaemia deaths (1950–87) and cases (1964–86) at ages 0–14 years (cases=1,814, deaths=1,894), respectively. Residence was obtained from birth certificates, cancer registry or death certificates, as applicable. The nuclear facilities with the main sources of tritium exposure included the AECL nuclear research and development laboratories at Chalk River, the nuclear power demonstration station at Rolphton, the Pickering Nuclear Generating Station (NGS), and the Bruce Nuclear Power Development. Analyses were performed separately for each of the nuclear facilities and two levels of geographic areas: the "county" and "nearby" area (<25 km radius of the facility). No evidence was found of any excess leukaemia incidence or mortality close to AECL or Rolphton, whether assessed by residence at death, residence at birth, at the county level or "nearby" area of the facilities. There were consistently fewer childhood leukaemia cases and deaths in Renfrew County compared with the general Ontario population. The occurrence of leukaemia in children in the vicinity of Bruce and Pickering was greater than expected although not statistically significantly so. In areas "nearby" Pickering (over the 1971–87 period), there were 33 leukaemia deaths aged 0–14 vs. 24.6 expected, SMR=1.34 (95% CI: 0.92–1.89); the incidence figures (over the 1971–86 period) were 72 cases compared with 62.8 expected (SIR=1.15, 95% CI: 0.90–1.44). Prior to the opening of the Pickering facility (1950–70), the mortality ratio by residence at birth for the nearby area was also higher than expected (SMR=1.08, O=80, E=74.1). These results do not constitute any evidence of a true

difference in leukaemia risk during the periods before and after the nuclear facility opened. In the area "nearby" Bruce (over the 1967–87 period), there were 3 leukaemia deaths vs. 1.1 expected (SMR=2.78, 95% CI: 0.56–8.13); the incidence figures (over the 1967–86 period) were 4 cases compared with 2.6 expected (SIR=1.57, 95% CI: 0.42–4.01). There was no indication of a birth cohort effect, as the mortality ratios based on place of birth were not significantly higher than the mortality ratios based on place of death. In summary, the confidence intervals included the null value and were generally wide because of the small observed and expected numbers. The results for the examined cases and deaths for leukaemia in children (ages 0–4) in the vicinity of Canadian nuclear facilities are similar (Clarke *et al*, 1989). When the areas "nearby" the Bruce and Pickering sites were pooled, the evidence became weaker (Clarke *et al*, 1991; McLaughlin *et al*, 1992b). The pooled estimate of the SMR by residence at birth for the areas "nearby" was 1.40 (95% CI: 0.98–1.9) (O=36; E=25.7). While the rate of childhood leukaemia around Bruce and Pickering may have been higher than the provincial average, there is no statistical evidence that the difference was due to anything but the natural variation in the occurrence of the disease. The rate of childhood leukaemia around Pickering was slightly greater than the Ontario average both before and after the plant opened, but was not statistically significant. However, because there are no estimates of tritium dose in these studies, no inference on risks from tritium can be made. The statistical power of the studies was also limited due to the rarity of childhood leukaemia and the small number of observed and expected cases and deaths.

Johnson and Rouleau (1991) compared rates of birth defects, stillbirths, and deaths within the first year of life among the offspring of residents living within 25 km of the Pickering NGS in Ontario (1971-1988) with those of the general Ontario population. Focus was on Ajax and Pickering townships as they are closest to the Pickering plant. They also investigated relationships between monthly airborne and waterborne tritium emissions from Pickering and the rates of these reproductive outcomes. Monthly airborne and waterborne releases of radioactive materials from Pickering NGS between 1971 and 1988 were provided, along with monthly data on airborne concentrations of tritium from 11 ground-monitoring stations located within 1 or 2 km from the plant. Data on the prevalence of birth defects were obtained from the Canadian Congenital Anomalies Surveillance System (1973–88) and data on stillbirths and deaths during the first year of life were obtained from Canadian Vital Statistics (1971–88).

The mortality rates of stillbirth, neonatal mortality and infant mortality were not significantly elevated between 1971 and 1988, but were significantly lower than the Ontario average. Rates of birth defects were not significantly elevated between 1973 and 1988; these were also generally lower than provincial rates, sometimes significantly so. The incidence of central nervous system (CNS) defects was significantly elevated in Pickering for the highest (12.5%) airborne tritium levels (OR in highest group=4.01 (95% CI: 1.25–14.04), based on 6 cases), although there was no statistically significant trend with tritium exposure (p=0.197). This association was not; however, repeatable using the Pickering ground monitoring data. The overall birth prevalence of CNS defects (1973–88) was 20% lower for Pickering than for Ontario as a whole. No associations were found between high ground monitoring levels and the prevalence of birth defects. There was a statistically significant elevation in the number of cases of Down syndrome (maternal age-adjusted) in Pickering (observed=24, expected=12.9) (SIR=1.85, 95% CI: 1.19–2.76), the only endpoint out of 22 diagnostic categories to show such excess. A non-significant correlation

(p=0.468), between Down syndrome and airborne tritium release levels was found, but there was no such correlation found with ground monitoring data. There were no such excess birth defect risks in Ajax where Down syndrome risk was non-significantly elevated (SIR=1.46, 95% CI: 0.80–2.44). A non-significant association was found with the highest ground monitored tritium levels (p=0.282), but no association with airborne tritium emission levels.

The authors cautioned against misinterpreting these data since the few positive results were likely due to chance. The radiation exposures from the nuclear plant were lower by a factor of 100 than the normal level of natural background radiation. The ecological design provided no individual tritium dose estimates, so inferences on risks from tritium cannot be made.

In 2007, the Durham Region Health Department (DRHD, 2007) examined rates of cancer incidence and mortality, congenital anomalies and stillbirths from 1981 to 2004 in areas surrounding the Pickering NGS and Darlington NGS. Durham Region is unique due to the presence of two NGSs located 28 km apart. Based on population estimates from 2003, 285,000 people live within 10 km of the two stations. In 2005, radiological monitoring of the environment was used to calculate the radiation dose to 8 critical groups around Pickering NGS and 9 critical groups around Darlington NGS. For the Pickering NGS, public dose was estimated to be 6.7 µSv as calculated for an adult located 1.25 km from the station. The public dose for the Darlington NGS was 0.9 µSv as calculated for an infant living nearby. The doses calculated for Pickering and Darlington represent 0.7% and 0.09% of the legal limit for public radiation exposure (1 mSv per year), respectively. Accounting for exposure from the stations, the total radiation levels in Ajax-Pickering and Clarington (the two closest municipalities) were low because the areas are naturally low in background radiation.

Durham's health indicators were selected based on the scientific literature's evidence of association with radiation exposure, and compared with two similar regions and four municipalities within the region. The study assumed that health effects from both NGSs, if they existed and could be measured, would be seen in Ajax–Pickering and Clarington but not in the other municipalities or the two comparison regions. Several data sources were used in this investigation, including Ontario cancer incidence and cancer mortality data, Canadian Congenital Anomalies Surveillance System, Ontario Maternal Multiple Marker Screening Database, vital statistics on stillbirth data, the Rapid Risk Factor Surveillance System and census and population estimates.

Leukaemia (excluding CLL) and thyroid cancer did show some elevated rates. Leukaemia incidence in males was significantly elevated in Clarington from 1993 to 2004 (SIR=1.51; 95% CI: 1.09–1.93), the period after Darlington began operating. However, the pattern was not clear since incidence was lower than expected in Clarington females in the same time period, although not significantly (SIR=0.77, 95% CI: 0.41–1.12). Leukaemia was not elevated in Ajax–Pickering for males or females from 1993 to 2004 (SIR =0.79, 95% CI: 0.58–1.01; SIR=1.01, 95% CI: 0.73–1.29, respectively) and mortality was significantly low in females (SMR=0.67, 95% CI: 0.39–0.96) from 1993 to 2004. Thyroid cancer incidence in Ajax–Pickering males was significantly elevated from 1993 to 2004 (SIR=1.57, 95% CI: 1.14–2.00). Thyroid cancer incidence in males from 1981 to 1992 and in females in both time periods was elevated, but not significantly so.

Durham Region had elevated incidence rates for all cancers for males (SIR=1.06, 95% CI: 1.04–1.08) and females (SIR=1.03, 95% CI: 1.01- 1.05). Cancer incidence, but not cancer mortality, was particularly elevated in Oshawa–Whitby. All childhood cancer and childhood leukaemia mortality and incidence rates were comparable to the Ontario provincial average. Breast cancer incidence was significantly elevated in Ajax–Pickering females (SIR=1.13, 95% CI: 1.02–1.23) from 1981 to 1992, but not in the following time period. Again, this was not reflected in the mortality rates. Brain cancer incidence, but not mortality, was elevated in Ajax–Pickering females (SIR=1.47, 95% CI: 1.04–1.91) from 1981–92, and similar results were seen for kidney cancer in Clarington females (SIR=1.47, 95% CI: 1.01–1.93) from 1993 to 2004. All other health indicators were significantly low or at provincial levels in Ajax–Pickering and Clarington. Rates of Down syndrome were comparable to those in Ontario. Clarington rates were lower than the Ontario average and the rates in Ajax-Pickering had declined since peaking in 1984–86, as noted by Johnson and Rouleau (1991).

Overall, the results were consistent with the original analysis from 1979 to 1993 (DRHD, 1996) and two Snapshot reports for the region on cancer (DRHU, 2003a) and healthy newborns (DRHU, 2003b). In general, rates of cancer incidence and mortality were similar to Ontario averages; prevalence of birth defects was significantly lower, and rates of Down syndrome were similar to those in the rest of Ontario. Given the extremely low levels of radiation exposures, which included tritium, it is unlikely that any radiation related effects would be observed.

4.4.4 Childhood Cancer and Leukaemia in Communities Near German Nuclear Power Plants

Several German studies have not explicitly addressed exposure to tritium. German radiation doses due to discharges from nuclear facilities are at most a few microsieverts (μSv) per year, and are mostly due to Carbon-14, radioiodine and noble gases. Typically, no tritium doses are available, and if they were, they would be negligible (personal communication, B Grosche, 2009). The exception is the Krümmel power plant whose boiling water reactor is of unique design and emits relatively high amounts of atmospheric airborne tritium releases that exceed those of Germany's other 19 reactors (Grosche *et al*, 1999; Laurier, 2002).

Michaelis *et al* (1992) studied the incidence of childhood cancer around the 15-km radius of 20 West Germany nuclear installations that started operating between 1960 and 1988. The researchers then compared this information with the incidence of 20 matched control regions. Incidence data was obtained from the population-based German Childhood Cancer Registry (GCCR), which covered approximately 95% of the incidence cases. A total of 1,610 cases diagnosed before 15 years of age lived in one of the study regions at diagnosis (1980 to 1990). Standardized incidence rates (SIRi) were calculated for all installation regions and control regions (SIRc) by calculating the ratio of observed to expected numbers of cases. The relative risk was calculated as RR=SIRi/SIRc with 95% confidence intervals. In addition, a subgroup of patients diagnosed between 1986 and 1990 were given questionnaires to check for possible confounding factors, which were not controlled for by the regional matching.

No increased rates were found for all cancers and leukaemia in children less than 15 years of age, within the 15-km zone of the nuclear plants. The RR was 0.97 (95% CI: 0.87–1.08, p=0.74)

for all cancers (812 cases) and 1.06 (95% CI: 0.88–1.28, p=0.29) for acute leukaemia in all regions within a 15-km radius of an installation. Increased RRs for acute leukaemia was observed in children less than five years of age in regions closest to installations (<5 km), especially those which started operation before 1970. Most of this increase was attributable to an unexpectedly low incidence in the control regions (SIRc =0.42 based on 5 cases), which could not be explained by analyzing possible confounding factors. However, using the same control regions, an even more pronounced increase of RRs was observed in regions where nuclear power plants (NPPs) had only been planned.

Table 4.14: Summary of Childhood Leukaemia Relative Risks in the Vicinity of German Nuclear Power Plants, 1980–95

Age	Distance (km) From Plant	Time Period	Number of Acute Leukaemia Cases	Relative Risk	95% Confidence Interval, p-Value
0-14 years	< 15 km	1980-1990	274	1.06	0.88–1.28, p=0.285
0-14 years	< 5 km	1980-1990	30	1.44	0.81–2.79, p=0.143
0-4 years	< 15 km	1980-1990	152	1.28	0.99–1.69, p=0.037
0-4 years	< 5 km	1980-1990	19	3.01	1.25–10.31, p=0.015
0-4 years	< 5 km	1991-1995	12	1.39	0.69–2.57
0-14 years	< 15km	1980-1995	461	1.0	0.87–1.16

Kaatsch *et al* (1998) extended the study of childhood cancer incidence near West German NPPs to include the period 1991 to 1995 to evaluate the results of their previous study (Michaelis *et al*, 1992). However, this study failed to reproduce the original exploratory results. There was a tendency towards an increased risk of acute leukaemia in children younger than 5 years of age within the 5 km radius of an installation as indicated in the lower section of Table 4.14. The RR was 1.39 but was not statistically significant (95% CI: 0.69–2.57). This finding was strongly influenced by the cases observed near the NPP in Krümmel, which was well known as a cluster before starting the study. In all the other 5 km radii of the nuclear installations, the same number of leukaemia cases as expected was observed. A pooled analysis of both studies based on 2,390 cases of childhood cancer resulted in a RR of 0.99 (95% CI: 0.91–1.07) for all cancers (N=1,362) and a RR of 1.00 (95% CI: 0.87–1.16) for acute leukaemia (children younger than 15 years of age who live within a 15 km radius), which suggests the previous results were most likely due to chance.

Grosche *et al* (1999) compared cases of childhood leukaemia in the vicinity of the Krümmel (KKK) NPP in Germany and the Savannah River Site (SRS) in South Carolina, US, because of public concern of increased occurrence of childhood leukaemia after the start-up of the Krümmel plant. The cluster was thought to be related to tritium on the basis of the assumption that there might have been undetected but considerable releases of tritium or other beta-emitters.

Thus, if tritium was responsible for the cluster, an increase in childhood leukaemia would also be found near other nuclear facilities that released substantial tritium quantities. Nine cases (2.8 expected) of childhood leukaemia were observed in the period 1990 to 1996 within 10 km of the Krümmel plant (SIR 3.25, 95% CI: 1.58–5.96); 41 cases (49.6 expected) of childhood leukaemia were observed over the period 1991 to 1995 in the Savannah River Region Health Information System (SIR 0.86, 95% CI: 0.59–1.21). Although there was no individual dosimetry, tritium discharges from KKK and SRS and estimated maximum effective doses for KKK were available. In 1991, discharges of tritium from KKK were 9.9×10^{11} Bq (airborne) and 9.5×10^{11} Bq (liquid). At SRS, they were 7.2×10^{15} Bq (airborne) and 9.9×10^{14} Bq (liquid). Grosche *et al* (1999) point out that tritium releases from the SRS exceed by several orders of magnitude those from the KKK plant. Thus, the results gave no indication that tritium discharges were involved in the excess leukaemia near the Krümmel plant.

In 2007, Hoffmann *et al* analysed the childhood leukaemia incidence in the Hamburg, region of Germany over a 16-year period (1990 to 2005). All incidence cases of leukaemia (<15 years of age) were ascertained for children living within a 5 km radius of the Krümmel NPP. No information on possible risk factors, including tritium, was available. Standardized incidence ratios (SIRs) were calculated using county and national incidence rates for the general population. Analyses were stratified by calendar period and attained age, and the study region was subdivided into areas north and south of the Elbe River. The study found 14 cases of childhood leukaemia compared with 4 expected between 1990 and 2005 in children living within 5 km of the Krümmel plant. This was the largest childhood leukaemia cluster reported to date worldwide, with a statistically significant SIR of 3.5, as illustrated in Table 4.15. From 1999 to 2005, the SIR was still elevated (SIR=2.7), although not statistically significant. The excess was not confined to the early 1990s and the authors drew attention to the persistent excess over time. The highest SIRs were among children 0 to 4 years of age (SIR=4.9) and for residents of the Elbmarsh region living south of the Elbe River (SIR=7.5) opposite to the Krümmel NPP.

Table 4.15: Summary of Childhood Leukaemia Standardized Incidence Ratios Near the Krümmel Nuclear Power Plant in Hamburg, Germany, 1990–2005

Age	Distance (km) From Nuclear Power Plant	Time Period	Number of Leukaemia Cases	Standardized Incidence Ratio	95% Confidence Interval
<15 years	<5	1990–2005	14	3.5	1.9–5.9
<15 years	<5	1999–2005	5	2.7	0.9–6.2
< 5 years	<5	1990–2005	10	4.9	2.4–9.0
<15 years	South of the Elbe River[a]	1990–2005	6	7.5	2.8–16.4

[a] *also <5 km from NPP*

The authors concluded that elevated rates of childhood leukaemia had persisted in this community for greater than 15 years and warranted further investigation. However, to date, no unique hazards have been identified in this population. Dose estimates for emissions from normal operations were orders of magnitude below the level at which any regional excess of childhood leukaemia would be expected (refer to Grosche *et al*, 1999). Similarly, it was highly unlikely that a high accidental release would have escaped environmental surveillance.

The KiKK Case-Control Study: Kinderkrebs in der Umgebung von Kernkraftwerken — Childhood Cancer Near Nuclear Power Plants

In 2003, the German Federal Office for Radiation Protection (BfS), in response to concerns resulting from the previous German Childhood Cancer Registry (GCCR) studies (Michaelis *et al*, 1992; Kaatsch *et al*, 1998; Grosche *et al*, 1999), initiated a case-control study of children less than 5 years of age. The study was based on the GCCR and looked at all malignancies.

Spix *et al* (2008) conducted the initial matched case-control study (the KiKK study) of all cancer cases in Germany available from the GCCR between 1980 and 2003 in children less than 5 years of age at diagnosis (1,592 cases and 4,735 controls). All cases were matched with controls for date of birth, age, sex and NPP area (at date of diagnosis). The distance of individual residences at the date of diagnosis from the nearest of 16 major NPPs was determined for each individual, to serve as a proxy for the radiation exposure caused by the facilities. To assess potential confounding, information on 20 potential confounders (social status, information on additional radiation exposure, other risk factors, immune system related issues, type of region and folic acid in pregnancy) was obtained from cases and controls through telephone interviews. Questions were also asked about the children's previous residences. The study focused on cases within the 5 km zone of the plants and found an increased risk of childhood cancer in children under five years old who lived near NPPs in Germany. The inner 5-km zone showed an increased risk (OR=1.47; lower one-sided 95% CL: 1.16). The effect was largely restricted to leukaemia (OR=1.76; lower one-sided 95% CL: 1.24).

Kaatsch *et al* (2008) conducted a follow-up to the initial KiKK study. The study focused on the 593 childhood leukaemia cases registered between 1980 and 2003 at the GCCR in children who were under 5 years of age and living near one of the 16 nuclear power sites when diagnosed. Distance from a NPP served as a proxy for the radiation exposure caused by the facilities. Population-based controls (1,766) were matched by age and sex. The study provided clear evidence that the risk of leukaemia for children younger than age 5 years increases with decreasing distance between their homes and a NPP (see Table 4.16). All leukaemias showed a statistically significant trend for 1/ (distance in km) with a positive regression coefficient (ß) of 1.75; cases lived closer to NPPs than controls. The same was seen for acute lymphoid leukaemia (ß =1.63) and acute non-lymphocytic leukaemia (ß =1.99), although the latter was not statistically significant.

Table 4.16: Estimated Parameters From the Conditional Logistic Regression Model with Continuous Exposure (1/distance in km) for Leukaemia and Subtypes (under 5 years of age) (from Table III, Kaatsch *et al*, 2008)

Diagnostic Group	ß[a]	Lower 95% Confidence Limit	Cases (N)	Controls (N)
All leukaemias	1.75	0.65	593	1,766
Acute lymphoid leukaemias	1.63	0.39	512	1,523
Acute nonlymphocytic leukaemias	1.99	-0.41	75	225

[a] *Regression coefficient; one-sided 95% confidence limit*

In Table 4.17, a categorical analysis showed a statistically significant OR for all leukaemias of 2.19 for residential proximity within 5 km of the plants, compared with residence outside this area. For acute lymphoid leukaemia the OR was 1.98 and for acute non-lymphocytic leukaemia the OR was 3.88. A risk for leukaemia was also elevated in the 10 km zone. The study showed that the risk for children under 5 years of age to develop leukaemia increased the closer they lived to a NPP. Results could not be attributed to a single reactor site, but were consistent for all 16 nuclear power sites in total.

Table 4.17: Estimated Odds Ratios for Two Distance Categories for All Leukaemias and Subtypes (Under 5 years of Age) (from Table V, Kaatsch *et al*, 2008)

Diagnostic Group	Odds Ratio	Lower 95% Confidence Limit[a]	Cases in 5 km Zone (N)
All leukaemias			
≤5 km to >5 km zone	2.19	1.51	37
≤10 km to >10 km zone	1.33	1.06	95
Acute lymphoid leukaemias			
≤5 km to >5 km zone	1.98	1.33	30
≤10 km to >10 km zone	1.34	1.05	84
Acute nonlymphocytic leukaemias			
≤5 km to >5 km zone	3.88	1.47	7
≤10 km to >10 km zone	1.30	0.66	10

[a] *95% CL, one-sided 95% confidence limit*

The results were largely attributed to cases in previous studies of the GCCR (Michaelis *et al*, 1992; Kaatsch *et al*, 1998), especially in the 5 km zone, as there was overlap between those studies. The increased risk is comparable to the risk found in these studies and was still detectable, although less obvious, in the period after these studies (1996–2003). This case-control study provides greater strength of evidence than the preceding ecological studies, which only compared cancer incidence rates between regions. However, radiation exposures could not be taken into consideration. Distance (between home and reactor) was taken as an alternative to exposure. There were also no data on previous residence history or the time spent at other locations outside of the home. The relationship between childhood leukaemia and proximity to NPPs cannot be explained by the public's radiation exposures from these plants. No estimates of tritium dose or any other radiation exposures from the plants were available in these studies. No information on other risk factors of childhood cancer was available (such as social class, pesticides, factors influencing the immune system, genetic predisposition). Without information on any of the possible causes of childhood leukaemia, one cannot make any inference on risks. The radiation exposures near the NPPs during routine operations were extremely small compared with exposure to ionizing radiation of the general public from other sources. There is a constant evaluation of the GCCR done within the frame of the European network. The coverage of the register for leukaemia, as well as for other malignancies is supposed to be above 95% since 1980 when the registry began. There is no indication that the reporting is better close to nuclear sites than elsewhere (personal communication B Grosche, 2009; Kaatch and Mergenthaler, 2008). The reported results were not consistent with the current understanding of radiation effects observed in many radiation biology and epidemiological studies. In light of this, the observed positive distance trend remains unexplained and no statements on the causes of the increased cancer rates can be made, according to the BfS and GCCR.

Little *et al* (2008) reviewed Kaatsch *et al* (2008) and noted that the KiKK study only considered residence at time of diagnosis. Misclassification as a result of lack of residence history would bias the association toward the null. Their three main explanations for the results were i) chance observation since spatial and space-time distributions of leukaemia and several other types of childhood cancer had previously been observed to be non-random (COMARE, 2006); ii) exposure of some individuals living in the vicinity of a NPP was much higher than what was available from the data; and iii) the Kinlen Hypothesis (Kinlen, 1988), which is an infectious cause due to population mixing.

Grosche (2008) conducted a further case-control analysis of childhood leukaemia in the vicinity of the 16 German nuclear power sites (the KiKK study) to determine if there was correlation between the proximity of the place of residence to a NPP and cancer risk among children below the age of five. He also determined if the elevated risk could be observed within 5 km from the sites.

Table 4.18: Comparison of Leukaemia Odds Ratios for Different Categories of Distance, as Derived From Regression and Categorical Analysis (from Table 3, Grosche (2008) and from Table IV, Kaatsch *et al*, 2008)

Distance	Cases (N)	Controls (N)	Odds Ratio (Based on Regression Analysis)	Odds Ratio (Based on Categorical Analysis)
<5 km	37	54	1.76	2.27
5–10 km	58	173	1.26	1.09
10–<30 km	332	1048	1.10	1.01
30–<50 km	135	387	1.05	1.11
50–<70 km	27	92	1.03	0.90
70+ km	4	12	1.02	1.00 (reference)

For the 5 km distance, regression analysis gave a smaller OR than the categorical analysis. For distances of 5 to 10 km, regression analysis gave a larger OR than the categorical analysis, and for greater distances, the 2 analyses were comparable (Table 4.18).

Table 4.19: Leukaemia Odds Ratios as Derived From Previous Ecological Studies and the Case-Control Study (from Table 4, Grosche (2008), and from Table VI, Kaatsch *et al*, 2008)

Study Period	Cases (N) 5-km zone	Ecological Study Relative Risk and 95% Confidence Interval	Case-Control Study Odds Ratio and One-Tailed Lower 95% Confidence Interval
1980–90	13	3.01 (1.25–10.3)	3.00 (1.54)
1991–95	10	1.39 (0.69–2.57)	2.10 (1.04)
1996–2003	14	–	1.78 (0.99)
1980–95	23	1.49 (0.98–2.20)	2.53 (1.57)
1980–2003	37	–	2.19 (1.51)

For three subsequent study periods there seemed to be a decrease in the OR within the 5 km distance. In Table 4.19, for the period 1980–90, the OR was 3.00 and for periods 1991–95 and 1996–2003, the ORs were 2.10 and 1.78, respectively.

For Part 2 of the study, telephone interviews were conducted for a subset of cases and controls (those diagnosed between 1993 and 2003) to collect information on possible confounders (SES, radiation exposure to sources other than from the NPPs, further risk factors mentioned

in the literature, child's immunological situation and others) that could help explain the earlier results. For all leukaemias, the regression coefficient was 0.44 with a lower 95% CI of -1.86, based on 237 cases and 463 controls. There was a strong response bias with persons living closer (within the 5 km radius) to the plant being less likely to respond to the questionnaire than those at a distance. This effect was less pronounced among the controls. Thus, possible confounders found in Part 2 were not used to explain the results of Part 1. The authors looked at Part 2 of the study separately. Based on information for 251 cases and 487 controls, the confounders had no impact on the estimate found. In conclusion, the observed trend in risk decreased over time. This could be indicative of some agent being involved for which the prevalence is reduced over time. However, whether this agent is related to the NPPs can only be answered when results are available from periods prior to the start-up of the facilities. Currently, there is no clear explanation for a causal relationship between any chemical or physical risk factor and the observed risk.

Assessment of the "Epidemiological Study on Childhood Cancer in the Vicinity of Nuclear Power Plants" (KiKK study): Position of the German Commission on Radiological Protection

The KiKK study results led to considerable public concern and scientific debate. The Federal Minister of the Environment, Nature Conservation and Nuclear Safety commissioned the German Radiological Protection Commission (SSK) to assess the KiKK Study and, especially, to answer if the radiation emitted by NPPs could be responsible for the study findings. The SSK appointed an interdisciplinary international working group of experts to review the current knowledge on radiation and leukaemia, to summarize an independent reanalysis of the KiKK data, and to make a final evaluation of the study's overall design, conduct, results and interpretations (SSK, 2008; Zeeb, 2008). The main conclusions of the SSK report are summarized as follows:

- The KiKK study's new data confirm the results of earlier exploratory studies that found an increased risk of leukaemia, for children younger than five, within a 5 km radius around German NPPs, relative to the risk in the outer areas around the relevant study areas. However, studies conducted in other countries produced conflicting results, so it cannot be definitively concluded that there is any evidence of increased rates of leukaemia, in general, in the vicinity of the NPPs.
- The KiKK Study exhibits numerous methodological weaknesses with regard to determination of exposure and surveying of influencing factors.
- The evidence for increased childhood cancer risks is limited to the 5 km zone around the NPPs. Calculation of excess cases for greater distances using attributable risks are not appropriate.
- The study examined distance from a NPP and not radiation exposure. It is not suitable for establishing a correlation with exposure to radiation from NPPs. All of the radioecological and risk-based circumstances reviewed by the SSK indicate that exposure to ionizing radiation caused by the NPPs cannot explain the results of the KiKK Study. The actual exposures caused by NPPs are lower by a factor of 1,000 than those that could cause the risks reported by the KiKK Study.
- The natural radiation exposure within the study area, and its fluctuations, are both greater by several orders of magnitude than the additional radiation exposure caused by the relevant NPPs.

- The KiKK study was unable to survey risk factors sufficiently and thus cannot be used to help explain the causal reasons for the observed distance dependence of leukaemia rates.

The reason for the increased leukaemia rate that the KiKK Study observed in children is unclear. Since leukaemia is caused by multiple factors, numerous influencing factors could have been responsible for the observed result. To understand the many relevant conflicting findings in the literature and the finding of the KiKK Study will require more extensive, interdisciplinary research into the causes and mechanisms of the development of childhood leukaemia.

4.4.5 Incidence of Childhood Leukaemia Near Nuclear Sites in France

French NPPs emit significant routine discharges of tritium because they use Pressurized Water Reactors. The dominant discharge pathway is the liquid discharges (gaseous discharges are about 10% of the liquid). In France, the La Hague reprocessing plant is a major contributor to liquid discharges of tritium (in the seawater of the English Channel), emitting about 100 times more than the NPP's tritium liquid discharges. A research reactor with heavy water is also operated in France with significant gaseous discharges of tritium. The tritium discharges from French NPPs seem to be in an amount intermediate between the lower UK gaz reactors and the Canadian CANDU reactors (personal communication, D Laurier, 2009).

In 2004, White-Koning *et al* published a report on childhood leukaemia cases among children less than 15 years of age around French nuclear sites. There were 670 cases of childhood leukaemia diagnosed within 20 km of the 29 French nuclear installations between 1990 and 1998 compared with 729 expected cases. Cases were provided by the National Registry of Childhood Leukaemia and Lymphoma, which has registered all cases diagnosed in France since 1990. Age- and sex-specific population counts were obtained from the French National Institute of Economic and Statistical Studies. Overall, the observed number of cases was consistent with the expected number of cases. The SIR was 0.92 (95% CI: 0.85–0.99). In Table 4.20, each of the four areas defined around the sites showed non-significant deficits of cases.

Table 4.20: Distribution of Childhood Leukaemia Cases and Standardized Incidence Ratios for different Distances From Nuclear Power Plants Operating in France between 1990 and 1998

Distance	Observed	Standardized Incidence Ratio	95% Confidence Interval
0-5 km	65	0.87	0.67–1.10
5-10 km	165	0.95	0.81–1.10
10-15 km	220	0.88	0.77–1.00
15-20 km	220	0.96	0.84–1.10

There was no statistical evidence of a decreasing trend in SIRs with distance from the sites for all children or for any of the three age groups studied. No evidence was found of a generally increased risk of childhood leukaemia around the nuclear sites between 1990 and 1998. There was no indication of the levels of tritium releases from these plants, so one cannot make any inference on risks from tritium. In addition to electricity production, the plants were also involved in uranium enrichment and conversion, nuclear fuel processing and reprocessing, various nuclear research activities, and included a fast neutron reactor designed to produce electricity and plutonium.

Evrard *et al* (2006) investigated the incidence of childhood leukaemia (1990–2001) around French nuclear installations (18 NPPs, 2 nuclear fuel cycle plants, a nuclear fuel reprocessing plant and 2 research centres), including three additional years of follow-up. Most important, instead of using distance as a surrogate for dose, the researchers estimated doses to the red bone marrow due to radioactive discharges. Since the levels of environmental radioactive contamination in France are generally below detection limits, doses had to be estimated. The Institute for Radiation Protection and Nuclear Safety used radionuclide discharge data with local climate data to model the environmental exposure levels. The typical composition of NPP discharges was taken into account, including the following nuclides: tritium, Carbon-14, Argon-41, Krypton-85, Xenon-133, Iodine-131, Iodine-133, Cobalt-58, Cobalt-60, Caesium-134 and Caesium-137. The estimated doses ranged from 0.06 to 1.33 µSv/year, with an arithmetic mean of 0.17 µSv/year, and a standard deviation of 0.48 µSv/year.

The French National Registry of Childhood Leukaemia and Lymphoma provided childhood leukaemia cases (age <15 years). The observed number of cases of acute leukaemia (O=750) for an area of 40 km^2 centered on 23 French nuclear installations between 1990 and 2001 was lower than expected (E=795.01), although not statistically so (SIR=0.94, 95% CI: 0.88–1.01). The SIR was not significantly greater than one in any of the five zones defined on the basis of the estimated doses. There was no evidence of an increasing trend in SIR with increasing estimated dose for all children or for any of the three age groups studied. This study confirmed there was no evidence of an increased incidence of childhood leukaemia around the 23 French nuclear sites. The estimated mean dose (<0.20 µSv/year) from gaseous discharges was very small in relation to estimated natural sources of exposure (2700 µSv/year) and estimated exposures from medical examinations (740 µSv/year). The doses due to releases in the vicinity of nuclear facilities were approximately 1,000 to 100,000 times lower than the average dose due to natural radiation sources.

Table 4.21: Distribution of Observed and Expected Numbers of Childhood Leukaemia Cases by Age and Category of Estimated Dose Due to Gaseous Discharge in the Vicinity of 23 Nuclear Sites in France (1990–2001) (from Table 2, Evrard *et al*, 2006)

Estimated Dose (µSv/year)	<0.045	0.045–0.072	0.072–0.316	0.316–1.0	≥1.0	Total
0–4 years						
Observed	111	149	110	19	5	394
Expected	134.60	145.01	109.39	20.69	5.38	415.08
SIR	0.82	1.03	1.01	0.92	0.93	0.95
95% CI	(0.68–0.99)	(0.87–1.21)	(0.83–1.21)	(0.55–1.43)	(0.30–2.17)	(0.86–1.05)
5–9 years						
Observed	72	71	52	6	1	202
Expected	76.81	75.63	61.02	12.49	3.27	229.22
SIR	0.94	0.94	0.85	0.48	0.31	0.88
95% CI	(0.73–1.18)	(0.73–1.18)	(0.64–1.12)	(0.18–1.05)	(0.01–1.70)	(0.76–1.01)
10–14 years						
Observed	59	41	41	12	1	154
Expected	50.93	48.40	40.71	8.42	2.25	150.71
SIR	1.16	0.85	1.01	1.42	0.44	1.02
95% CI	(0.88–1.49)	(0.61–1.15)	(0.72–1.37)	(0.74–2.49)	(0.01–2.47)	(0.87–1.20)

95% CI = 95% confidence interval
SIR = standardized incidence ratio

Laurier *et al* (2008a) published an analysis performed at the time of the original study (White-Koning *et al*, 2004) that was not included in the final publication. It allowed direct comparison with the results of the KiKK study (Kaatsch *et al*, 2008), focusing on French children aged 0 to 4 between 1990 and 1998.

Table 4.22: Distribution of Leukaemia Cases in Children Less Than 5 Years of Age and SIRs at Different Distances From France's 19 Operating Nuclear Power Plants Between 1990 and 1998 (from Table 1, Laurier *et al*, 2008a)

Distance	Observed	Expected	Standardized Incidence Ratio	95% Confidence Interval
0–5 km	5	5.2	0.96	0.31–2.24
5–10 km	20	15.4	1.30	0.79–2.01
10–15 km	18	18.3	0.99	0.58–1.56
15–20 km	71	69.3	1.03	0.80–1.29
Total	114	108.1	1.05	0.87–1.27

A total of 114 leukaemia cases were observed within 20 km of a NPP compared with 108.1 expected. These results show no excess risk in any of the distance categories or a decreasing trend of risk with increasing distance from the NPPs. Finally the SIR within 5 km of a NPP was 0.96 (95% CI: 0.31–2.24), indicating that the observed number of cases was what would be expected in the general population of France. These results provide no evidence of an excess leukaemia risk near NPPs in the specific age range of 0-4 years. The results were based on small numbers of cases, so the confidence intervals were wide. However, these results found no increased risk of leukaemia in young children living near French NPPs.

4.4.6 Meta-Analysis of Childhood Leukaemia in Proximity to Nuclear facilities

Baker and Hoel (2007) conducted a meta-analysis of studies of standardized incidence and mortality rates of childhood leukaemia around nuclear facilities. Seventeen studies, covering 136 nuclear facilities in nine countries (UK, Canada, France, U.S., Scotland, West and East Germany, Japan and Spain), met the criteria for at least one analysis. Three separate models were used to calculate a meta-standardized mortality ratio (SMR) or meta-standardized incidence ratio (SIR) (unadjusted, fixed effects and random effects models), stratified by age group (0–9, 0–25), geographical zone (all, <16 km) and endpoint (SMR, SIR).

Meta-SMRs and meta-SIRs were all greater than 1.0. Within geographical zones, the 0–9 age group experienced higher standardized rates than the 0–25 age group, suggesting that the younger age group accounted for the majority of the excess cases and deaths. Meta-SMRs for the fixed and random effects models for the 0–9 age group in the zone <16 km from a facility were 1.23 (95% CI: 1.04–1.46) and 1.24 (95% CI: 1.03–1.50), respectively (based on only 14 nuclear facilities after excluding sites that may have contributed to heterogeneity). The corresponding meta-SIRs, based on only 13 nuclear facilities after excluding sites that may have contributed to heterogeneity, were not statistically significant 1.14 (95% CI: 0.98–1.33) and 1.14 (95% CI: 0.98–1.33), respectively. The meta-analysis was able to show a slight increase in childhood leukaemia near nuclear facilities, but did not support a hypothesis to explain the excess. The authors detailed the various limitations of ecological studies that

prevented them from explaining elevated rates near nuclear facilities. The authors recognized that "because of their study's design, published studies that incorporated risk estimates of multiple nuclear facilities had to be excluded". Since there were no estimates of tritium dose in these studies, one cannot make an inference on risks from tritium.

4.4.7 Authoritative Reviews of Epidemiological Studies of Childhood Leukaemia Around Nuclear Facilities

Childhood leukaemia among young people aged 0–14 years at diagnosis is rare. The aetiology of childhood leukaemia is poorly understood; while some of the risk factors for leukaemia are known or suspected, they explain only a small number of cases. Most cases are without any known causes. The recognized risk factors are exposure to ionizing radiation, consumption of some medications, and some congenital malformations (such as Down syndrome). A high socio-economic status seems to be associated with an increased incidence of childhood leukaemia and other suggested risk factors include maternal smoking; infections due to population mixing (Kinlen, 1988) and exposure to pesticides or to benzene.

Laurier and Bard (1999) conducted the first comprehensive literature review of studies of childhood leukaemia in the vicinity of nuclear sites. The review included descriptive mortality and cancer incidence studies of known leukaemia clusters (Sellafield, Dounreay, Aldermaston-Burghfield, Krümmel, and La Hague) and analytical studies, primarily case control, to assess three main hypotheses: paternal pre-conception exposure, environmental exposure to ionizing radiation, and infectious cause. The descriptive studies of the frequency of leukaemia near nuclear sites were limited by their methodology. These studies showed that an excess of leukaemia cases among young people has persisted over time near some sites (Sellafield and Dounreay). Nonetheless, the results of the multi-site studies do not support the hypothesis that the frequency of leukaemia generally increases among young people living near nuclear sites. Furthermore, excesses of leukaemia have also been shown far from any nuclear site, around potential sites and studies of the geographic distribution of leukaemia show that incident cases tend toward spatial clustering. Most of the analytic studies had important limitations (size of populations, possible bias, or imprecision). However, it was possible to reject several hypotheses, in particular those related to parental pre-conception exposure to ionizing radiation and to environmental exposure to radiation. The authors recommended providing comprehensive and clear information on the facts about received doses and risk levels near nuclear installations, and implementing systematic and rigorous surveillance of leukaemia incidence cases around nuclear sites through registries. Finally, research on individual sensitivity, exposure, or effect biomarkers may be useful for future epidemiological purposes.

Laurier *et al* (2002) updated the review of studies that examined the risk of leukaemia among young people near nuclear installations. Since 1984, many descriptive (or ecological) cluster studies of childhood leukaemia have been conducted near nuclear installations. These studies have important limitations (such as small areas, small numbers of observed cases, aggregated data, no control of migration, no information on potential exposures) and most of them show no excess of leukaemia among young people living in the vicinity of these installations. An excess of leukaemia exists near some nuclear installations, at least for the reprocessing plants

at Sellafield and Dounreay and the Krümmel NPP. Nonetheless, excesses of leukaemia have also been identified away from any nuclear installations and the results of multi-site studies invalidate the hypothesis of an increased risk of leukaemia related to radioactive discharges from these facilities. Three main hypotheses have been explored to explain the leukaemia clusters; however, no analytic studies have yet found an explanation for leukaemia clusters near nuclear facilities. The results cannot explain a causal roll of environmental exposure to radioactivity near nuclear installations or paternal pre-conception exposure, and the hypothesis of an infectious agent associated with population mixing needs further investigation. The authors stressed the importance of recalling current knowledge when communicating risk and the use of systematic recording of cases. The authors proposed that commissions include members from various fields — such as facility operators and governmental and non-governmental experts — to better communicate directly with the general public.

Laurier *et al* (2008b) updated their review to include 198 local (considering 1 specific site) nuclear sites throughout 10 countries and 25 multi-site studies for 8 countries. There was a wide diversity in the quality of data, definitions of the study population and methods of analysis. In particular, the interpretation of local descriptive studies was often problematic due to low number of cases and methodological limitations. Among the local sites, excesses of childhood leukaemia cases could be considered as confirmed clusters in three sites: the UK reprocessing plants at Sellafield (West Cumbria) and Dounreay (Scotland) and the village of Elbmarsch near the German Krümmel NPP. For all three clusters, subsequent investigations have confirmed the existence of the local excess and its persistence over time. Other well-documented clusters (the Aldermaston and Burghfield sites in the UK and in France close to the La Hague reprocessing plant), were not able to conclude a current existence of excess of childhood leukaemia. For the large majority of local sites, no excess was reported. None of the multi-site studies indicated an increased risk globally. Thus, the recent KiKK studies of an excess of leukaemia in children aged 0–4 years around German NPPs were not supported by studies from other countries, and to date, nothing can explain the observed excess. Much research has looked for explanations for the excesses of leukaemia around specific nuclear sites among multiple potential risk factors. The hypothesis of an infectious agent associated with population mixing around nuclear sites is the most convincing (Kinlen, 1988); however, the infectious agent(s) have yet to be found. The main limitations in determining the causes of the excess leukaemia observed locally are the lack of known childhood leukaemia risk factors and lack of information of the presence/absence of risk factors. Genetic predisposition, nutrition, drug use, factors affecting the immune system (such as vaccinations or allergies), gestation and childhood development, and various environmental factors are all known to play a part in the aetiology of childhood leukaemia (Kaatsch and Mergenthaler, 2008). Only large-scale national or international analytical studies would be better able to characterise the origins of such clusters as well as to clarify the aetiology of leukaemia.

4.5 Review of Tritium Epidemiological Studies

4.5.1 United Kingdom Report of the Committee Examining Radiation Risk of Internal Emitters

The United Kingdom's Committee Examining Radiation Risk of Internal Emitters (CERRIE, 2004) was established to "consider present risk models for radiation and health that apply to exposure to radiation from internal radio-nuclides in the light of recent studies and to identify any further research that may be needed".

Over 200 publications and working papers were examined for evidence from radiobiology and epidemiology, although the tritium epidemiology was very limited. The Committee noted the many studies of workers in the nuclear industry occupationally exposed to radiation, although the largest of these studies considered external radiation only. Only recently have investigations of internal exposures become available. Some members felt that the association between prostate cancer and tritium and certain fission products found in Rooney *et al* (1993) indicated an underestimation of the risk of exposure to these radionuclides. However, this association was not confirmed using more recent data (Atkinson *et al*, 2007). Similarly, the studies of internal emitter exposures of nuclear workers found no associations with incidence of childhood leukaemia in their offspring. This was consistent with the Committee on Medical Aspects of Radiation in the Environment's (COMARE, 2002) Seventh Report which concluded that "we find no convincing evidence to suggest that ionizing radiation alone at the doses to which male radiation workers have been exposed results in an increased incidence of childhood cancer."

CERRIE believed that the epidemiological evidence for moderate and high levels of exposure to internally incorporated radionuclides (as a whole) showed an elevated risk of adverse health effects in those exposed. Although most members agreed that low-level intake of radionuclides also leads to some increased risk of adverse health effects as a result of the internal irradiation of organs and tissues, there was no consensus that the magnitude of risk could be estimated from the epidemiological evidence. CERRIE concluded that for low-level exposures, this increase might be undetectable. There is no clear evidence to date that current radiation risk estimates are substantially wrong and the available epidemiological evidence does not suggest that the predictions of current risk models were materially in error. Inherent limitations of epidemiological studies at low levels of exposure make it very difficult to reliably quantify health risk. The Committee agreed that epidemiological evidence is strengthened when supplemented by laboratory and theoretical information on underlying mechanisms to guide estimates of risk at low doses. CERRIE devoted particular attention to doses and risks associated with tritium.

The Committee on Medical Aspects of Radiation in the Environment (COMARE, 2004) reviewed the results of CERRIE and endorsed its general conclusions on radiation risks and dosimetry and agreed that available data on radiation risks do not support a speculative hypothesis that the risks from internal emitters are radically underestimated. Furthermore, COMARE agreed with the majority report of CERRIE that presently available biological evidence did not indicate a need for a fundamental change in radiological protection standards. They agreed with the CERRIE recommendation to conduct a review of tritium dosimetry and risks.

4.5.2 The Independent Advisory Group on Ionizing Radiation's Review of Epidemiological Studies of Exposure to Tritium

In response to the 2004 CERRIE recommendations, the United Kingdom's HPA asked its independent Advisory Group on Ionizing Radiation (AGIR) in 2004 to undertake a detailed review of risks from tritium. An AGIR sub-group was set up and provided a report in November 2007 (HPA, 2007). A systematic review of the epidemiological studies of exposure to tritium, in support of the AGIR report, was subsequently published by Little and Wakeford (2008).

The AGIR concluded that epidemiological studies of environmental tritium exposure, to residents living in the vicinity of nuclear facilities and to the offspring of workers exposed to tritium, were not sufficiently robust to reach firm conclusions on the risks posed. Although many epidemiological studies involving radiation workers were conducted worldwide, in general, the workforces were small and the studies did not contain enough detail to estimate risks from tritium exposure. Few studies include direct information on tritium exposures, and even fewer specifically relate tritium exposure to health risks. Tritium-specific doses were estimated for some workforces (such as the workers of the Sellafield and AWE in the UK, the Savannah River Site (SRS) in the United States, and the Canadian nuclear facilities), although only the workers from Canada, the United States, and AWE had tritium doses explicitly taken into account in the analyses. However, tritium doses were combined with other sources of exposure, so it was not possible to make inferences specific to tritium risks. In general, the small contribution of tritium dose to total dose in practically all circumstances further limits the ability to evaluate tritium risk in workers.

The AGIR concluded that all of the workforces considered were likely to have some workers with relatively high tritium exposures and good quality dosimetry records. Of the populations identified, the best prospects for robust analyses exist in the nuclear workers studies in Canada, the US SRS, and the five main tritium-exposed UK nuclear workforces: Sellafield, Chapelcross, Capenhurst, AWE and UKAEA. There is a need for further individual and pooled analyses of these groups. However, the limited number of tritium workers in the individual countries and their generally low tritium exposures would lead to studies with relatively low statistical power to detect any effects of exposure to tritium. The AGIR thus recommended an international collaborative epidemiological study, which would combine the tritium worker data from these and other countries, which would provide sufficient study power to properly assess tritium risk.

The Health Protection Agency (HPA, 2008) responded to the AGIR report and welcomed it as an authoritative and comprehensive review of relevant epidemiological studies of tritium-exposed populations. The HPA accepted the conclusions that the published epidemiological studies did not provide quantitative information on risks from tritium, but it noted that since tritium exposures were expected to be low, risks to workers and the general population were also expected to be low. The HPA agreed with the AGIR recommendations for further epidemiological studies of tritium exposed workers, especially an international collaboration on a pooled study. The HPA recognized the importance of maximizing the information that can be obtained from such studies, particularly concerning risk from chronic radiation exposure, including exposures to internal emitters.

In an invited editorial in the Journal of Radiation Protection, the ICRP agreed with the AGIR's conclusions concerning the importance of pursuing epidemiological studies of workers exposed to tritium. While it may be that these studies will lack the power to provide unequivocal conclusions, it is important that the most be made of opportunities to obtain human data (Cox *et al*, 2008).

4.6 Discussion

Many epidemiological studies of cancer and other adverse health outcomes involving radiation workers, their offspring, and members of the public living in the vicinity of nuclear facilities have been reviewed. In general, the usefulness of the available epidemiological studies is often limited by the lack of tritium specific doses, low doses, and small number of cases and the studies do not contain enough detail to estimate risks from tritium exposure.

Several studies of members of the public living in the vicinity of nuclear facilities assessed the relationship between the community's health (such as incidence and mortality rates of childhood leukaemia, non-Hodgkin's lymphoma, birth defects, and other health indicators) and the average environmental releases from, or residential proximity to, a facility. There were no individual estimates of tritium exposure (or other risk factors) in these studies. No inference of the health effects from tritium can be made because of the limitations of ecological studies (UNSCEAR, 2008). Given the extremely low levels of radiation exposures from the facilities (CNSC, 2009; DRHD, 2007; Evrad *et al*, 2006; Grosche *et al*, 1999; Jablon *et al*, 1991; Sever *et al*, 1988b), adverse health effects would be highly unlikely.

The recent German KiKK case-control studies by Spix *et al* (2008) and Kaatsch *et al* (2008) of childhood leukaemia have raised significant attention. There were no such results in France (Laurier *et al*, 2008a) or Britain (Bithell, 2008), and Grosche (2008) observed that the trend in risk decreased over time, which could indicate some agent being involved, for which the prevalence is reduced over time. Grosche *et al* (1999) found no indication that tritium discharges from the Krümmel NPP were involved in any excess of childhood leukaemia found nearby. Currently, there is no support for a causal relationship between any chemical or physical risk factor and the observed risk of childhood leukaemia among children younger than 5 years of age living within 5 km of German NPPs (SSK, 2008). The observed risk remains unexplained.

The authoritative reviews of childhood leukaemia in the vicinity of nuclear facilities (Laurier and Bard, 1999; Laurier *et al*, 2002; Laurier *et al*, 2008b) confirm only three leukaemia clusters that have persisted over time around nuclear facilities (Sellafield, Dounreay and Krümmel); however no clusters can be explained by a causal roll of environmental exposures to radioactivity near nuclear facilities or parent's pre-conception exposure.

Case-control studies of the offspring of workers exposed to tritium provided evidence against the existence of an association between childhood leukaemia or congenital anomalies and paternal pre-conception tritium exposure. Green *et al* (1997) and McLaughlin *et al* (1992a; 1993) provided information in a way that would allow direct inference on risk of childhood leukaemia and congenital anomalies in relation to paternal pre-conception exposure to tritium.

However, the numbers of cases and controls in the exposed group were small, so the study had little statistical power to identify a potential association. The UK HSE (1993) noted that potential exposure to tritium and trichloroethylene was associated with childhood leukaemia and NHL in Sellafield workers. However, the associations were based on non-numerical data and the same cases were involved in both associations, so the two relationships could not be separated. COMARE's Fourth and Seventh Reports (COMARE 1996; 2002) reviewed studies of the offspring of radiation workers and the latest laboratory and genetic research and concluded, based on the studies to date, there is no evidence of a causal link between workers' radiation exposure and cancer in their children. The other case-control studies added little information about tritium risk and childhood cancer or birth defects. Although it was difficult to reach firm conclusions on the risks posed, the absence of adverse results suggested that health risks should have been very low at the levels of tritium exposure received by workers throughout the world. It may be worth updating the Canadian case-control studies now that more than 20 years of data have been collected in Canada.

The cohort studies of radiation workers provide the best available information on the risk of tritium exposure. However, few studies have direct information on tritium exposure, and fewer still directly assess the health effects of tritium exposure alone. The studies of Beral *et al* (1988), Cragle *et al* (1998), Johnson *et al* (1999), Zablotska *et al* (2004), Schubauer-Berrigan *et al* (2007), and Richardson and Wing (2007) assessed health effects with tritium doses in combination with other (film-badge) doses. Thus, it is difficult to assess the component of risk associated specifically with tritium; especially since the tritium contribution to total dose was generally very small compared to other sources of radiation exposure. Hazelton *et al* (2006), for example, noted that whole-body tritium exposures were generally small in comparison to gamma exposures and that the dose-response for tritium in a restricted analysis was not statistically significant. The lack of an excess risk found from total occupational radiation dose, and the small contribution of tritium to the total dose, implies that any risk from tritium would be negligible.

The CERRIE, 2004 report recognized an elevated health risk at moderate and high levels of internal exposure. However, at low levels any increase in risk may be undetectable and there is no clear evidence that current radiation risk estimates are radically underestimated. COMARE (2004) endorsed the CERRIE, 2004 report. The AGIR report (HPA, 2007) review of epidemiological studies of exposure to tritium concluded that the available epidemiological literature of environmental and occupational tritium exposures do not provide enough detail to estimate risks from tritium exposure and recommended an international collaborative study of nuclear workers. The UK's Health Protection Agency (HPA, 2008) and the ICRP (Cox *et al*, 2008) supported the AGIR conclusions and recommendations.

Canadian workers are perhaps the best population to use for studying tritium health effects, given the use of heavy water in CANDU reactors and the use of tritium at AECL and tritium processing facilities. Other populations for robust analyses exist in the nuclear workers of the SRS (and possibly other sites such as Mound and Los Alamos), the five main tritium-exposed UK nuclear workforces (Sellafield, Chapelcross and Capenhurst, AWE and UKAEA). The SRS and Canadian workforces have relatively large numbers of workers with appreciable

tritium exposures (relative to the other groups), and would be potentially informative. Tritium exposures in the course of nuclear weapons production in France (mainly at Marcoule and Valduc) have also occurred. All of these country's workforces have some groups with relatively high exposures to tritium and apparently good dosimetry. These nuclear workforces could be used as the basis of future study. However, the limited number of tritium workers and their generally small tritium exposures within the individual countries are unlikely to be greatly informative about possible risks since there would be relatively low statistical power to detect any effects of exposure to tritium. An international collaborative study, which would combine the tritium worker data from these and other countries, is highly desirable in order to provide the necessary study power to properly assess tritium risk.

A protocol for the collection and assessment of tritium dosimetry data, over time and between countries is essential to ensure consistent data appropriate for pooling in the near future for an international collaborative study. In the UK, attempts to computerize the outstanding urinalysis data over the next few years are critical to enable the UK to contribute appropriately to any future international studies (personal communication, D McElvenny, 2009). In the United States, comprehensive dose reconstruction of SRS, Mound and potentially Los Alamos could be very feasibly conducted. A review of Canadian tritium workers in terms of tritium-specific doses could also be conducted. Although the French are interested in future collaborations, their tritium urinalysis data will take considerable time to be computerized. An international tritium study may be feasible once their tritium exposure data are available for analysis (personal communication, D Laurier, 2009).

Romanian CANDU reactor workers are also exposed to tritium but since their oldest reactor only began operations in the mid-1990s; they are not in a position to contribute much statistically to an international study. Likewise, workers involved in the early production of tritium at the Mayak site in the former USSR were relatively highly exposed. However, the information available concerning tritium doses received by these workers is not known. The level of exposures in the other major nuclear weapons state, China, also remains unknown.

Other heavy water moderated reactors will also be operational, for a variety of reasons (for example, materials testing reactors). The future operation of fusion reactors in France (specifically, ITER at Cadarache) is relevant to tritium, and the current operation of experimental fusion reactors (at Princeton in the US and at JET at Culham, UK) may be important, although tritium exposures at these sites is expected to be minimal. This is not necessarily going to be the case if commercial nuclear fusion reactors become operational, since these will rely on tritium generation in a lithium blanket and a tritium fuel cycle will be fundamental to fusion energy (personal communication, R Wakeford, 2009).

Future occupational exposure to tritium may raise concerns with the proposals for new power reactors in Canada and the operation of fusion reactors in Europe. Fusion reactors will require an initial charge of tritium, but will also "breed" tritium through irradiation by neutrons produced in fusion reactions of lithium in a blanket surrounding the reactor. Tritium will be extracted from the irradiated lithium for use in the reactor. Thus, potential tritium-related health risks are likely to remain a subject of discussion.

4.7 Conclusions

In Canada, radiation exposures resulting from tritium releases from nuclear facilities are much lower than those attributed to natural background radiation. In 2006, the tritium air concentrations in the vicinity of nuclear facilities varied from 0.38 to 35.66 Bq/m^3, and the corresponding radiation doses varied from 0.00045 to 0.00236 mSv/year. Tritium doses to members of the public around processing facilities were also very low (0.00001 to 0.0145 mSv/year) (CNSC, 2009). All of these doses are well below the regulatory dose limit (1 mSv/year) for a member of the public set by the Canadian Nuclear Safety Commission. Given the extremely low doses to the public from tritium emissions and epidemiological studies do not show any adverse health effects in radiation workers exposed to higher doses, it is highly unlikely that ecological health studies of members of the public would be able to produce any meaningful results regarding tritium risk. Published studies of health effects in Canadian and other populations living near nuclear facilities provide no substantive evidence that excesses in health outcomes observed in some studies are related to the miniscule levels of tritium exposure.

Canadian nuclear energy workers' radiation exposures are monitored and dose information is stored in the National Dose Registry. Canadian nuclear energy workers' radiation doses are typically less than 10% of the regulatory dose limit of 50 mSv/year and 100 mSv over five years (cumulatively). In 2006, occupational doses from tritium exposures ranged from 0.07 to 0.26 mSv for workers in nuclear generating stations, and from 0.30 to 0.90 mSv for workers in processing and research facilities. In all cases, the doses received by workers were far lower than the CNSC annual occupational regulatory dose limit (CNSC, 2009).

Many workforce studies have estimated tritium-specific individual doses. However, none of them, as presently reported, enable reliable inferences to be made on risks associated with exposure to tritium. In general, the available epidemiological studies on the offspring of radiation workers do not contain enough detail to estimate risks from tritium exposure. Our assessment takes these shortcomings into consideration. However, based on the extensive epidemiological research of other types of radiations received at much higher levels, there is little evidence to suggest that increased birth defects, cancer incidence or mortality occurs in populations exposed to tritium at current environmental or occupational levels. The lack of current evidence of an excess risk among these populations suggests that any tritium-specific risk is small and not distinguishable from the risk of similar health outcomes in the general population.

Recap: Section 4

- Published studies of populations living in the vicinity of nuclear facilities provide no substantive evidence that any adverse health outcomes are related to any radiation exposures resulting from the facilities.
- Based on the extensive epidemiological research and the lack of excess risk found from total radiation exposures, there is little evidence to suggest that increased birth defects, cancer incidence or mortality occurs in populations exposed to tritium at current environmental or occupational levels.
- In Canada, total radiation exposures to workers and the public are low. Tritium represents only a small fraction of all the radiation sources we are exposed to and the tritium risk is only a fraction of total radiation risk, which is very low.
- Epidemiological studies of workers with tritium specific exposures and good quality dosimetric information could be used as the basis for future studies. An international collaborative study combining the tritium workers data from multiple countries would be sufficient to provide the necessary study power to assess tritium risk directly.

5 RELATIVE BIOLOGICAL EFFECTIVENESS

In radiation biology, absorbed dose refers to the amount of radiation energy deposited within a unit mass, typically tissue or individual cells. However, it is clear that the deposited energy alone does not dictate the amount of biological damage and that other factors like the type of radiation and the chemical form of the radioisotope play a role. To equate absorbed doses from different radiations, and thus permit the use of a single unit of dose for radiation protection purposes, the effectiveness of the radiations must be quantified. Quantification requires a strict comparison of the effects of the radiation of interest with those effects caused by a standard or reference radiation. The ratio of the response of the two radiation types is termed the relative biological effectiveness (RBE). ICRP 103 defines RBE as *"The ratio of a dose of a low*-[linear energy transfer] LET *reference radiation to a dose of the radiation considered that gives an identical biological effect. RBE values vary (with the same type and energy of radiation) due to the dose, dose rate and biological endpoint considered."*

The ICRP definition of the RBE requires comparison with a low-linear-energy-transfer (LET) reference radiation. Traditionally, this has included both gamma radiation and 200–250 kVp x rays. With respect to tritium beta radiation, the selection of the reference radiation makes a significant difference in the resultant RBE. In addition, Little and Lambert (2008) and the AGIR (HPA, 2007) point out that the dose from the reference radiation must be delivered in the same fashion as that of the tritium irradiation, which implies a chronic exposure with an exponential decay if the concentration of the tritium in the body is not maintained at a constant value.

To further complicate matters, the response of the tissue or organ being irradiated may not be linear for the radiation of interest or the reference radiation. Straume and Carsten (1993) discuss this at some length, indicating that the RBE can vary significantly with changes in dose rate and radiation quality (LET). Therefore, for radiation protection purposes, it is desirable to assess the RBE for doses and dose rates that are comparable to those received in environmental and occupational settings. However, as the AGIR (HPA, 2007) points out, the dose response curve for acute doses of low-LET reference radiation is often curvilinear in relation to the response of radiations with higher LET (such as tritium's beta radiation). Studies at these lower doses give a maximum RBE value, which would be more appropriate for occupational and environmental exposures. This is referred to as the RBE_{MAX} or RBE_{M}.

There have been many experimental determinations of the RBE for tritium radiation, using various biological endpoints, both *in vitro* and *in vivo*, and using gamma and x-rays as the reference radiations. *In vivo* (Latin for "within the living") implies that the living tissue of an entire living animal is used in the study. *In vitro* (Latin for "within the glass") is the general designation given to experimental studies done on tissues or cells outside of the body; for example, in a Petri dish.

Several reviews of these studies have been conducted, some of them critical, that have highlighted errors or omissions in the work that might have affected the RBE determination. These too are briefly reviewed in the following section.

5.1 RBE Literature Reviews and Experimental Studies

Because tritium is perhaps the largest source of internal exposure in the Canadian nuclear industry (NDR, 2008), there has been considerable interest in its radiobiological effects since the early 1960s. With the possible exception of radon, the amount of research on the biological effects of tritium is arguably greater than for any other internal emitter of ionizing radiation.

Results of the studies have been collected and reviewed, with the greatest amount of debate centered on an appropriate RBE value for tritium for the purpose of assessing health risks (primarily cancer) in humans. The following is a synopsis of the major reviews of the biological effects of tritium and determinations of the tritium RBEs that have been published over the last two decades.

5.1.1 Straume and Carsten (1993)

Straume and Carsten (1993) provided a broad and comprehensive review of the literature available at the time on the carcinogenic, genetic, developmental, and reproductive effects associated with exposure to tritium. This research continues to be a credible reference in scientific literature.

Straume and Carsten (1993) identified 12 published RBE studies for tritiated water (HTO) compared with orthovoltage (200–500 kVp) x-rays and 21 RBE studies for HTO compared with gamma rays from Cesium-137 or Cobalt-60. Combining these studies, they calculated an arithmetic mean RBE value of 1.8 using x-rays as the reference radiation and 2.3 relative to gamma rays. They commented that their estimates were based upon studies that used radiation delivered at doses and dose rates higher than those generally received by radiation workers and members of the public; therefore, their estimated RBE values could have been lower than the actual RBE values than should be used for human risk assessment.

The Little and Lambert (2008) critique of the Straume and Carsten (1993) review pointed out that Straume and Carsten (1993) included a number of studies that did not have adequate concurrent external (x-ray or gamma ray) radiation-exposed groups (e.g., Prosser *et al*, 1983; Carsten and Commerford, 1976; Russell *et al*, 1979; and Furuno-Fukushi *et al*, 1987). In addition, some of the other calculations of RBE conducted by Straume and Carsten (1993) (for example, the tritium experiments of Prosser *et al*, 1983) combined with the Cobalt-60 experiments of Lloyd *et al* (1975) were based on non-concurrent experiments. Consequently, Little and Lambert (2008) suggested that the Straume and Carsten (1993) review was unreliable.

However, the overall RBE value recommended by Straume and Carsten (1993) using gamma rays as the reference radiation was very similar to that of Little and Lambert (2008) (2.3 versus 2.19), although the determination of the tritium RBE value using x-rays as the reference radiation was somewhat different (Little and Lambert calculated an RBE value of 1.17 versus Straume and Carsten's 1.8).

5.1.2 Advisory Group on Ionizing Radiation Report (HPA, 2007)

The report "Review of Risks from Tritium" of the independent Advisory Group on Ionizing Radiation (AGIR) was a follow-up to the work of the Committee Examining Risks of Internal Emitters (CERRIE). Based upon the CERRIE report, the U.K. National Radiological Protection Board (now the Radiation Protection Division of the HPA) charged the AGIR, in December 2004, to:

"...carry out a review of internal tritium dosimetry with particular attention to tritiated water and organic compounds containing tritium. The review should take into account a wide range of views and provide a scientifically sound consensus on the doses delivered by internal tritium exposure and the associated risks and uncertainties."

The AGIR (HPA, 2007) report discusses the RBE of tritium radiation as well as track-structure considerations, the relationship between the RBE and the dose and dose rate effectiveness factor (DDREF), the use of different reference radiations, and experimental studies. The biokinetic models of HTO and organically bound tritium (OBT) were discussed through an examination of the current ICRP models, a review of the key information underlying those models, a discussion of more recent models and the special aspects of DNA precursors. There was also a detailed review of reproductive effects in the female, especially on oocyte formation and fertilization.

The AGIR authors critically reviewed several papers that estimated the tritium RBE value under different experimental regimes, tabulating their results based on reference radiation and whether they were *in vivo* or *in vitro* studies. With one exception, they only included papers published in peer reviewed journals or conference proceedings; the exception being an article by Chopra and Heddle (1988), which they included because of the well-conducted experiments and data analysis.

The AGIR made the following conclusions regarding the tritium RBE value:

a) Various theoretical and experimental studies of radiation of LET similar to that of tritium beta particles led to the general expectation of an RBE value for tritium of at least 2 compared with gamma radiation.

b) Neither transmutation effects nor isotopic discrimination associated with tritium appear likely to have major effects, but any effect would be in the direction of tending to increase the observed RBE value.

c) Experimentally determined RBE values can vary significantly depending on the choice of reference radiation. It was recommended that high-energy gamma rays should be the preferred choice for reporting RBE values. Where lower-energy x-rays and gamma rays were used as the standard, an appropriate adjustment should be taken into account when discussing the results. In addition, the reference radiation used should be adequately described and include anything, such as filtration, that would modify the energy spectrum.

d) Interpretation of RBE experiments was complicated by dose rates that were rarely comparable and by reference radiation that may have been more effective than hard gamma rays.

e) In a wide variety of cellular and genetic studies, RBE values for HTO have generally been observed in the range from 1 to 2 when compared with orthovoltage x-rays, and in the range from 2 to 3 when compared with gamma rays.

f) For developmental endpoints, the RBE values for HTO were similar to those obtained from cellular and genetic studies.

g) Whole animal carcinogenesis studies yielded RBE values with central estimates generally in the range of 0.8–2.5 (x-rays and gamma rays as the reference radiations). However, the AGIR had several reservations with these studies. In particular, in some of the studies the frequency of cancers appears to have been saturated or nearly saturated at the lowest doses employed (about 1 Sv), so the slope of the dose response curve was above the relevant dose levels — which represent the area of interest for radiation protection purposes.

h) There is evidence that published RBE values could somewhat underestimate the actual RBE values relevant for human risk assessment, since many of the studies employed radiations delivered at higher doses and dose rates than those generally received by people

i) The AGIR considered the most likely RBE value relative to chronically delivered hard gamma rays was between 2 and 3 and considered a value of 2 most appropriate. This was based largely on an analysis of the available experimental data with rounding and biophysical considerations. Fractional values were not considered appropriate.

In addition to the above, the most significant recommendation of the AGIR report was related to the use of a provisional value of 2 for the RBE of tritium until an internationally agreed value becomes available:

"The ICRP has stated that 'the continued use of a w_R of 1 for all low-LET radiations … is not intended for retrospective assessment of individual risks of stochastic effects from radiation exposures (from Annex B of the ICRP recommendations, 2007a). It is our view that the preponderance of evidence is in favour of an RBE greater than 1 and we recommend that in the interpretation of epidemiological studies, and in individual retrospective risk assessments, a value more in keeping with the available scientific evidence should be employed rather than assuming that the radiation weighting factor (w_R) of 1 is a surrogate for RBE. Until such time as an internationally agreed RBE is available we propose that a provisional value of 2 be used. We understand the logic of the ICRP recommendation that w_R be taken as unity for all photon radiations, but suggest that a case can be made for using a value of 2 for w_R for tritium even in routine prospective radiation protection assessments".

In response to that recommendation, Cox *et al* (2008) stated that:

"The ICRP protection system is scientifically based but makes a number of simplifying assumptions so the doses from different radiation types can be summed and compared with

limits, constraints and reference levels that relate to whole-body radiation exposure. The underlying simplifications include the use of a radiation weighting factor value of 1 for all low-LET radiation, including tritium beta particles. For planning purposes, appropriate levels of protection are determined by constrained optimization, resulting in doses that will be typically a small fraction of the relevant dose limit. Increased complexity in the calculation of equivalent and effective dose would not improve protection and might suggest a degree of precision in the calculations that is unwarranted."

It can be concluded from that statement that the ICRP does not support revising the w_R for tritium because in their view it would not lead to dose reductions.

5.1.3 Little and Lambert (2008)

As part of their contribution to the AGIR (HPA, 2007) report, Little and Lambert (2008) conducted a comprehensive, critical interpretation of several studies with the intent of determining the low dose limiting relative biological effectiveness (RBE_M). They conducted a Medline database search looking for studies using the terms "tritium" and "risk". Of the papers initially identified, they generally only accepted those that were peer reviewed, written in English and had a concurrent x-ray or gamma-irradiated group. The biological endpoints of the tritium studies included carcinogenesis, chromosomal aberration, cell death, and others. Of an original 221 studies, 24 met the acceptance criteria. These studies were divided into *in vivo* and *in vitro* experiments, and sub-divided as either chronic or acute irradiation regimes. To be classified as a chronic irradiation, the external irradiation dose rate had to be comparable to the tritium exposure. The 24 studies were subsequently examined to remove any that were too deficient in other aspects of study design or statistical analysis.

RBE varies over dose ranges and is typically greatest at lower doses. Little and Lambert (2008) used the RBE estimates from the studies that were acceptable to compute an aggregate "best linear unbiased estimate (inverse-variance weighted) of the RBE" and the 95% confidence limit of the RBE estimates. Their definition of the RBE was based upon the ratio of the initial slopes (that is, lower doses) of the tritium and gamma (or x-ray) dose response curves which was roughly equivalent to the standard definition of the RBE_M.

In their summary of the carcinogenesis studies, Little and Lambert (2008) indicated that the overall aggregate results imply RBE values with a central estimate in the range of 1.2–2.5 and 97.5 upper percentile of no more than 3.0. The three studies that used chronic x-rays and chronic gamma irradiation yielded an aggregate RBE value of 1.19 (95 % CI: 0.88–1.49) and 2.49 (95% CI: 2.00–2.98), respectively.

Little and Lambert (2008) stated that they doubted the *in vivo* cancer data in the studies. Nevertheless, their estimates of RBE in relation to late health effects (such as cancer) were derived by combining the *in vivo* cancer data estimates for endpoints for other than cell survival (and related endpoints) to yield an aggregate RBE of 2.19 (95% CI: 2.04–2.33) and 1.17 (95% CI: 0.96–1.39) when using chronic gamma rays and chronic x-rays, respectively, as the reference radiation.

The statistical application of aggregating RBE from a number of studies to reduce the uncertainty of the data deserves some comment. Combining the results of several studies to reduce the overall uncertainty is a valid statistical practice, but is generally done when the studies being combined are similar determinations. Little and Lambert (2008) combined a number of different RBE studies, grouping them by the reference radiation (x-ray and gamma) and experimental conditions (*in vivo* or *in vitro*), but many of the combined studies had different endpoints, such as cell survival and lymphocyte aberrations. While the practice may give a better indication of an overall RBE value for radiation protection purposes, the accuracy of the aggregate uncertainty (roughly +/- 25%) may imply greater precision than actually exists and so should be treated with caution.

5.1.4 Kocher, Apostoaei and Hoffman (2005)

The term "radiation effectiveness factor" (REF) was used by Kocher *et al* (2005) to represent the biological effectiveness of a radiation dose for the purpose of estimating cancer risks and probability of causation in identified individuals. This differs from an RBE in that the REF applies strictly to the results of specific radiobiological studies under controlled conditions. Also, the REFs for induction of cancers in humans developed in this work were expressed as both a central estimate (median) and a subjective probability distribution (95% confidence levels) to represent their uncertainty. Of particular interest was the REF_L, which is the probability distribution of REF at low dose and dose rates. The REF is based upon a reference radiation of high-energy Cobalt-60 gamma rays, which is assigned a radiation effectiveness factor of unity, without uncertainty. Cobalt-60 gamma rays are used to enable comparison with estimates of cancer risk, the latter based primarily on studies of Japanese atomic bomb survivors who primarily received acute doses of high-energy gamma rays and a small, but potentially important contribution of high-LET neutrons. Many other studies of the biological effectiveness of different radiation types have also used Cobalt-60 gamma rays as the reference radiation.

Part of the work by Kocher *et al* (2005) was to estimate the RBE_M for tritium beta particles, where M represents the maximum value. Estimates of the RBE_M were taken from Tables 1–3 Straume and Carsten (1993) where three of five studies, using chronic exposure to x-rays, had a central estimate of 2 to 3 for RBE_M. They further reasoned that *"if a nominal biological effectiveness of X-rays relative to high-energy gamma rays of 2 is assumed on the basis of the probability distribution of REF_L for orthovoltage X-rays …, those data suggest that RBE_M for ^3H beta particles relative to gamma rays delivered chronically could be as high as about 4–6"*. Based on this reasoning, their REF_L for "electrons less than 15 keV had a 50th percentile value of 2.4 and a 95% confidence interval of 1.2 to 5.0."

5.1.5 Dietze and Alberts (2004)

Dietze and Alberts (2004) argued that the w_R and Q (the quality factor, the predecessor of w_R) for photons and electrons should remain at 1, even though experimental studies showed that soft x-rays have a significantly larger RBE value than Cobalt-60 gamma rays or 200 kVp x-rays. Further to their argument, they cited the ICRP's Publication 60, which stated:

> *". . . Simplicity is important to reflect our lack of precise information in man and an appreciation of the practical aspects of radiation protection. For example, the Commission does not believe it is helpful to adopt different quality-factor values for different photon energies."*

That being said, Dietz and Alberts (2004) admitted that when Publication 60 was written, the ICRP had not outlined the "practical aspects of radiation protection".

With respect to internal emitters, they explained that the effective dose from internal exposure is usually indirectly determined from parameters that were measured externally or from excretion data. This requires very complex models such as the alimentary tract model and the lung model that, in turn, were used to determine the distribution of radionuclides in different tissues and organs and to determine the respective organ dose. These models have various parameters, such as transfer factors and biological half-lives, many of which are only approximately known when derived from animal data or set to 1 where there is no evidence available. From this premise, Dietz and Alberts argued that "with the exception of tritium" a more detailed definition of w_R could not be expected to give a more precise estimate of dose. They then provided other arguments demonstrating the complexity and uncertainty involved in changing the w_R (for example, energy spectra or changes to dose coefficients).

5.1.6 Fairlie, I. (2007)

Fairlie (2007) argued in favour of revising the RBE value for tritium to 2 to 3, and that based on this change, the ICRP should also increase the w_R to 2–3 for a number of lower-energy beta-radiation-emitting radionuclides. He points out that the ICRP's Publication 92, like Publication 60, continued to recommend a value of 1 for the w_R for all photons and electrons for use in radiological protection. He believed this to be a mistake and that the w_R values should not be used for specific risk assessments.

He also highlights that ICRP Publication 92 acknowledges that there are practical arguments to use hard gamma rays as the reference radiation for RBE, including:

- Most experimental animal studies of cancer induction and life shortening (and deterministic effects) have been carried out with gamma rays, and, importantly, some with exposures at low dose rates.
- The most important body of data for estimating radiogenic cancers in humans is from the atomic bomb survivors, who were exposed primarily to gamma rays.
- Hard gamma rays have the lowest LET (dose average LET, LD, 0.4 keV/µm or less) among photon radiations.
- The distribution of the deposition of energy from gamma rays in large fields is more uniform than with x-rays.

Fairlie (2007) provides a table and a histogram summarizing some 40 RBE value estimations from several biological endpoints and for both x-rays and gamma rays as the reference radiation. However, in contrast to that of Little and Lambert (2008), the author did not limit his dataset to studies from peer-reviewed journals or those where the reference irradiation was delivered concurrently.

With respect to tritium radiation, Fairlie (2007) recommended:

- For prospective dose assessments, w_R values greater than 1 rising to about 3 should be assigned via a continuous RBE energy function to the low-energy electrons (average energy at emission <50 keV) from beta-emitting radionuclides.
- Tritium's w_R value should be increased to between 2 and 3.
- For specific risk estimations, epidemiological studies and retrospective dose assessments, the ICRP should clearly state that the most appropriate RBE value *and not the w_R value* should be used.
- The ICRP should give guidance on the methods and data sources that could be used for these values.

5.1.7 Environment Canada/Health Canada – Releases of Radionuclides From Nuclear Facilities (Impact on Non-Human Biota) (2003)

The *Canadian Environmental Protection Act,* 1999 (Environment Canada, 1999) requires the federal Ministers of the Environment and of Health to prepare and publish a Priority Substances List (PSL) that identifies substances, including chemicals, groups of chemicals, effluents and wastes, that may be harmful to the environment or constitute a danger to human health. The Act also requires both Ministers to assess these substances and determine whether they are "toxic" or capable of becoming "toxic" as defined in Section 64 of the Act.

In complying with the Act, the Ministries of Environment Canada and Health Canada undertook an assessment of the impact on non-human biota from the releases of radionuclides from nuclear facilities (Environment Canada/Health Canada, 2003). Tritium was included in the review since it is released to the environment from the operation of CANDU nuclear power reactors. Although non-human biota were the primary focus, much of the review included studies looking at the effects of tritium on mammals and so is relevant to this report. Reproductive effects of tritium exposure were of special interest, since reproductive organs are one of the most radiosensitive tissues and reproductive failure could affect biota populations. The report looked at many studies and reviews to determine what the investigators called an "ecodosimetry weighting factor". They reported the results of nine studies looking at reproductive effects of tritium in mammals and fish, which gave tritium radiation RBE values from 1.7 to 3.8 (the highest value was due to reduction in fish egg fertilization). The report also "gamma normalized" (multiplied the RBE by 2, using x-rays as a reference to make the value comparable to a gamma radiation reference) the RBE value of spermhead survival reported by Lambert (1969), giving an estimated RBE of 4.8. These RBE values were compared to those of Straume and Carsten (1993), resulting in an "ecodosimetry weighting factor" of 3 for tritium radiation for ecotoxicological risk assessment purposes.

5.1.8 Myers and Johnson (1991)

The report by Myers and Johnson (1991), prepared for the Atomic Energy Control Board (predecessor to the Canadian Nuclear Safety Commission) Advisory Committee on Radiological Protection, provides a good overview of tritium gas (HT), HTO and OBT metabolism. Although it predated Straume and Carsten (1993), it provided an overview of currently available literature,

noting that information on the RBE of tritium beta particles for radiation induced cancer was extremely limited. There were only two published studies located and both related to radiation-induced acceleration of the development of mammary tumours in female rats. The studies presented a tritium RBE of 1.8 compared to chronic gamma radiation or 1.2 compared to 200 "kVec x-rays" at low dose rates. Myers and Johnson (1991) argued that the reference radiation for the tritium RBE should be set using x-rays as reference radiation "since x-rays have been traditionally accepted as reference radiation by the ICRP". Using the existing data and using 200 kVp x-ray as the reference radiation, they stated that the data suggest that the quality factor (Q) should be closer to one. Interestingly, the authors pointed out that using 200 kVec x-rays as the reference radiation would imply that a Q of 0.4 or 0.5 for Cobalt-60 gamma rays would more closely correspond to the RBE and data. However, they added, it would create major practical complications in the measurement of radiation doses for purposes of radiation protection (for example, personal dosimeters cannot distinguish between x-rays and Cobalt-60 gamma rays). The position expressed by Myers and Johnson (1991), which advocates an RBE for tritium of less than 1, is in contrast to most of the other studies reviewed in this section.

5.2 Summary of Relative Biological Effectiveness Determinations

The relative biological effectiveness (RBE) is the absorbed dose of a reference radiation type needed to cause a specific effect divided by the absorbed dose of the radiation of interest that causes the same effect. However, RBE values can and do vary by dose, dose rate and biological endpoint. Due to differences in radiosensitivity of tissues, organs and organisms, different endpoints (effects), *in vitro* or *in vivo* test systems, and the choice of the reference radiation, comparisons of RBE measurements are not simple and these values are expected to vary considerably.

Following the format of AGIR (HPA, 2007), Little and Lambert (2008), and Greenpeace (2007), the following is a summary of studies measuring the RBE of tritium beta radiation. The results are presented in two tables: *in vivo* (Tables 5.1.1 and 5.1.2) and *in vitro* (Tables 5.2.1 and 5.2.2) studies. Each table in turn is divided between those that used x-ray as the reference radiation (Tables 5.1.1 and 5.2.1) and those that used gamma radiation (Tables 5.1.2 and 5.2.2) as the reference. All attempts were made to include studies covered in the reviews mentioned above, particularly those published in peer-reviewed journals. Studies reported in conference proceedings were not included.

5.2.1 *In Vivo* Studies Using X-rays as the Reference Radiation

The objective of the study by Johnson *et al* (1995) was to determine the RBE of HTO compared to x-rays for the induction of myeloid leukaemia in male mice of the CBA/H strain. The researchers estimated lifetime incidence of myeloid leukaemia in 7 groups of 750 mice, with each group being given single injections of HTO of 90, 180 or 270 MBq per mouse, resulting in total doses of 0.85, 1.86, and 3.04 Gy. The x-ray exposure was chronic, approximating the tritium dose rate with doses of 1.06, 1.98 and 2.64 Gy. At first, they used a 200 kVcp x-ray machine, but it failed partway through the study and was replaced with a 150 kVp x-ray machine with filters to approximate the average energy of the 200 kVcp x-rays. The incidence of myeloid

leukaemia increased from 0.13% (control) to 6–8% (treated). Johnson *et al* noted that the incidence of myeloid leukaemia reached a plateau at about 2 to 3 Gy, reasoning it might be due to inactivation of myeloid leukaemia precursor cells at higher levels of radiation. The calculated RBE value for tritium beta rays ranged from 1.0 ± 0.5 to 1.3 ± 0.3 (best estimate 1.2 ± 0.3). Little and Lambert (2008) reanalyzed the data and also found that the RBE values were statistically consistent with 1.

Lambert (1969) assessed spermatogonia survival in male mice injected at the age of 10–12 weeks with HTO or tritiated thymidine (^{3}HTdR) and in a reference group exposed to 200 kVp x-rays. Mice injected with ^{3}HTdR at 185 kBq/g body mass and HTO at 740 kBq/g body mass had a reduced surviving fraction of resting primary spermatogonia at the same level as a 0.30 Gy dose of 200 kVp x-rays over 72 hours. If it was assumed that the cell death was initiated in the first 19 hours of exposure, then a recalculation of the dose would have an equivalent x-ray dose of 0.11 Gy, so the RBE for HTO and ^{3}HTdR would be 2.3 and 1.3, respectively. The 19-hour limit was chosen to account for the life span of both intermediate and type B spermatogonia, postulated to die before division, which would happen in the first 19 hours of the experiment. Spermatogonial cell death occurred with doses of 74 kBq/g body mass or more, and ^{3}HTdR was found to be about 4 times more effective in killing spermatogonia than HTO, due to essentially all the ^{3}HTdR being collected in the nucleus of the cell. Because essential data, such as the number of animals, was missing and the statistical analysis was not provided, Little and Lambert (2008) were unable to reanalyze the data.

Gragtmans *et al* (1984) looked at mammary tumour induction in rats after exposure to tritium beta radiation and 200 kVp x-rays delivered both chronically and acutely. X-rays were chosen as the reference radiation since it was similar to that originally proposed by the ICRP in 1954. The incidence of mammary tumours over time was compared to that of control groups in a rat strain where these tumours occur naturally without experimental radiation. Tritium was injected intraperitoneally at concentrations of 45 to 370 MBq/100 g body weight followed by four additional injections at two-day intervals, producing doses of 0.46, 0.92 1.63 and 3.85 Gy. The chronic x-ray dose was delivered continuously over 10 days to produce cumulative doses of 0.29, 0.57, 1.1 and 2.0 Gy. The acute x-ray dose was 0.57 and 1.78 Gy, delivered over one hour. There were about 120 animals in each irradiation group and the controls. RBE value estimates were based upon mammary tumour incidence, mammary tumour cumulative percent at 450 days post irradiation, and the time to induce tumours in 50% of the irradiated group. Compared to the chronic x-irradiation, the tritium radiation had an RBE value of 1.1 to 1.3, but was not statistically different from 1.0. The acute x-irradiation appeared to be 1.3 to 1.6 times more effective than chronic X irradiation for acceleration of the appearance of mammary tumours, with an RBE of 0.68 and 0.83 for cumulative incidence and cumulative percentage respectively. Little and Lambert's (2008) reanalysis of the data gave the same RBE, stating though that the 95% confidence levels included an RBE value of 1. They also commented that the use of the endpoint of acceleration of mammary tumours that occur in large proportion, even in control animals, "makes interpretation of this study, for purposes of deriving a radiation dose response, difficult."

Looking at spermatogonia survival and chromosome aberrations, Chopra and Heddle (1988) treated mice with HTO and 250 kVp x-rays. Little and Lambert (2008) noted the quality of this study, as it was the only exception to their rule of using peer-reviewed reports. They were impressed with the thoroughness of its experimental design and the analytical protocol. Chromosome aberrations in lymphocytes were studied in female mice, and aberrations in spermatocytes were studied in male mice. The female mice were given 1.5–6 Gy from x-rays over a 10-day period to mimic the tritium dose of 2 or 6 Gy from HTO. Male mice were given 1.5–4.5 Gy from x-rays or 1.5–4.5 Gy from HTO. The spermatocyte study involved 79 mice, of which 15 were controls. The mice given x-ray exposures were exposed at an exponentially decreasing dose rate to mimic the dose rate received from HTO. The calculated RBE for tritium was 1.21 (95% CI: 0.8–1.9) for chromosome aberrations in spermatogonia and 1.14 (95% CI: 0.8–1.5) for chromosome aberrations in peripheral blood cells. This was not statistically different from a value of 1.

Kozlowski *et al* (2001) assessed *in utero* haematopoietic sensitivity to alpha, beta or x-irradiation in mice. They counted stable chromosomal aberrations in the bone marrow cells of female mice and their offspring that were exposed to HTO *in utero* and of a reference group exposed to x-rays. The HTO group received HTO or homogenized tritiated watercress via gastric intubation for the 20 days of pregnancy, the former at concentrations of 1.1 MBq/mL, implying total activity of 133 MBq, the latter at 21 MBq/mL (total intake of about 60 MBq). Total doses were estimated to be 0.7 Gy for the HTO group and 0.4 Gy for the group receiving tritiated watercress. In each case, all but 0.1 Gy was received during pregnancy. Reference groups were exposed to 250 kVp x-rays at 0.73 Gy/min on either day 7 or 14 of pregnancy, with a total dose of 0.5 Gy. Similar levels of stable chromosomal aberrations were seen in the offspring and their mothers, both for x-rays and tritium, and both as HTO and in watercress (although HTO was likely the dominant form of tritium in the watercress). Kozlowski *et al* (2001) concluded that there was no evidence of greater *in utero* sensitivity and indicated that the results "were consistent with an RBE value of 1–2". However, they did not calculate an exact value. Little and Lambert (2008) fit a simple linear model to parts of the data and calculated an RBE of 0.56 for the total dataset (mother and offspring, HTO and tritiated watercress groups). They did suggest that the estimate could be doubled or more to account for the acute x-ray dose since an acute dose is about twice as effective as a chronic delivery to cause stable chromosomal aberrations. They also estimated an RBE for tritium of 0.64 in the offspring from all tritium, of 0.49 in the mothers from all tritium, and of 0.84 for all mice from the tritiated watercress.

5.2.2 *In Vivo* Studies Using Gamma Rays as the Reference Radiation

Furchner (1957) determined the RBE of tritium by looking at mouse survival from one-time injections of HTO and compared the survival rate to that of a chronic exposure to Cobalt-60 gamma rays delivered in a manner that mimicked the biological half-life of a single injection of HTO. Five single injections HTO at concentrations of 25.9 to 52.2 MBq/g delivered doses of 5.3 to 16.5 Gy. The reference Cobalt-60 gamma irradiation was delivered at a decreasing rate to mimic the tritium exponential decay, delivering total doses of 12.3 to 16.5 Gy. An RBE of 1.7 was calculated, which compared favourably with other studies of the time.

Using mouse oocytes to estimate the RBE, Dobson and Kwan (1976) injected young, pregnant adult female mice intraperitoneally with HTO on the day of fertilization and then provided drinking water with appropriate concentrations of HTO to maintain specific HTO levels in bodily fluids. This was continued throughout pregnancy and lactation. Radiation doses from the tritium were estimated at 2.2, 6.6, 13.2 and 19.8 mGy/d. Controls were irradiated with Cobalt-60 gamma radiation at rates of 10, 21, or 32 mGy/d. At 14 days after birth, female offspring from all exposed and control groups were killed, with an ovary removed, and oocytes counted from each mouse. Oocyte survival decreased exponentially with dose and there was no significant dose rate effect or threshold within their dose range. The response to the protracted gamma irradiation was significantly different, with an evident linear quadratic response with a large upward convexity. Dobson and Kwan hypothesized that this might have been a dose and dose rate effect, but affected the RBE in that it was higher at lower doses, with an RBE of 1.8 at 0.4 Gy, 2.5 at 0.2 Gy. As the dose decreased, it reached a limiting value in the vicinity of 3.0.

Dobson and Kwan (1978) repeated their 1976 experiment using essentially identical procedures but with different dose regimes. The data followed the same trends as the earlier study, again showing a dose and dose rate effect inversely proportional to the RBE. This was again due to the curvilinear nature of the response to the gamma reference radiation. The RBE in the lower dose ranges is of greatest interest but it is also the most difficult to measure. This study's conclusion was similar to that of the first, stating that for "very low-level exposures to HTO and Cobalt-60 gamma rays, the RBE was found to reach 2.8".

Little and Lambert (2008) raised doubts about the comparability of the second chronically exposed group: The first study (Dobson and Kwan, 1976) indicated that oocyte sensitivity varied significantly over the period from conception to 14 days of age, but it was not clear how the second study accounted for this.

Carr and Nolan (1979) looked at testis mass loss in mice induced by ^{3}HTdR, HTO, and Cobalt-60 gamma irradiation. Male CBA mice were injected intraperitoneally with 0.037–0.74 MBq/g body mass ^{3}HTdR or 0.37–1.5 MBq/g body mass HTO at about 100 days of age. A reference group was exposed to chronically delivered Cobalt-60 gamma rays given at a decreasing dose rate, which matched the dose rate from HTO (tritium simulator). The average testis dose for HTO was estimated as 0.14–0.58 Gy, and for ^{3}HTdR as ~0.03–~0.70 Gy. A single Cobalt-60 gamma ray dose of 0.578 Gy was delivered. The testis mass showed a complex pattern after irradiation, first decreasing and then increasing to near its initial value. As an endpoint, Carr and Nolan (1979) used the testis estimated integrated mass loss up to 10 weeks after injection. The RBE of the tritium beta particle relative to Cobalt-60 was 1.43 (95% CI: 1.06–1.80) for HTO and 2.07 for ^{3}HTdR. Little and Lambert (2008) pointed out that there is only a single Cobalt-60 gamma ray dose point (that is, 0.578 Gy), so the RBE estimates are only applicable at this point.

Zhou *et al* (1986) assessed radiation-induced dominant lethal mutations in female mice injected with HTO at 8 weeks of age. Six groups of 24 mice were injected once with tritiated water at concentrations between 0.17 and 4.1 MBq/g body weight, delivering a dose over 10 days of 0.039 to 0.912 Gy. A control group that received no HTO in the injections was included. A

second group of mice was exposed to Cobalt-60 gamma rays at doses equal to the daily dose due to the various tritium injections (at a decreasing dose rate). The total dose for the gamma-irradiated group over 10 days was 0.526 to 2.699 Gy. The female mice were then mated with male mice 21 days after irradiation ceased. Eighteen days after breeding, the females were sacrificed and their ovaries were examined for pregnancy, number of corpora lutae (yellow glandular masses in the ovary, formed by an ovarian follicle that has matured and discharged its oocyte), viable embryos, early embryonic death, and later embryonic death. Mutation frequency induced by the radiations was calculated and an RBE of 2.5 was determined. As in other studies, Little and Lambert (2008) recalculated that RBE and estimated it to be 2.94 (95% CI: 2.00–4.28), which differed little from the estimate of Zhou *et al* (1986).

Using apoptosis of mouse intestine cells as the endpoint, Ijiri (1989) irradiated mice with beta radiation from HTO injected intraperitoneally and with Cesium-137 gamma rays. Both dose regimens involved doses being delivered over 6 hours. The HTO injections varied from 0.15 to 150 GBq/kg body weight, delivering dose rates of 0.049 to 48.5 mGy/h and total doses of 0.29 to 291 mGy. For the reference group, animals were exposed to Cesium-137 gamma rays at dose rates from 0.0006 to 0.48 Gy/h over 6 h, giving total doses of 3.6 to 2,880 mGy. Measuring the amount of apoptotic cells in the crypts of the small intestine and descending colons, Ijiri (1989) then used the dose response data to calculate D_0 (dose required to reduce the population to 37%) from which the RBE could be calculated. D_0 values for the small intestine and descending colon were 210 mGy and 380 mGy respectively, for gamma rays, and 130 mGy and 280 mGy for the HTO exposures, respectively. The relatively low D_0 is indicative of the high radiosensitivity of the target cells and apoptotic response. The calculated RBE relative to the gamma radiation was 2.1 (95% CI: 1.7–2.5) for the small intestine and 1.8 (95% CI: 1.4–2.2) for the descending colon. Little and Lambert (2008) criticized the study for not providing critical details such as the analytical method. The Little and Lambert (2008) estimate of the RBE was 1.6 (95% CI: 1.2–2.0) for the small intestine and 1.4 (95% CI: 1.2–1.6) for the descending colon.

Satow *et al* (1989a) also looked at tritium effectiveness in oocyte killing in mice. Immature oocytes, which are highly sensitive to radiation, were exposed to HTO, Cesium-137 gamma rays, Cobalt-60 gamma rays or Californium-252 fission neutrons. On the 14th day after birth, female mice were injected with HTO at doses of 1.7, 3.4, 6.81, and 10.21 MBq/10 g body weight, delivering respective doses of 0.039, 0.077, 0.139 and 0.246 Gy. Doses within the same range were delivered acutely by Cesium-137 gamma rays, Cobalt-60 gamma rays or Californium-252 fission neutrons, also at 14 days of age. Ovaries were removed 14 days after that and examined for surviving oocytes. As the authors expected, the number of surviving oocytes decreased exponentially with increasing doses of HTO and Cesium-137. The RBEs of HTO compared to Cesium-137 ranged from 1.1 to 3.5, with a tendency to increase as doses decreased, consistent with the findings of Dobson and Kwan (1976; 1978). The relative effectiveness of the different types of radiations in order of increasing effectiveness was Cesium-137, Cobalt-60, HTO and Californium-252. Lambert and Little (2008) commented on the few details of the statistical analysis and noted that the RBE appeared greater at doses below 0.1 Gy. Overall they thought the study was well conducted, but lacked details such as number of animals, age at sacrifice and statistical analysis. They did not recalculate the RBE in this case, possibly due to the lack of detail in the statistical analysis.

As a follow-up to his first paper, Satow *et al* (1989b) did similar work using rats instead of mice. The study looked at the teratogenic effects on rat embryos comparing the HTO induced malformations with those caused by Cesium-137 gamma rays. Six groups of pregnant rats were injected intraperitoneally with water or HTO containing 1,850, 2,775, 3,700, 4,625 or 5,550 MBq HTO/300 g body weight on day 9 of pregnancy. The tritium exposures produced respective doses of 53, 79.5, 106, 132.5, and 159 Gy. To obtain RBE values of HTO in rats, six groups of pregnant rats were exposed to Cesium-137 gamma rays delivered to simulate tritium decay on days 9 to 18 of pregnancy. The rats were sacrificed on day 18 and their embryos were examined for external and internal malformations. The Cesium-137 exposures resulted in doses of 1.75 to 6.80 Gy, inducing 98.4% malformation in survived embryos and 71.7% of the total implants on day 9 of pregnancy. Satow *et al* (1989b) calculated a low dose RBE of 2.60 and admitted the doses were very high (and so the RBE_M could be much higher). They did not provide confidence limits. Little and Lambert (2008) reanalyzed the data using a logistic model to recalculate the dose and then normalized the results per surviving foetus. With these corrections, they calculated an RBE of 1.01 (95% CI: 0.57–1.78). They thought the study was well performed, but again that the statistical analysis was sub-optimal.

In their 1989 study, Zhou *et al* (1989) expanded their RBE assessment to dominant lethal mutations, dominant skeletal mutations, dominant lethal mutations in spermatocytes, survival of primary oocyte, and spermatogonial and chromosomal aberrations in spermatocytes in mice. The mice were exposed to HTO at 6–10 weeks of age and a reference group exposed to Cobalt-60 gamma rays administered at the same rate as the tritium radiation. Groups of mice were exposed by two different models: by single injection of HTO versus Cobalt-60 external exposure with dose rates simulating the exponential tritium decay rate; or by continual intake of tritium versus Cobalt-60 external exposure at a constant dose rate. For the constant dose rate, the mice were first injected with tritium and then given tritiated drinking water to maintain the dose rate. Female mice assayed for the dominant lethal mutation of oocytes received doses of 0.20 to 0.60 Gy from tritium and 0.70 to 2.87 Gy from Cobalt-60. The cumulative doses for the dominant lethal mutation of spermatogonial assay were 0.19 to 1.01 Gy for the animals exposed to tritium and 0.743 to 2.074 Gy for those exposed to Cobalt-60. The groups of male mice whose offspring were assayed for dominant skeleton mutation had doses of 0.19 to 1.01 Gy from tritium and 0.74 to 2.87 Gy from Cobalt-60. The estimated RBEs for dominant lethal mutation of oocytes, dominant skeleton mutations in spermatogonia, dominant lethal mutation of spermatocytes, primary oocyte survival, spermatogonial survival and numbers of germ cells were 3.4 to 2.8, 3.9 to 3.5, 3.9 to 1.6, 2.0 to 1.4, and 2.8 to 2.1, respectively. Little and Lambert (2008) pointed out some inconsistencies between the doses reported in the text and in the accompanying tables. In addition, the paper lacked critical details, such as the number of animals, whether the mice were matched by age in the various parts of the experiments, or if any control groups (0 dose) were used.

Seyama *et al* (1991) undertook several studies looking at the cumulative incidence of tumours in mice over different exposure regimens for tritium beta particles, neutrons, Cobalt-60 gamma rays, and Cesium-137 gamma rays. Groups of mice had single intraperitoneal injections of HTO at activities of 1.4×10^8, 2.8×10^8, 5.6×10^8, 7.4×10^8 Bq. The estimated doses from these injections were 1.97 Gy, 3.95 Gy, 7.90 Gy and 10.53 Gy, respectively. At 400 days, tumour

incidence was 4%, 8%, 18% and 24%, respectively. However, by 500 days, incidences were not much different among the groups — indicating that even the lowest dose (1.97 Gy) was sufficient to elicit the same incidence of tumours, with the higher doses simply accelerating the onset. Increased incidence of T-cell lymphoma was also induced with four weekly injections at similar doses. An increased tumour incidence over controls was seen in the ovary, liver, lung, mammary glands and uterus. There were also high incidences of lymphoma and leukaemia. Seyama *et al* (1991) calculated the RBE for tritium against Cobalt-60 and Cesium-137 gamma radiation for both acute and chronic exposures (simulating the tritium dose). They interpreted the data to infer that the acute gamma exposure had an efficiency equivalent to the HTO injections, but that the protracted gamma exposures were less effective than the HTO and acute gamma exposures, indicating an RBE of about 2.5. However, Little and Lambert (2008) pointed out that Seyama *et al* (1991) did not provide enough data to confirm their results or to indicate their statistical analysis and so they gave little weight to the study.

5.2.3 *In Vitro* Studies Using X-rays as the Reference Radiation

Prosser *et al* (1983) compared chromosomal aberrations in human lymphocytes from acute (30-minute and 24-hour) exposures to HTO *in vitro* and from 250 kVp x-rays. The x-ray exposure was delivered at 1 Gy/min which was also acute, but at a much greater delivery rate than the HTO. The x-ray exposure data appeared to have been collected a few years earlier, but in the same laboratory. Doses ranged from 0.102 to 4.13 Gy. The work suggested an RBE_M of 1.13 ± 0.18, with 250 kVp x-rays as the reference radiation. Prosser admitted that the study was not appropriate for radiation protection purposes due to the very short-term exposure (hours), which would not generally occur for doses of tritium of this magnitude. Prosser *et al* (1983) was not reviewed in detail by Little and Lambert (2008), due to the acute delivery of the reference radiation.

In an earlier lymphocyte study, Bocian *et al* (1978) assessed chromosome aberrations in human peripheral blood from two healthy female donors. The blood was exposed to HTO over 2 hours yielding a dose rate of 0.142–1.276 Gy/h and total doses of 0.284–2.552 Gy. A low-dose-rate HTO group was also exposed over 53 hours to HTO, yielding dose rates of 0.0055–0.0461 Gy/h and total doses of 0.28–2.45 Gy. The reference group was exposed to 180 kV x-rays at 113.2 Gy/h, with total doses of 0.5–3.0 Gy. All samples were assessed for chromosomal aberrations (dicentrics, centric rings, terminal and interstitial deletions) and chromatid aberrations (chromatid and isochromatid breaks, gaps, deletions, single fragments and chromatid exchanges). Analysis concentrated on dicentrics and centric rings, although data were also presented for terminal and interstitial deletions and chromatid aberrations. Chromatid aberrations were only observed in excess at the highest dose. They derived an RBE of 1.17 (95% CI: 1.13–1.21) for the acute exposure data. Prosser (1983) re-examined the data using a curve fitting program and calculated an RBE range of 1.91 ± 0.65 to 1.16 ± 0.1, although the data were insufficient in the lower dose range to permit calculation of an RBE_M.

Another lymphocyte study was conducted by Vulpis (1984), who assessed chromosome aberrations in human peripheral blood lymphocytes taken from a healthy male donor. The blood was exposed over 20 to 150 minutes to HTO at various concentrations, yielding dose rates of 0.75–2.80 Gy/h and total doses of 0.25–7.00 Gy. Concern was raised by the numerous washings

of the cells to remove the tritium, but the author said that evidence showed it did not appear to inhibit chromosome transformation. A comparison set of blood samples was exposed to 250 kVp x-rays at 0.0059 Gy/s (21.2 Gy/h), delivering total doses of 0.05–9 Gy. The x-ray exposure did not appear to be concurrent with the HTO treatment. However, the author argued that the x-ray irradiation was under the same conditions. All samples were assessed for chromosomal aberrations resulting in an RBE of 2.6 at a dose of 0.25 Gy, decreasing to 1.17 at 7 Gy.

In reassessing the Vulpis (1984) study, Little and Lambert (2008) pointed out that little detail was given on the x-ray irradiation regime and that the regime may not have been concurrent. Their recalculation of the limiting value gave an RBE_M of 8 (95% CI: 0.2–15.8). They also stated that if the x-ray reference irradiation had been delivered chronically, it would have been "somewhat less effective resulting in an elevation of these RBE estimates by a factor of 2 or so". Nonetheless, Little and Lambert (2008) thought the study had been reasonably well conducted and analyzed. The major weaknesses they raised were the absence of a control (unexposed) group, the lack of information on the x-ray reference group and, as previously mentioned, that the exposures were possibly not concurrent.

In his assessment of mice cell transformations Little (1986) exposed mice cells to HTO at concentrations from 0.93 to 19 MBq/mL, yielding a dose rate of 0.0025–0.10 Gy/h over periods from 5 to 168 hours. Another group of cells were exposed to 220 kV x-rays at a dose rate of 48 Gy/h, which was at a much greater dose rate than the HTO exposures. Little and Lambert (2008) pointed out that the dose rates and HTO exposure levels did not quite match. Although Little (1986) did not estimate an RBE, he did remark that x-rays were comparably less effective than HTO (by a factor of approximately 2) at low doses (0.25–1.0 Gy), but more effective, also by a factor of roughly 2, at higher doses. Little and Lambert (2008) commented that "[the study] appears to have been reasonably well conducted, but there is little or no statistical analysis, in particular no derivation of RBE, and the absence of a control (unexposed) group, as well as the lack of information on the x-ray reference group, is a distinct weakness."

In two papers, Kamiguchi *et al* (1990 a, b) reported how they assessed chromosome aberrations in nine sperm samples from five healthy Japanese male donors. Sperm samples were exposed over about 80 minutes to HTO at concentrations from 57 to 900 MBq/mL. Kamiguchi *et al* (1990 a, b) noted that a number of assumptions were necessary to calculate dose, so they calculated dose ranges of 0.25–3.74 Gy on maximal dosimetric assumptions and 0.14–2.06 Gy on minimal dosimetric assumptions. The original sperm samples were split, with half receiving HTO exposure and the other half kept as the control. To calculate the RBE, a second experiment consisted of 28 semen samples taken from 5 healthy Japanese male donors exposed at a dose rate of 26.2 Gy/h of 220 kVp x-rays, yielding total doses of 0.23–1.82 Gy. Histological samples were examined for chromosome breaks, fragments, deletions, gaps and exchanges. Break and fragment aberrations were predominant in all irradiations, followed by exchange, gap and deletion in that order. A dose-dependent relationship was shown for break, fragment and exchange aberrations, but not for deletion and gap aberrations. In comparing the HTO exposed group to that of the x-ray irradiated group, Kamiguchi *et al* (1990 a, b) derived RBE estimates as follows:

- for break-type aberrations: 1.14 and 2.07 for maximal and minimal dose estimates, respectively
- for exchange-type aberrations: 1.54 and 2.81 for maximal and minimal dose estimates, respectively

- for chromosome-type aberrations: 1.08 and 1.96 for maximal and minimal dose estimates respectively
- for chromatid-type aberrations: 1.65 and 3.00 for maximal and minimal dose estimates, respectively.

No confidence intervals were provided. Little and Lambert (2008) recalculated the RBEs using the mean dose between the maximum and minimum doses and got much the same RBEs, but with uncertainty limits (see Table 5.2.1 for their recalculated values). They thought the study was reasonably well constructed, but that the analytical analysis was poor. They also said that a chronic x-ray irradiation would have been less effective and would have resulted in an increased RBE of 2 or more.

5.2.4 *In Vitro* Studies Using Gamma Rays as the Reference Radiation

Ueno *et al* (1982) assessed three different cellular responses: cell survival, micronuclei and mutation to 6-thioguanine resistance in cultured mouse lymphocytic leukaemia L5178Y cells. The cells were exposed to HTO at concentrations ranging from 22–190 MBq/mL over various periods and to Cobalt-60 gamma radiation at 0.12–0.48 Gy/h over periods of 4.5 to nearly 100 hours. Total dose from tritium was not specified, but as interpreted in Little and Lambert (2008), the total dose read from the graphs infers a range of at least ~0.5 to ~11.0 Gy. Ueno *et al* (1982) reported RBEs of 1.5 for cell killing, 2.0 for micronuclei, and 1.8 for mutation induction. They also reported no difference in response for dose rates of 0.12 Gy/h and 0.24 Gy/h. Little and Lambert (2008) criticized the paper for leaving out key details and using suboptimal statistical analysis, and therefore advised caution in using the results.

Yamada *et al* (1982) studied the effect of chronic tritium radiation from HTO and Cobalt-60 gamma radiation on the pre-implantation mouse development *in vitro*. In assessing the survival of early (two-cell) embryos in mice, embryos received doses of about 0.6 to 16.3 Gy for both the HTO and Cobalt-60 irradiations (as reported in Little and Lambert, 2008). They derived RBE values of 1.09 with respect to the pronuclear embryo (the fertilized egg, prior to fusion of genetic material); 1.70 with respect to the early two-cell embryos; and 1.25 with respect to the late two-cell embryos (no confidence intervals were provided). Little and Lambert (2008) thought the study was sound, although they stated that its statistical analysis looked suboptimal.

Matsuda *et al* (1986) reported studies of the induction of chromosomal aberrations by or Cobalt-60 gamma radiation in the zygotes of eggs and sperm from mice and fertilized *in vitro*. Three to five hours after insemination, the zygotes were exposed to concentrations of HTO that ranged from 19 to 74 MBq/mL, for periods of 2 hours. This yielded a dose rate of 0.0425–0.17 Gy/h and the resulting doses were 0.085–0.34 Gy. Zygotes were also exposed to Cobalt-60 gamma rays at similar dose rates and times after fertilization, with a dose range of 0.052–0.295 Gy. Chromosomal aberrations (chromosome type, gap and break, fragment, exchange), and chromatid type (gap and break, minute, exchange) were counted in all samples. Matsuda *et al* (1986) derived RBE values of 2.0 for gamma radiation and 1.6 for x-rays (no confidence intervals provided) in comparison with the results from a previous study (Matsuda, 1985) where the dose rate was 34.2 Gy/h. Little and Lambert (2008) reassessed the data using a simple linear

Poisson model and calculated an RBE of 1.62 (95% CI: 1.30–2.07) which is close to the Matsuda *et al* (1986) estimate. Contrary to Matsuda, Little and Lambert did not find any evidence of linear-quadratic curvature of the response.

Tanaka *et al* (1994) investigated the HTO dose-response relationship for aberrations in human lymphocytes and bone marrow cells at low *in vitro* radiation doses ranging from 0.1 to 1 Gy. Samples included blood from 13 healthy donors and bone marrow cells from 19 subjects with no history of haematological disease. The lymphocytes were exposed to HTO concentrations from 5.6–138.5 MBq/mL, yielding dose rates of 0.0120–0.30 Gy/h. Exposures from 6.7–80 hours gave doses of 0.14–2.10 Gy. Similarly, the bone marrow cells were exposed to HTO at 555 MBq/mL, yielding a dose rate of 0.2 Gy/h and total doses of 0.13–1.11 Gy. For a reference radiation assessment, Tanaka *et al* (1994) exposed human lymphocytes to Cobalt-60 and Cesium-137 gamma radiation, and human bone marrow cells to both HTO and Cobalt-60 gamma radiation at dose rates of 1.2 Gy/h and 0.012 Gy/h respectively. It appears that they needed to use the two gamma radiation sources to provide the desired dose range. Total doses for lymphocytes ranged from 0 to 2.1 Gy from HTO, and from 0.05 to 4.0 Gy from Cobalt-60 gamma rays. Bone marrow exposures from HTO gave 0 to 1.11 Gy and 0.25 to 2.0 Gy from the Cobalt-60 radiation. Tabulated doses from Cesium-137 exposures were not given, but from the graphs, Little and Lambert (2008) interpreted that doses were in the range of 0.2–1.5 Gy. Lymphocytes were scored for unstable chromosome aberrations such as dicentrics, centric rings, acentric rings, and fragments. Similarly, bone marrow cells were scored for chromatid breaks, chromatid gaps, chromatid exchanges, chromosome breaks and chromosome gaps. For the blood cells, Tanaka *et al* (1994) reported RBE values for HTO beta rays relative to Cobalt-60 and Cesium-137 gamma rays of 2.0–2.7 for centric, dicentric and centric/dicentric chromosome aberrations in blood lymphocytes. For the bone marrow assessment, the RBE was 1.13 for chromosomal and 3.1 for chromatid aberrations in bone marrow using only Cobalt-60 as the reference. The Cesium-137 comparison gave an RBE relative to HTO of 2.0 at a dose rate of 0.02 Gy/min. Tanaka *et al* (1994) also looked at the dose rate effect on the RBE and summarized that their study "showed a clear dose rate effect from HTO β [beta] rays" and that the RBE for lymphocyte exposures should be considered a value of 2 for low-HTO dose rates (0.20 mGy/min) and a value of 3 at high-HTO dose rates (20 mGy/min).

The RBEs from Tanaka *et al* (1994) were considerably higher than those from similar studies, such as those performed by Dobson and Kwan (1978), Vulpis (1984) and Prosser *et al* (1983). Tanaka *et al* (1994) spent considerable effort trying to reconcile the differences. Part of the rationale was the assumed water content of the cell in the dosimetry calculations, but significant differences remained even when they recalculated the results of the other studies. Some of this remaining difference was attributed to the dose rate of the reference radiations.

While Little and Lambert (2008) reviewed the actual experiment favourably, they criticized the statistical analysis of Tanaka *et al* (1994), in that the researchers did not include uncertainty intervals and fitted the data to a linear model by ordinary least squares. Little and Lambert (2008) reanalyzed the data and did not get very different results from those reported by Tanaka *et al* (1994). However, they pointed out that Tanaka *et al* (1994) did not provide sufficient data for the Cesium-137 reference group to permit reanalysis, particularly for the estimation of RBE_M.

Table 5.1.1: *In Vivo* Studies using X-rays as the Reference Radiation

Study	Biological Endpoint	Radiation	Reference Radiation	Dose Range (Gy)	Tritium RBE (95% Confidence Interval Where Indicated)
Johnson *et al* (1995)	Myeloid leukaemia in mice	HTO and chronic x-rays	200/150 kVcp x-ray	0.85–3.04 β, 1.06–2.64 X	1.24 (0.63–1.85)
Lambert (1969)	Spermatogonial survival in mice	HTO and chronic x-rays	200 kVp x-ray	0.05 β, 0.011 X	2.3
Lambert (1969)	Spermatogonial survival in mice	^{3}HTdR and chronic x-rays	200 kVp x-ray	0.084 β, 0.011 X	1.3
Gragtmans *et al* (1984)	Cumulative incidence mammary tumours in S-D rats	HTO, acute and chronic x-rays	200 kVp x-ray	0.46–3.85 β, 0.57–1.78 X (acute) 0.29–2.00 X (chronic)	1.17 (0.82–1.52) 0.68
Gragtmans *et al* (1984)	Cumulative percentage mammary tumours in S-D rats	HTO, acute and chronic x-rays	200 kVp x-ray	0.46–3.85 β, 0.57–1.78 X (acute) 0.29–2.00 X (chronic)	1.35 (0.89–1.60) 0.83
Chopra and Heddle (1988)	Chromosome aberrations in peripheral blood in mice	HTO and chronic x-rays	250 kVp x-ray	1.5–6.0 β, 1.5–6 X	1.14 (0.8–1.5)
Chopra and Heddle (1988)	Chromosome aberrations in spermatogonia in mice	HTO and chronic x-rays	250 kVp x-ray	1.5–4.5 β, 1.5–4.5 X	1.21 (0.8–1.9)
Kozlowski *et al* (2001)	Chromosome aberrations in bone marrow in mice: total	HTO and acute x-rays	250 kVp x-ray	0.4–0.7 X, 0.5 γ	0.56 (0.31–0.96)

β Tritium dose
X X-ray dose
γ Gamma dose
*** recalculation by Prosser et al (1983)*

5.1.2: *In Vivo* Studies using Gamma Rays as the Reference Radiation

Study	Effect	Radiation	Reference Radiation	Dose Range (Gy)	Tritium RBE (95% Confidence Interval Where Indicated)
Furchner (1957)	Mortality in mice	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	5.3–16.5 β	1.7
Dobson and Kwan (1976; 1978)	Oocyte survival in mice	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	0.07–0.88 β, 0.22–1.25 γ	2.8
Carr and Nolan (1979)	Testes weight loss in mice	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	0.14–0.58 β, 0.578 γ	1.43 (1.06–1.80)
Carr and Nolan (1979)	Testes weight loss in mice	^{3}HTdR and chronic γ	Cobalt-60 γ (tritium simulator)	0.03–0.70 β, 0.578 γ	2.07 (1.58–2.56)
Zhou *et al* (1986)	Dominant lethal mutations in female mice	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	0.04–0.91 β, 0.53–2.70 γ	2.5 2.94 (2.00–4.28)*
Ijiri (1989)	Survival of small intestinal cells in mice	HTO and chronic γ	Cesium-137 γ (tritium simulator)	0–0.2 β, 0.0–0.4 γ	2.1 (1.7–2.5) 1.6 (1.2–2.0)*
Ijiri (1989)	Survival of descending colon cells in mice	HTO and chronic γ	Cesium-137 γ (tritium simulator)	0–0.2 β, 0.0–0.4 γ	1.8 (1.4–2.2) 1.4 (1.2–1.6)*
Satow *et al* (1989a)	Oocyte survival in mice	HTO and chronic γ	Cesium-137 γ (tritium simulator)	0.04–0.25 β, 0.06–0.21 γ	1.1–3.5
Satow *et al* (1989a)	Teratogenic effects in rats	HTO and chronic γ	Cesium-137 γ (tritium simulator)	2.0–6.0 β, 1.75–6.80 γ	2.6 1.01 (0.57–1.78)*
Zhou *et al* (1989)	Dominant lethals (oocytes)	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	0.2–0.6 β, 0.74–2.07 γ	3.4–2.8
Zhou *et al* (1989)	Dominant lethals (spermatogonia)	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	0.2–0.60 β, 0.74–2.07 γ	3.88–1.61
Zhou *et al* (1989)	Dominant skeletal mutations	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	0.19–1.01β, 0.74–2.87 γ	3.91–3.48

Study	Effect	Radiation	Reference Radiation	Dose Range (Gy)	Tritium RBE (95% Confidence Interval Where Indicated)
Zhou *et al* (1989)	Spermatogonial survival	HTO and chronic γ	Cobalt-60 γ (tritium simulator)	0.19–1.01β, 0.74–2.87 γ	2.0–1.4
Seyama *et al* (1991)	Cancer in mice	HTO and chronic-γ	Cesium-137 γ (tritium simulator)	0.27, 2.7 β and γ	2.5**

** recalculated value by Little and Lambert (2008)*
*** caculcated at 500 days*

Table 5.2.1: *In Vitro* Studies Using X-rays as the Reference Radiation

Study	Effect	Radiation	Reference Radiation	Dose Range (Gy)	Tritium RBE (95% Confidence Interval Where Indicated)
Prosser *et al* (1983)	Chromosome aberrations in human lymphocytes	Acute HTO and acute x-ray	250 kVp x-ray	2–4 β (30 min) 0.1–4.1 X (24 hr)	1.13 (0.78–1.48) RBE_M
Bocian *et al* (1978)	Chromosome aberrations in human lymphocytes	HTO and acute x-ray	180 kV x-ray	0.28–2.45 β, 0.5–3.0 X	1.17 (1.13–1.21) 1.91 (0.64–3.18)**
Vulpis (1984)	Chromosome aberrations in human lymphocytes	HTO and acute x-ray	250 kVp x-ray	0.25–7.0 β, 0.05–9.0 X	2.6 at 0.25 Gy, 1.10 at 7 Gy 8.0 (0.2–15.8)*
Little (1986)	Transformation in mouse cells	HTO and acute x-ray	220 kV x-ray	0.25–5.0, 0.5–4.0 X	< 1–2
Kamiguchi *et al* (1990a, b)	Chromosome-type aberrations in human sperm	HTO and acute x-ray	220 kVp x-ray	0.14–2.06 β, 0.25–3.74 β, 0.23–1.82 X	1.08 max dose est, 1.96 min dose est 1.39 (1.26–1.54)*
Kamiguchi *et al* (1990a)	Chromatid-type aberrations in human sperm	HTO and acute x-rays	220 kVp x-ray	0.14–2.06 β, 0.25–3.74 β, 0.23–1.82 X	1.65 max dose est, 3.0 max dose est 2.17 (1.73–2.73)*

Study	Effect	Radiation	Reference Radiation	Dose Range (Gy)	Tritium RBE (95% Confidence Interval Where Indicated)
Kamiguchi *et al* (1990a)	Chromosome breakage aberrations in human sperm	HTO and acute x-ray	220 kVp x-ray	0.14–2.06 β, 0.25–3.74 β, 0.23–1.82 X	1.14 max dose est, 2.07 min dose est 1.47 (1.33–1.62)*
Kamiguchi *et al* (1990a)	Chromosome-exchange aberrations in human sperm	HTO and acute x-ray	220 kVp x-ray	0.14–2.06 β, 0.25–3.74 β, 0.23–1.82 X	1.54 min dose est 2.81 min dose est 1.96 (1.49–2.62)*

β–Tritium dose ** recalculation by Little and Lambert*
X– X-ray dose *** recalculated by Prosser (1983)*

Table 5.2.2: *In Vitro* Studies Using Gamma Rays as the Reference Radiation

Study	Effect	Radiation	Reference Radiation	Dose Range (Gy)	Tritium RBE (95% CI Where Indicated)
Ueno *et al* (1982)	Cell survival in mammalian cells	HTO and chronic γ	Cobalt-60 γ	~1.0–11.0 β, ~0.5–11.0 γ	1.5
Ueno *et al* (1982)	Micronuclei in mammalian cells	HTO and chronic γ	Cobalt-60 γ	~1.0–8.0 β, ~2.0–9.0 γ	2.0
Ueno *et al* (1982)	Mutation induction in cells	HTO and chronic γ	Cobalt-60 γ	~1.0–11 β ~0.5– ~1 γ	1.8
Yamada *et al* (1982)	Mouse pronuclear embryo cell survival	HTO and chronic γ	Cobalt-60 γ	0.6–16.3 β, γ*	1.09
Yamada *et al* (1982)	Mouse 2-cell embryo survival	HTO and chronic γ	Cobalt-60 γ	0.6–16.3 β, γ*	1.70
Yamada *et al* (1982)	Mouse late 2-cell embryo survival	HTO and chronic γ	Cobalt-60 γ	0.6–16.3 β, γ*	1.25
Matsuda *et al* (1986)	Chromosome aberrations in mouse zygotes	HTO and chronic γ	Cobalt-60 γ	0.09–0.34 β, 0.05–0.30 γ	2.0 1.62 (1.30–2.07)*

Study	Effect	Radiation	Reference Radiation	Dose Range (Gy)	Tritium RBE (95% CI Where Indicated)
Tanaka *et al* (1994)	Dicentric chromosome aberrations in human lymphocytes	HTO and chronic γ	Cobalt-60 and Cesium-137 γ	0.14–2.10 β, 0.05–4.0 γ	2.3 2.39 (2.20–2.59)*
Tanaka *et al* (1994)	Chromosome aberrations in human lymphocytes: centric rings	HTO and chronic γ	Cobalt-60 and Cesium-137 γ	0.14–2.10 β, 0.05–4.0 γ	2.7 3.14 (2.56–3.86)*
Tanaka *et al* (1994)	Chromosome aberrations in human lymphocytes: dicentrics and centric rings	HTO and chronic γ	Cobalt-60 and Cesium-137 γ	0.14–2.10 β, 0.05–4.0 γ	2.4 2.52 (2.33–2.72)*
Tanaka *et al* (1994)	Chromosome aberrations total in human bone marrow cells	HTO and chronic γ	Cobalt-60 and Cesium-137 γ	0.13–1.11 β, 0.25–2.0 γ	1.13 1.30 (0.96–1.76)*
Tanaka *et al* (1994)	Chromosome aberrations total in human bone marrow cells	HTO and chronic γ	Cobalt-60 and Cesium-137 γ	0.13–1.11 β, 0.25–2.0 γ	3.1 4.96 (3.73–6.59)*

** recalculation by Little and Lambert*

5.2.5 Relative Biological Effectiveness Studies – Summary

Table 5.3 provides a statistical summary of the RBE determinations under many different experimental variables, such as acute and chronic exposures, gamma ray or x-ray as the reference radiation, *in vitro* and *in vivo* conditions, etc. Column 2 contains the mean RBE of studies with similar experimental conditions as well as the 95% confidence interval that indicated the statistical significance in comparing different experimental regimes. When Little and Lambert (2008) recalculated RBE values, these are provided in Column 3 of the table. In addition to the studies reviewed here, the studies used to calculate the mean RBE values, which were reviewed by Little and Lambert (2008) and Straume and Carsten (1993), are included in Columns 4 and 5, respectively.

As noted earlier in the review of Little and Lambert (2008), caution is warranted when averaging and calculating confidence intervals of measurements that may not be independent determinations of the same quantity. For example, an RBE value for lymphocyte aberrations

is a much different determination than an RBE value for cell survival. Combining the measurements may lead to false confidence in the interval values. However, where a broad value is desired (for example, for radiation protection purposes) there is qualitative value.

Straume and Carsten (1993) only calculated an aggregate mean for two sets of studies: those using x-rays as a reference radiation and those using gamma radiation as a reference radiation. For this report, 95 % confidence intervals were calculated, and the mean and 95% confidence limits were also calculated for some other groups of studies (indicated by an asterisk [*] in the table).

To permit computation of a mean value and confidence interval, an average value was used whenever a range was given (for example, Kamiguchi, 1990a), the exception to this would be whenever the RBE_M was determined; in such cases, the RBE_M is used directly. Due to the small sample size, some of the averages were greatly affected by one or two outlying studies; for example the study by Kozlowski *et al* (2001) that looked at chromosome aberrations in mice bone marrow had four RBE determinations below 1, with one value at 0.49. Conversely, Little and Lambert's recalculation of the Vulpis (1984) data on chromosome aberrations gave an RBE of 8. Note that there were no tritium radiation *in vitro* RBE studies with acute gamma radiation as the reference radiation, nor were there chronic *in vitro* studies with a chronic x-ray reference radiation.

Table 5.3: Statistical Summary of Studies Determining the RBE of Tritium Radiation Under Different Experimental Conditions (95% confidence interval provided in brackets)

	Mean (95% Confidence Interval)	Mean with Little & Lambert Recalculations	Little and Lambert (2008)	Straume and Carsten (1993)
All *in vivo*	1.84 (1.49–2.18)	1.75 (1.40–2.11)		
All *in vitro*	1.85 (1.61–2.08)	2.14 (1.45–2.84)		
In vivo acute x-ray ref.	0.81 (0.46–1.17)	–	0.56 (0.31–0.96)	
In vivo chronic x-ray ref.	1.34 (0.94–1.74)	–	1.17 (0.96–1.39)	
In vivo chronic gamma ref.	2.36 (2.03–2.68)	2.21 (1.80–2.72)	1.63 (1.49–1.77)	
In vitro gamma ref.	1.91 (1.56–2.27)	2.11 (1.50–2.72)	1.98 (1.85–2.12)	
In vitro acute x-ray ref.	1.80 (1.39–2.20)	2.34 (0.94–3.74)	1.45 (1.32–1.58)	
All chronic x-ray ref.	1.34 (0.94–1.73)	Insufficient data		1.67* (1.31–2.03)*

	Mean (95% Confidence Interval)	Mean with Little & Lambert Recalculations	Little and Lambert (2008)	Straume and Carsten (1993)
All acute x-ray ref.	1.28 (0.93–1.63)	1.56 (0.70–2.42)		1.69* (1.26–2.12)*
All chronic gamma ref.	2.15 (1.89–2.41)	2.16 (1.80–2.52)		2.36* (1.96–2.76)*
All acute gamma ref.	Insufficient data	Insufficient data		1.95* (1.14–2.77)*
All chronic	2.00 (1.75–2.25)	2.01 (1.69–2.33)		
All acute	1.28 (0.53–1.64)	1.56 (0.70–2.42)		
All x-ray ref.	1.44 (1.15–1.73)	1.69 (0.97–2.42)	1.17 (0.96–1.39)	1.8 (1.44–2.16)*
All gamma ray ref.	2.15 (1.90–2.41)	2.16 (1.81–2.51)	2.19 (2.04–2.33)	2.3 (1.94–2.67)*
RBE all studies combined	1.88 (1.66–2.09)	2.01 (1.66–2.37)		2.11* (1.82–2.4)*
Cancer studies with chronic gamma			2.49 (2.00–2.98)	
Cancer studies with chronic x-ray			1.19 (0.88–1.49)	
All except studies of survival and inactivation, with chronic gamma ray			2.19 (2.04–2.33)	
All except studies of survival and inactivation, with chronic x-ray			1.17 (0.96–1.39)	

** indicates values were calculated for this report*

Not surprisingly, there is little difference between the mean values calculated here and those of Little and Lambert (2008) and Straume and Carsten (1993) since the three reviews used largely the same underlying studies for their calculations. Notwithstanding, a number of observations can be drawn from the table:

- There is no significant difference between *in vivo* and *in vitro* studies.
- There are significant differences in RBE values depending of whether the reference radiation is x-ray or gamma radiation and if the reference radiation was delivered chronically or acutely. This was also found in other reviews.

- The studies with a chronic gamma reference radiation have a mean RBE of about 30% higher than those that used chronic x-ray as the reference radiation. Unfortunately, there are not enough studies to compare chronic gamma radiation as the reference with acute gamma irradiation, other than that using the Straume and Carsten (1993) data. Even with this, there is a large confidence interval, due partly to the availability of only four studies.
- With x-rays as the reference radiation, the mean RBE is about 1.3 to 1.5 and with a gamma radiation reference, the RBE is about 2.2. If all the RBE studies are combined —including studies using either x-rays or gamma radiation as the reference — the biological effectiveness of tritium radiation is about 2, although admittedly this calculation takes some liberty in statistical application.

5.3 Factors Affecting RBE

As seen in Table 5.3, the calculated RBE value for tritium can vary by as much as a factor of five from study to study. This is due partly to varying levels of tissue radiosensitivity, including sensitivity to low-energy beta radiation. Tritium's RBE value is also affected by differences in energies of the reference radiation, dose, dose rate and choice of biological end-point. In any one determination of the RBE, all these factors need to be kept as constant as possible, but when it comes to comparing RBEs, it is difficult to ascertain which determination is more relevant. These issues are discussed in the following sections.

5.3.1 Reference Radiation

To determine the RBE of a specific type of radiation, a reference radiation must be selected to enable a comparison. For this function, a typical selection is low-LET radiation; for example, 200–250 kVp x-rays or gamma radiation from Cobalt-60 (1,173 and 1,332 keV) or Cesium-137 (662 keV). As shown by the tritium RBE determinations, there is a significant difference in the relative effectiveness of tritium's beta particles.

This difference in effectiveness is made readily apparent by looking at the amount of energy deposited. For example, ICRP Publication 92 (2003) states:

> *"The significant difference… …between the (dose-average) LET of Cobalt-60 (about 0.4 keV/µm) or Cesium-137 gamma rays (about 0.8 keV/µm), and that of 200 kV X-rays (about 3.5 keV/µm) makes it clear that RBE values can differ substantially depending on which photon radiation is taken as reference."*

Indeed, the ICRP Publication 92 review of studies by Bond *et al* (1978), Sasaki *et al* (1989), Sasaki (1991), and Schmid *et al* (2002), demonstrates that the RBE varies significantly between 250 kVp x-rays, Cesium-137, gamma rays and Cobalt-60 gamma rays. ICRP Publication 92 makes the following argument in paragraph 28 for choosing high-energy gamma radiation:

"While there is no need for an exclusive convention, it is nevertheless convenient to adopt a reference radiation that is understood to apply whenever there is no explicit statement to the contrary. There are practical arguments to favour gamma rays for this purpose. It is difficult and

expensive to determine the initial slope of dose responses of the induction of cancer in animals, especially with low-dose-rate X-rays rather than low-dose-rate gamma rays. For this and a number of other reasons, hard gamma rays are preferable as the reference radiation because:

- *most experimental animal studies of cancer induction and life shortening (and deterministic effects) have been carried out with gamma rays, and, importantly, some with exposures at low dose rates;*
- *the most important body of data for estimating radiogenic cancers in humans are from the atomic bomb survivors who were exposed to gamma rays;*
- *hard gamma rays have the lowest LET (dose average LET, LD, 0.4 keV/μm or less) among photon radiations;*
- *the distribution of the deposition of energy from gamma rays in large fields is more uniform than with X-rays."*

Notwithstanding these points, the ICRP's most recent recommendations in Publication 103 (2007) state:

"(115) ***Reference radiation.*** *Values of RBE obtained experimentally depend on the reference radiation chosen. Generally, low-LET photon radiation is taken as the reference, although no specific energy has been agreed upon for this purpose. When radiation weighting factors were selected for Publication 60, a broad range of experimental RBE data using either high energy X-rays above about 200 kV or cobalt-60 or caesium-137 gamma radiation was considered (see Annex B). This approach is also used in these recommendations; although it should be recognized that experimentally different RBE values can result depending upon the choice of the reference radiation between X-rays and higher energy gamma radiation (e.g., cobalt-60)."*

It is clear that the differences between the effectiveness of gamma radiation and x-rays are well known and have been reasonably well quantified. It is also evident that the ICRP does not see the need to use one reference radiation over another in its approach to radiation protection. More specifically, the ICRP uses a broad approach, using RBE data as an input to the choice of w_R values for use within its recommended protection system. This is discussed in more detail in Chapter 7.

5.3.2 Dose and Dose Rate Effects

As ICRP Publication 60 explains, most risk estimates of radiation exposure have been derived from populations who have received relatively high doses of radiation at high dose rates. The radiological risk model proposed by the ICRP, the so called linear, non-threshold model, projects a straight line from the lowest doses where a risk has been identified (about 100 Gy for atomic bomb survivors) to background dose. This model provides a risk estimate for those doses where, due to scientific uncertainty, it is not possible to definitively identify effects that might be caused by radiation exposure. However, ICRP Publication 60 argued that "there was sufficient evidence to justify making an allowance for non-linearity when interpreting dose data from low-LET radiation at high doses and high dose rates to give estimates of the probability of effects at low dose and low dose rates". On this basis, for doses less than 0.2 Gy and dose rates less than 0.1 Gy/h, the ICRP decided to reduce the risk probability coefficients determined

from high doses and high dose rates by a factor of 2. However, they admitted that this value was somewhat arbitrary and potentially conservative. The reduction factor was called the Dose and Dose Rate Effectiveness Factor (DDREF), and it was included in the probability coefficients for all equivalent doses resulting from absorbed doses below 0.2 Gy and for higher doses, when the dose rate was less than 0.1 Gy/h.

Since doses from intakes of tritium are low-LET and generally considered chronic irradiation, the DDREF of 2 is taken into account when calculating dose due to tritium. Unfortunately there is not much experimental evidence to dispute or concur with a DDREF of 2 for tritium exposures.

In Publication 103 (2007), the ICRP reasoned that "the statistical precision afforded by these studies and other uncertainties associated with the ability to adequately control for confounding factors do not allow for a precise estimate of the DDREF at this time" and it continued to use a DDREF of 2.

Trabalka and Kocher (2007) discussed a DDREF of 2 for low-LET radiations, including tritium, at some length. They reviewed the data on energy dependence of the DDREF for low-LET radiation, such as that emitted by tritium, and discussed the implications for cancer risk assessments. Their review indicated that while the data were limited, there was evidence of a general trend for decreasing DDREF values with decreasing photon energy, as well as an increasing value for RBE_M. They also noted that the DDREF for tritium beta particles is about 20% less than the DDREF of acute 200 kVp x-rays.

Through their review of various studies, Trabalka and Kocher (2007) also revealed that the dose rate effectiveness factor (DREF) may differ considerably from the low dose effectiveness factor (LDEF) under chronic or fractionated exposures. This would possibly invalidate the assumption that a LDEF and a DREF can be combined into a single quantity, the DDREF. While these researchers pointed out they did not seek to resolve the issues about DDREF for cancer risk assessments, they wanted to emphasize the need for further investigation of the energy dependence of DDREF and RBE values, using endpoints relevant to cancer induction in humans. They also emphasized the need to investigate the validity of the linear-quadratic dose-response model, which is used to derive RBEs in many critical radiobiological studies, given the evidence that this model may be incorrect.

With respect to dose rate, Little and Lambert (2008) point out that because tritium doses are delivered chronically, more importance should be attached to studies where the reference group's radiation was also delivered chronically — and at a similar (normally exponentially decreasing) dose rate where possible. For most of the studies reviewed by Little and Lambert (2008), and in this report, the doses and dose rates from the tritium and reference radiations were at much higher levels than those received in occupational or public exposure settings.

The RBE_M is ideally estimated by the initial slopes of the tritium and reference radiation dose response curves. However, the slopes of these lines at low doses are very difficult to establish. Different radiations, different doses and dose rates, and different endpoints produce different responses, some being straight, some being curved. Biological responses to x-ray and gamma

ray exposures are generally curvilinear, typically a gradually rising curve becoming linear after a certain dose. This type of curvilinearity could result in a greater difference in response between the reference radiation and the radiation being evaluated for an RBE (for example, tritium beta particles), especially if the radiation under evaluation had a linear response. If this occurs, then the RBE would be greater at doses relevant to radiation protection, that is at lower doses and dose rates. Little and Lambert (2008) acknowledged the impact of curvilinearity and, where possible, tested the dose response curves for curvature or otherwise tried to fit models over the selected dose ranges.

In summary, not enough is known about how dose and dose rate affect RBE to make a general conclusion. However, it seems reasonable that when deriving RBE estimates, to give greater weight to RBE determinations with dose and dose rates closest to those, in an occupational or public setting.

5.3.3 Dosimetric Considerations

Any determination of an RBE requires an estimate of the absorbed dose. Absorbed dose is defined as the amount of radiation energy deposited per unit mass of an absorbing material. The SI unit for absorbed dose is the gray (Gy), which is equal to 1 joule of energy absorbed per kilogram of absorbing material, or about 6.24×10^{12} keV per gram. It is reasonably straightforward to estimate the absorbed dose for HTO, as it is established that HTO behaves like normal water and distributes itself reasonably uniformly throughout the body and in cells. Knowing the concentration of tritium in the cellular water permits the determination of the amount of energy released within a specified volume.

A major source of uncertainty in tritium dosimetry is the estimate of the water content of the organism for *in vivo* studies or the cell for *in vitro* studies. The National Council on Radiation Protection and Measurements (NCRP) (1979) has suggested a factor of 0.6 to 0.75 for cell water content. Researchers typically assume a factor of 0.70 for water content. It is possible to compare dose effects among different studies by recalculating dose values, as long as the researchers specified the dose factors they used in their work. Unfortunately, the assumed water content was not always provided in the studies reviewed here, and this could account for as much as 10 % of the difference between RBE estimates. In addition, there will be differences between organ/tissues in their water content; therefore, the dose will also differ, leading to additional uncertainties with *in vivo* doses.

5.3.4 Experimental Environments

Generally speaking, *in vitro* studies (studies done on cells outside the body) are used to investigate specific cellualer functions or mechanisms. It is easier to control the conditions of these types of studies, so fewer variables might affect the results. While, reactions may be amplified, results should be more evident. Conversely, *in vivo* experiments (studies done within a body) will show the overall effect of the treatment on the organism, and other systems within the organism (such as blood supply) may mitigate the effect.

For radiation protection purposes, *in vivo* studies would be more appropriate, since the organism is irradiated as a whole, which closely mimics the usual case in occupational or public settings. As shown in Table 5.3, the overall *in vitro* RBE is slightly higher than that derived from the *in vivo* studies, although the difference is not statistically significant. Differences in RBE values can be expected according to the sensitivity of the species and strain of animal used for *in vivo* studies. Both *in vivo* and *in vitro* studies have merits, but *in vivo* studies are preferred because they relate to tissue/organ responses, which may include ameliorating or accentuating effects of tissue environments and cell-cell interactions.

5.3.5 Biological Endpoints

Endpoints of most interest in radiological protection are those, such as cancer that are closest to the expected effects induced by radiation in an occupational or public setting. Many studies reviewed here examined cell death in known radiosensitive tissues. Unfortunately, cancer induction studies in test animals are complicated by variability in animal strains and latency periods (the time from the exposure to the carcinogen until the cancer outcome is detected) that may exceed the natural lifetime of the animal. Only three of the studies identified here used cancer as an endpoint (Johnson *et al*, 1995; Gragtmans *et al*, 1984; Seyama *et al*, 1991). Some of these studies are thought to have accelerated cancer incidence rather than induce the disease itself (which is, nevertheless, a non-trivial, adverse effect).

Cell mutations and chromosome aberrations are likely the next most relevant endpoints for radiation protection, as they represent chromosome damage that could lead to cancer in different tissues. However, as Little and Lambert (2008) noted, chromosome damage may be only one of many steps in carcinogenesis. Hill (2004) also pointed out that many studies use the induction of dicentric aberrations as an endpoint, because it is a reliable and repeatable method for comparing biological response. The radiation response of chromosmome abberations has supported the assumption of a linear-quadratic dose-response model and assumptions about radiation weighting factors for neutrons. However, from a radiation protection standpoint, these effects are lethal to the cell and so may be less relevant to risk assessment. Studies of cell death in known radiosensitive tissues (such mouse oocytes, spermatogonia) are even less relevant due to higher dose regime; nevertheless the RBE values for these studies are similar to those of other studies.

In summary, more research using endpoints relevant to occupational and public settings — such as *in vivo* cancer induction or cell mutation induced *in vitro* — is required. RBE values from such studies would provide information that would be more relevant to risk assessments.

5.3.6 Electron Energy and Ionization Path Lengths: Why Tritium Radiation Is More Effective Than Gamma Radiation

The experimental evidence seen in this and other reviews provides a convincing argument that the RBE for tritium radiation is greater than that of 200–250 kVp x-rays and Cobalt-60 or Cesium-137 gamma radiation.

The amount of energy lost per unit distance is referred to as the linear energy transfer (LET), often expressed in units of keV/µm. Interactions between radiation and molecules will cause ionization in some of the molecules. Electromagnetic radiation, such as gamma rays and x-rays has a much lower LET than alpha particles. As Table 5.4 indicates (ICRU, 1970), low-energy photons and electrons release more energy per micrometre than higher-energy photons. However, the lower-energy photons release much less total energy and travel much shorter distances than their higher-energy counterparts.

Table 5.4: Track Average LET in Water for Various Radiations Based on a Cut-Off Energy, Δ, of 100 eV (based on ICRU, 1970)

Radiation	$\overline{L}_{\Delta,T}$ (keV/µm)
Cobalt-60 γ radiation (1,173 and 1,332 keV)	0.22
200 kVp x-rays	1.7
Tritium beta radiation (mean 5.7 keV)	4.7
50 kVp x-rays	6.3

Photons (gamma rays and x-rays) act indirectly and the type of interaction is energy related, causing molecular ionization through photon absorption (photoelectric and pair production) or scattering events (Compton interactions). Particle radiation, such as tritium's beta radiation, can damage key molecules like DNA through both direct and indirect interaction. This damage occurs from the production of free radicals (for example, hydroxyl) caused by the ionization of water molecules — which may, in turn, damage DNA.

The most significant cellular damage caused by radiation is breakage of the DNA molecular chain. DNA is a double helix, meaning there are two corresponding and linked molecular chains containing corresponding nucleic acids. Radiation-induced DNA damage usually results in damage to the base molecules, single strand breaks (SSBs), double strand breaks (DSBs), DNA-protein cross-links, or a combination of some or all of these. The degree of damage is related to the density of the radiation track. A large deposition of energy within a DNA molecule may cause a cluster of damage. If the damage is great, then it may not be fully reparable and can cause cell death or permanent chromosome damage.

Using Monte Carlo codes, Moiseenko *et al* (2001a) modeled DSBs and SSBs in cells exposed to tritium and low-energy photons. Their major finding was that a deposition of 10 eV by direct energy deposition could result in a SSB. They further studied base damage associated with DSB and were able to differentiate between simple DSBs and complex DSBs, finding that complex DSBs were accompanied by more extensive base damage compared to simple DSBs.

Moiseenko *et al* (2001b) later developed a Monte Carlo model to calculate yields of DSBs in DNA following irradiation from Cesium-137 gamma radiation, orthovoltage x-rays (typically 150–300 kVp) and tritium beta particles. The calculated RBE for DSB production for tritium

(with Cesium-137 as the reference) was 1.2 for the total DSB yield and 1.3 for complex DSBs. They explained that x-rays and tritium beta particles tend to deposit energy in a more clustered fashion, and there is a higher probability of a few energy deposition events within a few nanometres. They concluded that tritium beta-particles are more efficient in producing DNA DSB compared to Cesium-137 gamma rays and that the relative effectiveness is even greater for the production of complex DSBs. No difference was observed between tritium beta-particles and 70 keV photons representative of orthovoltage x-rays.

Doing similar work, Nikjoo *et al* (2001; 2002a, b) used models to calculate the DNA damage produced by 100 eV–100 keV electrons. They found that the direct energy deposition in DNA represented a larger proportion of the damage at the lower energy, although the contribution from the hydroxyl radicals was also substantial — both in terms of the absolute yield of the breaks and the complexity of the damage.

Nikjoo *et al* (2002b) later reported that while most of the damage caused by low-energy electrons and ultra-soft x-rays is in the form of SSB that are easily repaired. However, the researchers also concluded that a significant portion (~20-30%) of the DSB were complex, with several strand breaks within a few base pairs of each other. They explained that this clustered damage is postulated to be largely responsible for the greater RBE of high-LET radiations.

Because ultra soft x-rays produce secondary electrons in the cell similar in density to those of tritium, these x-rays can be used to mimic the effects of tritium beta radiation (HPA, 2007). Similar studies —such as those by Goodhead and Nikjoo (1990), Hill *et al* (2001), and Hill (2004) — showed that within a range of biological endpoints, RBE values typically increase with decreasing ultra-soft x-ray energies.

Nikjoo and Goodhead (1991) suggested that the most significant biological effects are caused by sizeable clusters of energy deposition and that the net biological effect increases with the severity of the initial damage. Most of this type of damage is thought to be due to low energy secondary electrons that are produced as the radiation slows down. They concluded by stating that the lower-energy electrons are more effective than higher-energy ones (for example greater than 100 keV) in producing complex damage and that this was observed in experiments with ultrasoft x-rays.

Another important aspect is the location of the tritium atom when it disintegrates. HTO will be relatively evenly distributed throughout tissues and cells. On the other hand, organically bound tritium (OBT) may be incorporated into important molecules such as DNA. The release of a beta particle from that position has a greater probability of causing damage than an HTO molecule in the cellular fluid, for example. With respect to the impact of OBT, Chen (2006) used a Monte Carlo code to generate simulated tracks in order to compare the dose mean linear energies (keV/µm) for HTO and OBT molecules in spherical regions with diameters of 10 nm to 2 µm. The results indicated that a mean linear energy for OBT was a factor of 1.7 higher than for HTO, using the assumption that the extent of the increase would depend on the OBT molecule's location within the cell.

Hill (2004) reviewed several studies looking at *in vitro* endpoints such as dicentric aberrations in human chromosomes, transformations, micronuclei induction, and mutations over a range of photon energies, from ultra soft x-rays to Cobalt-60 gamma rays. There was a pronounced trend of increasing RBE values with decreasing photon energy in a range of biological endpoints, particularly in the induction of dicentrics in human lymphocytes. Hill (2004) noted that because of differences in cell types and biological endpoints, the extent to which photon energy caused RBE values to rise was still uncertain. Recent data by Frankenburg (2002) gave an RBE_M of ~4 for soft (mammography) x-rays compared to 200 kVp x-rays.

Krumrey *et al* (2004) studied the RBE_M on lymphocytes' exposure to very low-energy x-rays produced by synchrotrons. Photon energies ranging from 1.83 keV to 17.4 keV gave RBEs of 1.18 ± 0.52 to as high as 7.70 ± 2.98 relative to Cobalt-60 radiation, with energies between 10 keV and 4.8 keV being the most effective. However, the RBE was not linear with radiation energy, with a peak occurring at about 7 keV and then dropping. Sasaki *et al* (1989) observed a similar effect, suggesting it might be due to "over-dispersion of the dicentrics due to unequal distribution of the radiation dose to either the cell populations or within the cell itself."

In conclusion, computational models appear to confirm that the higher RBE of tritium, as well as that of other low-energy radiation, is at least partly due to the high-LET and correspondingly short path length of tritium beta particles. The relatively large deposition of energy within a very small volume induces single- and double-strand breaks and also causes complex damage that may not be reparable. When the tritium is incorporated into DNA, there is a higher probability of biological damage.

5.4 Summary and Conclusions

The RBE provides a referenced correction factor for comparing the effects of different radiations, giving direction for the development of a universal measurement of dose, the sievert (Sv). Much of the discussion in this report and those of others, such as the AGIR (HPA, 2007) and Straume and Carsten (1993), has centered upon an appropriate single value for the RBE of tritium. Although there have been more than 50 different estimates of this value, it is clear considerable variation exists. This, combined with uncertainty in radiobiological data, makes it difficult to select one value. The choice of a reference radiation accounts for much of this variability, due to the difference in the RBE of x-rays and higher-energy gamma rays. Other factors contributing to the observed range include:

- differences in radiosensitivity of tissues, organs and organisms
- different biological endpoints
- variation in dose and dose rate effectiveness factors
- dosimetry
- choice of *in vitro* or *in vivo* test systems

For occupational and public exposures, the most relevant endpoint is radiogenic cancer, (particularly radiation delivered at occupational or slightly greater levels), but there are very few studies at occupational dose levels, since most experiments use more than 1 Gy. However, overwhelming evidence supports an RBE for tritium of at least 2 when pooling the data from

all studies, including those examining the most relevant endpoints, which were reviewed in this report. Given the range of observed values, an RBE of at least 2 for tritium beta particles should be seen as a general indication of the greater effectiveness of these particles, vs. low-LET radiation. This would apply to cancer induction in humans in the absence of better experimental data and specifically, any reliable epidemiological data.

Recap: Section 5

- Relative biological effectiveness (RBE) is a relative measure of the effectiveness of different radiation types in inducing a specified health effect. It contributes to the basis for a universal measurement of dose for radiation protection purposes, which is the sievert (Sv).
- The choice for a single value for the RBE of tritium is limited because of variation in the radiobiological data and the choice of the endpoint (i.e., type of cancer).
- The review of studies determining a single value for the RBE of tritium radiation indicates that where x-rays are chosen as the reference radiation, an RBE value of 1.4 would be appropriate. If gamma radiation is chosen as the reference, an RBE value closer to 2.2 would be indicated. This means that the health risk of tritium is respectively 1.4 and 2.2 times higher than for these other types of radiation.
- Gamma radiation appears to be the preferred choice of a reference radiation. Gamma radiation is usually used when studying effects of chronic (long term) radiation exposures and it is the largest source of radiation exposure to workers.

6 DOSIMETRY AND BIOKINETICS

Calculating the committed effective dose received as a result of taking tritium into the body is done in two steps. First, a model describing the behaviour of the tritiated compound taken into the body is used to predict where the tritium will go in the body and the rate at which it will be removed from the body. Such a model is known as a biokinetic model. Second, a dosimetric model is used to calculate how much tritium will decay while it is in the various organs and tissues of the body and how much of the energy from the beta particles it emits during decay will be absorbed by the body. This allows us to calculate the dose resulting from the intake of tritium. Because tritium is removed gradually from the body after an intake, the committed effective dose takes into account the dose received for 50 years following the intake of a radionuclide into the body.

Since the energy carried by tritium beta radiation is of short range, all of its energy is absorbed in the tissues and organs in which the tritium atoms are located. This describes the dosimetric model for tritium. The biokinetic model for tritium is more complex and depends on the type of tritiated compound taken into the body.

This section presents the main biokinetic models used for calculating dose as a result of taking tritium compounds into the body, either by inhalation, ingestion or absorption through the skin. In particular, it presents the tritium biokinetic models recommended by the International Commission on Radiological Protection (ICRP) and the basis for these models. Other models are also considered, which consider types of exposures that are not considered by the ICRP models, or give a more accurate description of the biokinetics of certain tritiated compounds. Examples of applications of the tritium dosimetric model are also provided by presenting dose coefficients calculated with the biokinetic models discussed.

6.1 Overview of Current ICRP Models for Tritiated Water and Organically Bound Tritium

Tritium may enter the body by inhalation, absorption through skin, and ingestion. The first two are the most frequent forms of intake in the workplace, while all three routes of intake can contribute to exposures to members of the public. Skin contact with tritium-contaminated surfaces, such as metal, glass, has been shown to result in the formation of OBT in the body. Skin contact is therefore considered as a different mode of intake compared to the absorption of HTO through skin, and has also been shown to be a route of intake in the workplace (Hill and Johnson, 1993).

The fate of tritium once taken into the body is determined mostly by its chemical form in the external environment. One can expect to find HTO in most workplaces and environmental media where tritium is present. Organic molecules containing tritium are known as OBT compounds. In most OBT compounds, tritium that is bound to oxygen, nitrogen, phosphorus or sulphur will exchange freely with hydrogen in water. Therefore, it has the same metabolism and distribution in the body as HTO and is called the exchangeable bound tritium fraction. Tritium bound to carbon will not exchange with hydrogen in water. Tritium in such C–H

bonds is known as non-exchangeable bound tritium. In general, considerations of the biokinetics of OBT refer to the non-exchangeable component that exhibits retention times determined by carbon turnover rather than HTO kinetics.

Tritiated compounds may also exist in particulate forms, such as airborne particles that contain tritium. The retention and clearance of these particulates in the respiratory tract depend on several factors; for example, the particle's size and chemical composition. For the purpose of dose assessment, tritium absorbed into blood after tritiated particulates have been inhaled is treated as HTO after it has left the lungs (Cheng *et al*, 1995; Cheng *et al*, 1999; Cheng *et al*, 2002; ICRP, 1995a). Although tritium beta rays are partially self-attenuated within the particle, the dose to the lower lung — from particles that slowly dissolve — can be up to two orders of magnitude higher than that from the same activity of inhaled HTO (Richardson and Hong, 2001).

The tritiated compounds are therefore categorized according to the metabolic model that best describes their dynamics after uptake. Two primary metabolic models, which are discussed in this section, are used to estimate the dose from tritiated compounds:

- **the HTO model,** which is used to estimate the dose resulting from intakes of HTO or other tritiated compounds that partially convert to HTO after being taken into the body
- **the OBT model,** used to estimate the dose resulting from intakes of various tritiated organic compounds (non-exchangeable bound tritium)

A third model, which applies to tritium absorbed through the skin from HT-contaminated surfaces, is also described. Finally, the biokinetics of tritiated compounds in relation to pregnancy and to nursing is discussed in this section.

6.2 Internal Dosimetry of Tritiated Compounds using the ICRP HTO Model

6.2.1 The ICRP Model for the Inhalation and Ingestion of Tritiated Water

The ICRP HTO model (ICRP, 1989), illustrated in Figure 6.1, is used to assess doses for:

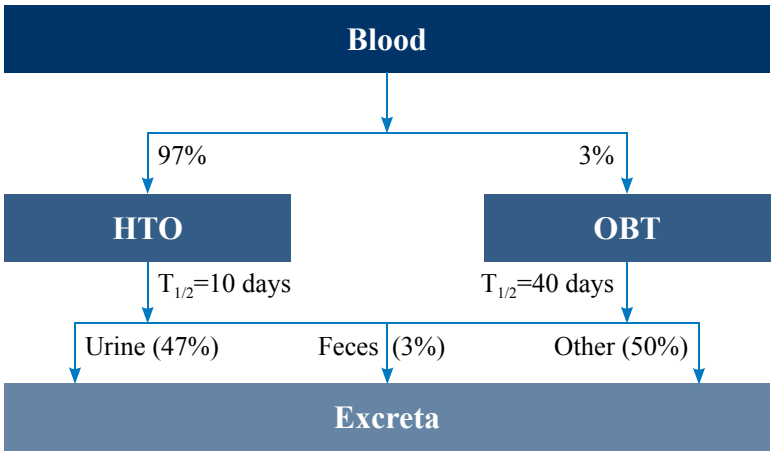
- intakes of tritiated water (HTO)
- HTO formed following intakes as tritiated gas (HT)
- tritiated hydrocarbon vapours and gases
- tritiated particulates

For intakes as HTO, the model assumes instantaneous translocation to blood. It is further assumed that HTO is transferred from the blood, with a biological half-life of 6 hours and then distributed uniformly throughout the body. The model assumes that 97% of tritium taken in remains as HTO once distributed, while 3% is converted to OBT. In adults, HTO is retained with a biological half-life of 10 days, and OBT is retained with the biological half-life of carbon, which is 40 days. HTO is assumed to be distributed uniformly throughout the 42 L of body water. The assumed partitioning between HTO and OBT after acute intakes of HTO in various age groups, as well as corresponding biological half-lives, are given in Table 6.1 (ICRP, 1993).

Table 6.1: Parameters Describing the Distribution and Retention of tritium After acute intakes of Tritiated Water

Age	Distribution (%)		Biological Half-Life (Days)	
	HTO Component	OBT Component	HTO Component	OBT Component
3 months	97	3	3.0	8
1 year	97	3	3.5	15
5 years	97	3	4.6	19
10 years	97	3	5.7	26
15 years	97	3	7.9	32
Adult	97	3	10.0	40

Figure 6.1: ICRP Model for the Biokinetics of Tritiated Water



The committed effective dose-per-unit intake (dose coefficient) to adults resulting from the intake of HTO, as recommended by the ICRP (ICRP, 1993; ICRP, 1995a), is based on Figure 6.1. This model considers the ICRP's recommendations for radiation weighting factors as well as tissue weighting factors. The committed effective dose-per-unit intake is the computed effective dose received up to 50 years following a single intake for adults, and up to 70 years for intakes by infants and children. The value for intakes of HTO by adults computed by the ICRP is 1.8×10^{-11} Sv/Bq. A slightly different dose coefficient, 2.0×10^{-11} Sv/Bq, has been recommended by Health Canada and the CNSC (Health and Welfare Canada, 1983; CNSC, 2005) and incorporated in past regulatory documents (Atomic Energy Control Board [AECB], 1987). The ICRP dose coefficient is based on the assumption that dose from HTO is received by 68.8 kg of tissue, which includes several kilograms of non-cellular bone. This value was derived from the total body mass of 70 kg minus the masses of the contents of the gastrointestinal tract (1,005 g), urinary bladder (102 g) and of the gall bladder (62 g) (ICRP, 1975). Because the relevant dose is that to the nucleus of sensitive cells from contained HTO, the AECB recommended using a dose coefficient of 2.0×10^{-11} Sv/Bq to assess the dose resulting from intakes of HTO. This recommendation considered dose received by 63 kg of soft tissue: a mass equal to the mass of the total body (70 kg), minus the skeleton mass (10 kg). Because the latter includes marrow, which is radiosensitive and therefore must be included in the dose

calculation, the mass of marrow (3kg) was included. The dose coefficient of 2.0×10^{-11} Sv/Bq considered dose to a mass of 70kg – 10 kg + 3 kg = 63 kg (ICRP, 1975). Furthermore, the dose coefficient recommended by the Federal Provincial Working Group on Bioassay and *In Vivo* Monitoring (Health and Welfare Canada, 1983), 2.0×10^{-11} Sv/Bq, assumed that 97.8 % of tritium entering the body as HTO remained as HTO, with a biological half-life of 9.7 days, while 2.2% was converted to OBT and was retained with a biological half-life of 48.5 days (Johnson, 1982).

More recently (Trivedi, 1998), the ICRP model for HTO (ICRP, 1993) was used to calculate the dose to 68.8 kg of soft tissue, with corrections using the updated values of 10.5 kg for skeleton mass and 3.65 kg for marrow mass (ICRP, 1995b). The resulting dose coefficient was 2.0×10^{-11} Sv/Bq, a value that the CNSC continues to recommend and use (CNSC, 2005).

The contribution of the OBT fraction to dose in the ICRP's HTO model has been shown to be about 10% (ICRP, 1979; Johnson, 1982). This has been verified to be adequate for dose estimates under both acute and chronic intakes (Trivedi *et al*, 1997b; Trivedi *et al*, 2000).

6.2.2 Absorption of HTO Through Skin

HTO is also known to be absorbed through skin from the vapour phase or the liquid phase; that is, by immersion (DeLong *et al*, 1954; Pinson and Langham, 1957; Osborne, 1966). The ICRP (1995a) addresses HTO intake via skin absorption by reference to Osborne (1966), Hill and Johnson (1993), and Myers and Johnson (1991), the latter being a literature review. About 1% of HTO activity per m^3 in air is taken to be absorbed through the skin per minute. This results in absorption through the skin contributing about one third of the total HTO intake for a given HTO concentration in air when the exposed individual is active during exposure (breathing in more air than when at rest). Using the same assumptions, the amount of HTO absorbed through the skin in a given time is about equal to the amount inhaled in the same period of time when the exposed individual is at rest during exposure.

6.2.3 Inhalation of Elemental Tritium Gas

Following inhalation of elemental tritium gas (HT), a small fraction (about 0.01%) (Peterman *et al*, 1985) of the inhaled activity is dissolved in body fluids and then oxidized to HTO. The latter is the predominant contributor to dose. HT gas is not significantly absorbed through the skin and does not readily convert to HTO on the skin. Irradiation of the lungs from inhaled HT gas does not significantly increase the committed effective dose (ICRP, 1994a) because of the short range in tissue of this tritium beta particle (see Section 6.5.3). The dose coefficient for the inhalation of HT gas is therefore taken to be 0.01% of that used for the inhalation of HTO.

6.2.4 Tritiated Hydrocarbons

Various forms of tritiated hydrocarbons have been identified. Tritiated methane (CTH_3) is the only such tritiated compound for which the ICRP recommends a dose coefficient based on the HTO model. CTH_3 is known to form as a result of microbial degradation within tritiated waste. About 1% of inhaled CTH_3 is assumed to be converted to HTO (Phipps *et al*, 1990). The dose

coefficient for CTH_3 is therefore 1% of that for HTO. The HTO model is not recommended for interpreting bioassay data collected following an intake of CTH_3; the use of workplace or environmental data is more appropriate. The ICRP approach is considered to give a conservative dose coefficient (Phipps *et al*, 1990).

6.2.5 Metal Tritides

Metal tritides (tritium bearing metals) can form as a result of tritium sorbing to metals. Such compounds are used for research to store tritium and can also be found in neutron generators and accelerators. Helium forms in the tritium-containing metal during the decay of tritium, and the resulting pressure from the helium can cause particles to break off from the metal tritide surface. Data on the metabolism of inhaled metal tritide particulates are scarce. This group of tritiated compounds can be classified according to their rate of absorption from the respiratory tract. Compounds have been classified as having a fast (Type F), moderate (Type M), or slow (Type S) absorption rate (ICRP, 1994a) to blood from the respiratory tract. Dose coefficients for the inhalation of metal tritide particulates are based on the assumption that tritium follows HTO dynamics after leaving the respiratory tract (ICRP, 1995a). However, general information on tritiated particulates is limited, with most available data related to metal tritides (Cheng *et al*, 1995; Cheng *et al*, 1999; Cheng *et al*, 2002; ICRP, 1995a). In the absence of specific information, the ICRP recommends designating tritiated inorganic particulates as Type M (ICRP, 1994a), meaning their rate of absorption from the respiratory tract to blood is moderate.

6.2.6 Summary of Dose Coefficients Based on the ICRP HTO Model

Table 6.2 presents the ICRP's recommended dose coefficients for tritiated particulates, as well as for other tritiated compounds (ICRP, 1996).

Table 6.2: ICRP Dose Coefficients Based on the ICRP HTO Model for Various Tritiated Compounds, Modes of Intake and Age Groups

Tritiated Compound	Mode of intake	Dose coefficient (Sv/Bq)	
		Infants (1 year old)	Adults
HTO*	Inhalation	4.8×10^{-11}	1.8×10^{-11}
HTO	Ingestion	4.8×10^{-11}	1.8×10^{-11}
HT	Inhalation	4.8×10^{-11}	1.8×10^{-15}
CTH_3	Inhalation	4.8×10^{-13}	1.8×10^{-13}
Type F particulates[2]	Inhalation	2.0×10^{-11}	6.2×10^{-12}
Type M particulates[2]	Inhalation	2.7×10^{-10}	4.5×10^{-11}
Type S particulates[2]	Inhalation	1.0×10^{-9}	2.6×10^{-10}

** The dose coefficient for the inhalation of HTO does not include absorption through the skin and should be increased by a factor of 1.5 for workers and 2 for members of the public, in order to account for it.*

2 Dose coefficients shown for particulates of 1 µm activity median aerodynamic diameter (AMAD).

Table 6.3 illustrates the effect of age on the dose-per-unit intake for the inhalation of HTO and compares these dose coefficients to the value for adults.

Table 6.3: ICRP Dose Coefficients for HTO Inhalation for Various Age Groups

Age	Dose Coefficient ($Sv\ Bq^{-1}$)	Ratio of Dose Coefficient to That of Adult
3 months	6.4×10^{-11}	3.6
1 year	4.8×10^{-11}	2.7
5 years	3.1×10^{-11}	1.7
10 years	2.3×10^{-11}	1.3
15 years	1.8×10^{-11}	1.0
Adult	1.8×10^{-11}	1.0

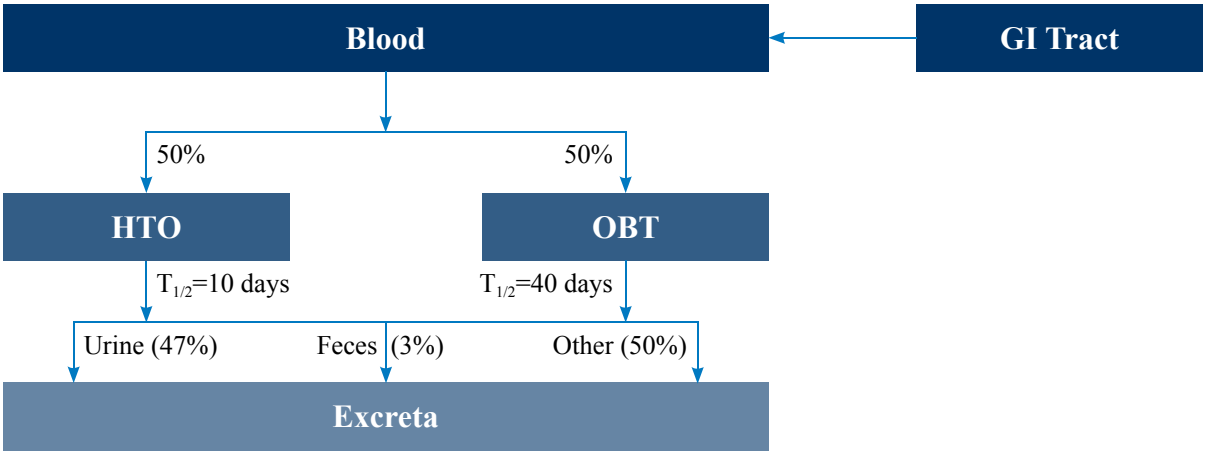
6.3 Internal Dosimetry of Tritiated Compounds Using the ICRP OBT Model

Figure 6.2 illustrates the ICRP model (1989; 1995a) used to assess doses that result from the intake of unspecified organic forms of OBT. It assumes that OBT, once taken into the body, is translocated to blood completely and instantaneously and then distributed uniformly throughout body tissues. In the absence of specific information on the inhaled organic compound, it is assumed that tritium absorbed to blood will behave as it does after ingestion (that is, that 50% is retained as OBT in body tissues and that 50% is catabolised to HTO) and that its turnover time will be similar to those of water.

It is assumed that tritium inhaled as organic compounds is absorbed to blood instantaneously and is transferred from blood with a biological half-life of 6 hours, with 50% retained as OBT in body tissues and 50% catabolised to HTO (ICRP, 2001).

Data on the metabolic processes and retention of non-biological tritiated organic compounds (such as tritiated oils and solvents) following inhalation are scarce (Hill and Johnson, 1993). These compounds are therefore not considered further in this section.

Figure 6.2: ICRP Model for the Biokinetics of Organically Bound Tritium



Tritiated organic compounds in diet may include tritiated proteins, fats, and carbohydrates. The ICRP model for the ingestion of OBT (ICRP, 1989) is intended to represent normal dietary content of these different forms. The model was developed in the absence of good information about the specific proportions of OBT in components of the human diet and how tritium is incorporated into organic molecules in body tissues.

In this model, it is assumed that all ingested tritiated organic compounds are completely absorbed from the gastrointestinal tract to blood, after which the tritium from these compounds is uniformly distributed in tissue. In reality, the distribution of tritium in the various tissues will depend on the chemical form of the tritium and the metabolic activity of the individual tissue.

Experimental studies of the relative incorporation of tritium into OBT in body tissues following intakes of HTO and OBT suggest that about 9% to 45% of tritium from dietary OBT is incorporated into body OBT. The ICRP OBT model therefore conservatively assumes that after tritium is absorbed from blood (in adults), further to ingestion as OBT:

- 50% of tritium will follow the metabolic behaviour of carbon, having a biological half-life of 40 days
- 50% of tritium will behave as HTO, having a biological half-life of 10 days

It should be noted that less than 10% of OBT in diet is excreted in the form of OBT in urine (mostly in the form of urea), and ~3% OBT is excreted in feces.

Table 6.4 gives the assumed partitioning between HTO and OBT and corresponding biological half-lives, after dietary intakes of OBT in various age groups (ICRP, 1993). The ICRP's recommended dose coefficients for OBT are shown in Table 6.5 (ICRP, 1996). Table 6.6 shows the effect of age on dose-per-unit intake for the ingestion of OBT.

Table 6.4: ICRP (1993) Partitioning Between HTO and OBT After Dietary Intakes of OBT

Age	Distribution (%)		Biological Half-Life (Days)	
	HTO Component	OBT Component	HTO Component	OBT Component
3 months	50	50	3.0	8
1 year	50	50	3.5	15
5 years	50	50	4.6	19
10 years	50	50	5.7	26
15 years	50	50	7.9	32
Adult	50	50	10.0	40

Table 6.5: ICRP (1996) Dose Coefficients Based on the ICRP OBT Model for Various Modes of Intake and Age Groups

Tritiated Compound	Mode of Intake	Dose Coefficient (Sv/Bq)	
		Infants (1 year old)	Adults
OBT	Inhalation	1.1×10^{-10}	4.1×10^{-11}
OBT	Ingestion	1.2×10^{-10}	4.2×10^{-11}

Table 6.6: ICRP (1996) Dose Coefficients for OBT Ingestion for Various Age Groups

Age	Dose Coefficient (Sv Bq)	Ratio of Dose Coefficient to That of Adult
3 months	1.2×10^{-10}	2.9
1 year	1.2×10^{-10}	2.9
5 years	7.3×10^{-11}	1.7
10 years	5.7×10^{-11}	1.4
15 years	4.2×10^{-11}	1.0
Adult	4.2×10^{-11}	1.0

6.4 Intakes of Tritium in Relation to Pregnancy and Nursing

6.4.1 Pregnancy and Tritium Intake

The ICRP (2001) has provided biokinetic and dosimetric models and dose coefficients for the embryo, the foetus and the newborn as a result of intakes of radionuclides by the mother.

In prenatal dosimetry, the term “embryo” refers to the developing offspring up to the end of week 8 of pregnancy, including the initial stages of growth up to the end of organogenesis. At

this time, the embryo weighs less than about 10 g. During this stage, dose to the foetus is assumed to be the same as that to the uterus wall.

The term "foetus" refers to the developing offspring after week 8 of pregnancy. During this stage of pregnancy, doses to foetal organs and tissues are calculated using biokinetic models that describe tritium behaviour in the foetus itself, as this behaviour will differ from the assumed tritium behaviour in the mother. For the ICRP (2001) report, models that take into account existing relevant biokinetic data were developed to calculate dose to offspring. Data collected from studies in animals, and in humans where available, and were used as the basis for biokinetic models for the transfer of radionuclides to the foetus. These data also provide a basis for the relative concentrations of radionuclides averaged for the whole-body of the foetus (C_F) and the mother (C_M). The ratios of C_F:C_M are mainly taken from studies presenting data at short times post-intake. The ICRP (2001) report conservatively assumed that the recommended C_F:C_M ratios applied to the time of intake and remained constant throughout pregnancy.

The ICRP (2001) report presents dose coefficients for both chronic and acute maternal intakes by inhalation or ingestion. Acute intakes from 6 months before conception until the end of week 35 of pregnancy are considered. The report also provides chronic intakes lasting from 5 years or 1 year before conception until the time of conception, as well as chronic intakes lasting for the duration of the pregnancy. Effective doses to the offspring until birth, per unit intake by the mother, are presented, along with total committed effective doses to the offspring up to age 70, including doses resulting from radionuclides retained by the offspring at birth and doses received *in utero*.

HTO rapidly crosses the placenta after it is inhaled or ingested by the mother. Dose to the foetus resulting from such intakes depends on the water content of the foetus over the course of its development. As gestation progresses, water content decreases, while amounts of protein, fat and minerals increases. The percentage of total body water decreases from about 93%–95% at week 6 of pregnancy to 70%–72% at birth. For comparison, the percentage of total body water in a non-pregnant woman is about 50%. While maternal total body water content is known to increase during pregnancy, studies disagree on the absolute values of total body water content. This disagreement is related to data on foetal body water content and the derivation of the amniotic fluid volume. However, calculations have shown that the maternal biological half-life of HTO varies from about 10 days at the start of pregnancy to about 12 days at term. This variation in the biological half-life does not significantly affect the ICRP foetal dose coefficients for HTO (ICRP, 2001).

Until week 8 of pregnancy, the dose to the embryo is taken to be equal to that of the uterus. This dose is proportional to the concentration of HTO in maternal body water. For dose to the foetus (after week 8), the HTO concentration in foetal body water is taken to be equal to that in the mother.

Using an average body water content of 80% for the foetus and 50% for the mother, the ICRP uses a C_F:C_M ratio of 1.6 for HTO dose coefficients. This C_F:C_M ratio of 1.6 is applied to both the HTO and OBT components for intakes of OBT. Foetal tritium is assumed to be uniformly

distributed throughout all tissues. Following birth, the biokinetic model for the 3-month-old (ICRP, 1989) is used to assess dose to the newborn. Table 6.7 presents selected prenatal dose coefficients with comparisons to dose coefficients for the 3-month-old.

Table 6.7: ICRP (2001) Selected Prenatal and Infant Dose Coefficients

Tritiated Compound Type and Mode of Intake	Dose Coefficient for Offspring (Sv/Bq)		Dose Coefficients for 3 Month-Old (Sv/Bq)
	Acute Maternal Intakes[a]	Chronic Maternal Intakes[b]	
HTO inhalation	3.6×10^{-11}	3.1×10^{-11}	6.4×10^{-11}
HTO ingestion	3.6×10^{-11}	3.1×10^{-11}	6.4×10^{-11}
OBT ingestion	7.6×10^{-11}	6.3×10^{-11}	1.2×10^{-10}

a Values are for acute intakes at the end of week 10 of pregnancy. Acute intakes occurring at other times yield lower dose coefficients.

b Chronic intake begins at start of pregnancy and lasts for the duration of the pregnancy. These dose coefficients are greater than other chronic dose coefficients tabulated by the ICRP (2001), namely for chronic intakes starting 5 years and 1 year before pregnancy and lasting until the start of pregnancy.

6.4.2 Nursing and Tritium Intake

The ICRP (2004) has recommended dose coefficients for newborns from intakes of radionuclides in maternal milk resulting from maternal intakes. As with prenatal doses, acute and chronic intakes by the mother are considered for intakes by both ingestion and inhalation. Nursing is assumed to continue for 6 months after birth, and ingestion dose coefficients for infants are applied (ICRP, 1993). Maternal intakes during pregnancy and during lactation are also considered. The ICRP's approach estimates the activity of radionuclides transferred to milk as a function of maternal intake for various intake scenarios (acute or chronic intake regimes, and for various maternal intake times relative to birth).

The HTO and OBT models described in sections 6.2 and 6.3 were modified by the ICRP (2004) to account for transfer to milk. The rate of OBT transfer to milk was taken to be that of carbon. The ICRP (2004) presented dose coefficients based on the assumptions of 6 feeds per day and an average daily intake by the infant of 0.8 L. Table 6.8 shows selected dose coefficients for doses to nursing infants resulting from maternal intakes of tritium.

Table 6.8: ICRP (2004) Selected Nursing Infant Dose Coefficients

Tritiated Compound Type and Mode of Intake	Dose Coefficient (Sv/Bq)	
	Acute maternal Intakes[a]	Chronic maternal Intakes[b]
HTO inhalation	2.2×10^{-11}	2.0×10^{-11}
HTO ingestion	2.2×10^{-11}	2.0×10^{-11}
OBT ingestion	3.5×10^{-11}	3.0×10^{-11}

[a] *Values are based on acute maternal intake at 1 week after birth. Acute intakes occurring at other times yield lower dose coefficients.*

[b] *Values are based on chronic intake during lactation period (up to 6 months after birth). These dose coefficients are greater than those for chronic intakes occurring during the pregnancy.*

6.5 Review of Currently Available Information About the Biokinetics of Tritiated Compounds

6.5.1 Dosimetry of Tritiated Compounds Using the HTO Model

The parameters in the ICRP's HTO biokinetic model described in Section 6.2 include the water and carbon biological half-lives and the HTO/OBT partitioning coefficients. The bases for biological half-lives and the HTO/OBT partitioning coefficients are discussed below.

Several studies have examined the biological half-life of HTO in adults. Butler and Leroy (1965) found this parameter to vary with water intake (decreasing with increasing water intake rate), ambient temperature (decreasing with increasing ambient temperature) and age (decreasing with increasing age in adults). In this study, 310 cases of HTO intakes showed the biological half-life to vary from about 4 to 18 days, with a mean of 9.5 days. Other studies used fewer cases, but showed similar results for HTO (Hill and Johnson, 1993): from 6 days for 8 cases (Rudran, 1988), to 12 days for 5 cases (Balonov *et al*, 1974). The ICRP's HTO model adopted a biological half-life of 10 days for adults.

The biological half-life of 40 days that is used for the OBT compartment in body tissues is based on carbon turnover in the body. This was derived from the ratio of the Reference Man (ICRP, 1975) carbon body content (16 kg) to the daily carbon intake (0.3 kg per day) and yields a biological half-life for carbon (0.693 × 16 kg/0.3 kg per day = 37 days). The calculated value of 37 days was rounded to 40 days in the ICRP model.

Some studies have also reported a longer-lived component, which represents retained tritium that has a biological half-life greater than water or that of carbon in the HTO model. Such a component contributes to the committed effective dose and may influence how bioassay data are interpreted. Example results from such studies are shown in Table 6.9. In general, OBT in compartment 3 has a long biological half-life relative to the half-life of 40 days used in the ICRP model for OBT. OBT in this long-lived compartment represents less than 1% of total OBT. Taylor (2003) has taken this long-lived compartment into account in HTO modelling. This is discussed further later in this section.

Table 6.9: Selected Tritium Retention Half-Lives in Humans Following Intakes of Tritiated Water

Study	Number of Cases	Biological Half-Life (Days)		
		Compartment 1 (Body Water)	Compartment 2 (Organically Bound)	Compartment 3 (Organically Bound)
Pinson and Langham (1957)	9	11.3		
Foy *et al* (1960)	10	5–11 (mean: 7.5)		
Wylie *et al* (1963)	7	6.4–12.1 (mean: 8.5)		
Butler and Leroy (1965)	310	4–18 (mean: 9.5)		
Osborne (1966)	30	6.4–14.4 (mean: 10.5)		
Snyder *et al* (1968)	1	8.7	34	
Sanders and Reinig (1968)	1	6.1[a]	23	344
Minder (1969)	1		10–30	139 to 230
Lambert *et al* (1971)	1	9.1[b]	36	
Moghissi *et al* (1971)[c]	2		21 and 33	280 and 2,020[d]
Moghissi *et al* (1972)[e]	3		21 and 26	280 and 550 350 ± 190[f]
Bennet (1972)		8.7	30	550
Balonov *et al* (1974)		12	39 to 76	
Rudran (1988)	8	3.3–7.7 (mean: 6.0)	30.8–131 (mean: 81.7)	
Trivedi *et al* (1994)	8	6.2– 12.8[g] (mean: 8.4)	58–104 (mean: 74 ± 18)	

[a] *Oral diuretic administered from days 3 to 35 post-intake*
[b] *HT/ HTO acute intake*
[c] *Data for two tritium luminous dial painters collected 6 to 10 months after termination of employment*
[d] *Long-term behaviour of the data in one subject is attributed to seasonal effects, as described by Pinson (1957)*
[e] *Based on additional data from subjects used in Moghissi* et al *1971*
[f] *Data for a third subject, which was introduced in this study*
[g] *During the initial period when the exposed individuals increased fluid intakes, for one month post-intake, the biological half-life varied from 5.0 to 8.1 days with a mean of 6.3 days.*

The partitioning of HTO and OBT after intakes of tritium as HT was examined by Takeda and Kasida (1979) as part of a study of the biokinetics of HTO in rats. These investigators found that "initially, the ratio of tissue-bound tritium to total tritium was about 3% in the kidney and 1–5% in other tissues". Based on this study, the ICRP model assumes that 3% of initial HTO intakes are partitioned to OBT. Other investigators have found values of less than 1%; for example, Snyder *et al* (1968) reported a value of 0.4%, based on a single human exposure case. A study of an unplanned acute HTO intake incident involving eight male workers suggested a long-term component (average $T_{½}$ of 74 ± 18 days), which accounted for 0.5% ± 0.2% of the initial HTO intake (Trivedi *et al*, 1994). Balonov *et al* (1974) also reported a long-term component partitioning fraction of 0.5% for a human subject (compared to 3% in the ICRP HTO model).

More recently, a three-compartment model was developed to assess HTO excretion data from the limited human data that have been published (Taylor, 2003). A three-component exponential function was derived to represent the urinary excretion data from these studies. However, it was noted that results showed reasonably wide variations, both in observed biological half-lives and in proportions of total tritium entering the compartments (OBT), which turn over more slowly (Taylor, 2003). The model parameters are shown in Figure 6.10. The resulting dose-per-unit intake of HTO by adults, based on this model, is 1.7×10^{-11} Sv/Bq. The current ICRP dose coefficient for HTO is 1.8×10^{-11} Sv/Bq (ICRP, 1994). The addition of a long retained component in the biokinetic model implies a significant change in the interpretation of bioassay results for samples collected several weeks to months after an acute intake. This change would not be relevant for routine monitoring situations, where the dose is estimated by interpolating the tritium concentration in body water, between tritium-in-urine measurements taken frequently (for instance, every two weeks).

This latter method of dose estimation is independent of the time between intake and submission of a urine sample for tritium-in-urine measurement. Worker monitoring programs based on urine bioassay are typically used for routine monitoring when tritium doses are not significant, typically in cases that involve less than a few mSv per year. Also, these programs are designed so that urine samples are submitted frequently enough to ensure accurate dose estimates. The method currently used to estimate doses from measurements of the concentration of tritium in urine has been described (Health Canada, 1983). Workers' tritium-in-urine concentration is determined using liquid scintillation analysis. Linear interpolation is carried out between successive bioassay results, in order to calculate the workers' effective dose received between urine samples. Doses received during each annual monitoring period are summed to obtain the annual dose. The committed effective dose, resulting from intakes of tritium during the year, but received during the following year (as a result of tritium retention in the body) is also calculated by multiplying the year's last bioassay sample result by a committed dose factor (Health Canada, 1983; AECB, 1987).

Taylor's model would be relevant for special bioassay monitoring following unplanned significant intakes of HTO, where individual monitoring may extend several weeks post-intake and when the individual has been removed from work that might result in further intakes of tritium.

Table 6.10: Parameters for the HTO Model Recommended by Taylor (2003)

Model Component	Distribution (%)	Biological Half-Life (Days)
HTO	99	10
OBT_1	0.98	40
OBT_2	0.02	350

[1] *Short-term OBT compartement*

[2] *Long-term OBT compartement*

6.5.2 Absorption of HTO Through Skin

The absorption of tritium through skin from either the vapour phase or the liquid phase has been investigated by various authors, such as DeLong *et al* (1954), Pinson and Langham (1957), and Osborne (1966). DeLong *et al* (1954) exposed mice, rats and human adult volunteers (all males) to HTO vapour in air. Animals were sacrificed following exposure and urine samples were collected from human subjects for 48 hours after the end of exposure. Water absorption rates, calculated from measurements of tritium in blood and total body water, suggest a lag in the distribution of the absorbed water. Absorption of tritium through the skin was the same when skin was covered with a cloth (cotton) as when it was not covered. The rate of water absorption was also found to be proportional to water vapour pressure. This suggests a single diffusion mechanism for percutaneous absorption. The data also suggests that the rate of percutaneous absorption of tritium from HTO in air is about the same as the rate of pulmonary absorption from the same atmosphere.

Pinson and Langham (1957) exposed human subjects' forearm skin to HTO in the form vapour as well as water. When exposed to HTO vapour, the average absorption rate was 0.018 $mg/cm^2/min$, compared with exposure to HTO in the liquid phase, where the absorption rate through skin was 0.04 to 0.065 $mg/cm^2/min$. The average absorption rate when exposed to HTO vapour was larger than could be accounted for by diffusion due to vapour pressure alone. A faster rate of uptake during short exposures was explained by a blotter effect[3]. The study also found that the skin absorption rate increased with increasing skin temperature. As with DeLong (1954), Pinson and Langham (1957) found that "the quantity of HTO entering the body through the total skin, when exposed to an atmosphere containing a given activity per unit volume, would be about equal to that entering through the lungs".

Osborne (1966) exposed volunteers (whole-body exposure) to HTO in air and measured tritium in urine. As with Pinson and Langham (1957), Osborne found a correlation between skin absorption rate and skin temperature. Overall, skin absorption rates were found to be similar to those reported by Pinson and Langham (1957). Osborne also reported that the total skin intake rate assumed by the ICRP at that time (ICRP, 1959) was twice the average intake rate observed. The assumption used in ICRP (1959) was that the amount of tritium absorbed through the skin was equal to the amount inhaled. The assumption now is that the amount of tritium absorbed through the skin is half the amount inhaled.

3 Blotter effect, or capillary action, is the ability of a material to draw a liquid into it.

6.5.3 The inhalation of elemental tritium gas

The ICRP (1979) recommended basing HT inhalation dose primarily on exposure of the lung, as opposed to exposure of the skin. Oxidation of HT to HTO *in vivo* was not considered at that time. The Derived Air Concentration[4] for HT recommended at that time by the ICRP was 2×10^{10} Bq/m^3 compared with that for HTO, which was 8×10^5 Bq/m^3.

A small fraction of inhaled elemental tritium gas is converted to HTO in the body. The absorption of HT through skin appears to be negligible and it does not convert to HTO on contact with skin (Hill and Johnson, 1993). Compared to HTO, HT is slightly soluble in body fluids and has a much lower uptake into biological systems. After inhalation, most HT is exhaled, but a small fraction is dissolved in body fluids and then oxidized to HTO by bacteria in the GI tract (Ichimasa *et al*, 1986). This is the only known biological site of HT oxidation (Ichimasa *et al*, 1986).

The studies of Pinson and Laugham (1957) and Peterman *et al* (1985) indicate that exposure to HT results in the excretion of HTO in urine, and that HTO formed from the oxidation of HT is retained in the body and excreted with the usual biological half-life of about 10 days. About 0.01% of HT gas inhaled by human volunteers was converted to HTO in the body (Peterman *et al*, 1985).

Using HT and HTO biokinetic models proposed by Peterman *et al* (1985), in parallel with human volunteer HT inhalation data, it was concluded at the time that the committed effective dose from inhaled HT was dominated by two roughly equal contributors: dose to lungs resulting from HT in inhaled air, and dose from HTO formed by the oxidation of HT.

The ICRP has since recommended (ICRP, 1994a, b) a revised dose coefficient for inhalation of HT gas. This stems from two sources: the work by Peterman *et al* (1985), described above, and the ICRP's revision of the human respiratory tract model — in particular, consideration of human respiratory tract morphology. The short range of tritium beta particles (6 µm in tissue) is such that most of the energy is not deposited in target cells of the respiratory tract. The average cell depth of these cells' nuclei range from about 10 to 50 µm in the extrathoracic, bronchial and bronchiolar regions of the respiratory tract (ICRP, 1994a). In the current ICRP (1994a) model of the respiratory tract, tritium beta particles are taken to deliver dose only in the alveolar-interstitial (AI) region after inhalation of HT. As discussed by Trivedi and Gentner (1999), the nuclei of target cells within the AI region are at depths of less than 10 µm and can be assumed to receive some dose from HT.

The lung dose rate calculated with the ICRP Publication 66 model (ICRP, 1994a) is about one third of the mean lung dose rate calculated with the ICRP Publication 30 (ICRP, 1979) model. As a result, the effective dose-per-unit intake resulting from oxidized HT is several times higher than that due to the direct irradiation of the lungs by HT gas.

4 A typical worker breathing air, with a constant concentration of a specified radionuclide equal to the derived air concentration (DAC), as defined in ICRP (1979), for a working year, would receive a committed effective dose of 50 mSv.

The revised ICRP HT dose coefficient, 1.8×10^{-15} Sv/Bq, is 10,000 times less than the coefficient for HTO (ICRP, 1994b). This dose coefficient includes only the oxidation of HT into HTO, and not direct irradiation of the lungs by HT gas in air. The latter might increase the committed effective dose by about 20%. In cases where the dose is predominantly due to HT, exposure of the lungs should be taken into account.

It also follows from the above that the committed effective dose resulting from HT inhalation can be estimated using measurements of HTO concentration in urine (Trivedi and Gentner, 1999).

An upper limit on the lung dose resulting from HT gas in the lungs can be calculated from HTO-in-urine measurements. However, this upper bound assumes that the entire intake occurred as HT. Some or all of the HTO in urine may have actually resulted from the inhalation of HTO. Calculated in this manner, the contribution of lung dose to the committed effective dose is most likely overestimated, unless the HT to HTO ratio in air is known (Trivedi and Gentner, 1999). Consequently, when workers are exposed to both HTO and HT, the main contributor to dose is HTO and doses are not significant, it is adequate to calculate their dose from measureents of HTO in urine, without calculating an upper bound to lung dose from HT. When the dose is significant (e.g., more than a few mSv for workers, or close to the dose limit for members of the public), and due mainly to HT, exposure of the lungs should be taken into account by increasing the HT dose coefficient by 20%.

6.5.4 Intake Resulting From Skin Contact With Tritium-Gas-Contaminated Surfaces

Studies have examined the behaviour of tritium in the body as a result of skin contact with HT-contaminated metal surfaces (HT dissolves in most materials). These studies found that OBT from such skin contact exposures (Eakins *et al*, 1975) is excreted in urine. In turn, the type of tritiated compound produced in the body as a result of the skin's contact with tritium will determine the resulting committed effective dose.

Elemental tritium gas and HTO are known to sorb to surfaces. There is negligible absorption of airborne elemental tritium gas through skin, but exposure of skin to tritium-gas-contaminated surfaces has been shown to result in the absorption of tritium — both as HTO and OBT (Eakins *et al*, 1975). When metal surfaces contaminated with tritium gas were applied to the inside forearm of four human volunteers, urinary excretion of tritium was found to reach a maximum rate about 24 hours after exposure. In each subject, the excretion of total tritium at the peak time was about 20 times the amount of HTO excreted; that is, 5% of the tritium urinary excretion rate at the time of maximum excretion rate was due to HTO. The remaining tritium (that was not HTO) was determined to be organically bound. One to three weeks after the exposure, the rate of total tritium excreted was the same as that of HTO. Following intake via this route, up to 50% of the excreted OBT has been found to be excreted via urine following a biological half-life of about 1 to 2 days, and the rest of the OBT following a biological half-life of 0.1 to 0.2 days. HTO formed as a result of such skin exposure to HT-contaminated surfaces has been found to be excreted in urine with a biological half-life of about 14 days.

About 0.5% of the tritium initially sorbed to the surface to which the volunteers were exposed was absorbed as HTO, and about 0.3% was absorbed as OBT. The results did not depend on the type of material; as long as the surface adsorbed tritium gas (similar results were obtained for various types of metals and for glass). In addition, the amount of tritium absorbed was found to be independent of the duration of exposure. The effective dose resulting from such intakes of tritium was estimated to range from 8.7×10^{-12} to 9.7×10^{-12} Sv/Bq absorbed (Johnson and Dunford, 1985).

6.5.5 Ingestion of Organically Bound Tritium

While HTO distributes reasonably uniformly throughout body tissues, OBT formed in body tissues after intakes of OBT will be distributed among tissues according to their relative metabolic activities. OBT distribution will also depend on the chemical nature of the compound ingested. However, greater uptake by tissues with higher metabolic activity will generally be associated with shorter retention times, because of higher turnover. The non-uniform distribution of OBT is discussed in this section.

Experimental evidence indicates that, after an intake of OBT, about 9 times more tritium is bound to organic compounds in major tissues, compared with intakes of HTO (Rochalska and Szot, 1977). Takeda and Kasida (1979) also found that following HTO intakes in animals, 1% to 5% of tritium became incorporated in organic constituents of tissues. Therefore, 9% to 45% of tritium taken in as OBT would be expected to be incorporated in organic molecules in tissue. The ICRP's assumption that 50% of tritium remains as OBT after an intake of OBT stems from this reasoning.

The ICRP's HTO and OBT models (ICRP, 1989) therefore predict that 17 times more tritium (50% vs. 3%) will be incorporated as OBT following an acute OBT intake, compared to an HTO intake over a period of time (chronic intake). This is consistent with experimental results of Moghissi *et al* (1971), Rochalska and Szot (1977), Sanders and Reinig (1968), Snyder *et al* (1968), and Takeda and Kasida (1979), which indicate ratios ranging from 3 to 20. It should be noted that the ICRP's OBT model predicts 43 times more OBT in the body than does the Taylor (2003) HTO model. However, Rodgers (1992) found a ratio of about 12, suggesting that the current ICRP HTO model more accurately predicts the amount of OBT in the body from chronic intakes of HTO than does Taylor's HTO model.

The relative amounts of tritium incorporated into OBT following chronic intakes of HTO and OBT can be estimated from results of the study by Rodgers (1992). This study, carried out using mice, involved chronic intakes of HTO, OBT, or both for 56 days. At 56 days after the start of chronic intakes, the amounts of HTO and OBT in the mice would have been at steady state. The levels of OBT and HTO in the mice were then examined for about one month after the chronic exposure ended.

In the case of mice exposed to HTO only, the OBT concentration in tissues was about 22% of the HTO concentration. The ICRP HTO model (ICRP, 1989) predicts this value to be about 12% at steady state, while the Taylor (2003) model predicts this value to be about 5%.

In the case of mice exposed to OBT only, the OBT concentration in tissues was about a factor of 6 greater than the HTO concentration. This compared to the factor of 4 predicted by the ICRP OBT model (ICRP, 1989).

This study also found that the amount of OBT in tissues resulting from OBT intake was about 12 times greater than the amount of OBT in tissues resulting from HTO intakes, which is in close agreement with the results from Rochalska and Szot (1977). Although the ICRP models appear to underestimate the amounts of OBT retained in the body in some cases of chronic intakes, they predict that the dose attributable to OBT, from intakes of OBT, is 10 times greater than the dose from OBT from intakes of HTO. This is in agreement with Rodgers' findings. Overall, it can be concluded that these studies are generally consistent and that the ICRP model does not underestimate dose.

Rogers (1992) observed that after chronic exposure had ended, OBT was lost from the mice at a rate best described by a two-compartment model, with about 40% of OBT being cleared rapidly (with half-lives of 2.0 to 3.2 days in mice), and the remaining OBT being cleared much more slowly (with half-lives of 24 to 30 days in mice). The faster-clearing compartment's rate constant was not significantly different from those associated with HTO clearance from mice. Rogers attributed this faster-clearing compartment to loosely bound or exchangeable OBT. The slower-clearing compartment was due to non-exchangeable OBT.

Rodgers (1992) also found that when exposed to HTO only, the HTO in the mice contributed more than 95% of the total tritium dose during the chronic exposure. In the case of mice exposed to OBT only, the study found that about 50% of the total dose was attributable to OBT in tissue (in adult humans, the HTO:OBT dose ratio follows the ratio of the half-lives; 10 days:40 days). However, after the end of chronic intake, due to the longer biological half-life of OBT, the total dose resulting from OBT (in the case of mice exposed to OBT only) was about one order of magnitude greater than that of mice exposed to HTO only. This dominance of the dose attributable to OBT began after the end of chronic intake, as HTO cleared faster than OBT. The latter is consistent with predictions of the ICRP's OBT model; that is, a dose from OBT that is one order of magnitude greater after the end of chronic intake.

In order to relate the study by Rodgers (1992) to human dietary intakes of tritium, a study by Trivedi *et al* (1997b) is worthy of consideration. OBT:HTO ratios greater than 1 have been observed in some foods grown near environmental sources of tritium. The range of the OBT:HTO ratio in dietary intakes varies according to many factors, such as diet and atmospheric conditions. A study of doses received by a population residing near a nuclear facility showed that OBT contributes about 16% of the total tritium dose from all sources of tritium exposure (Trivedi *et al*, 1997c). In this case, the average OBT:HTO ratio in food items consumed by these individuals was 0.04. This value was mainly influenced by the proportion of food that was not locally grown, but that was imported into the study region. From this information, Trivedi and Gentner (1999) concluded that "unless the population living near tritium facilities consumes locally grown food items for a large proportion of the year (an uncommon situation around Canadian CANDU stations), dietary intake of OBT has only minor contributions to dose".

There are some uncertainties associated with OBT metabolism as described by the ICRP's OBT model, particularly the retention of OBT in children and the effect of organ growth on OBT retention. Also, the relative depositions of OBT in various organs and tissues are not fully known for all age groups. This implies there is no age-dependent biokinetic model for dietary intakes of OBT that accounts for age-related physiological and anatomical variations. HTO turnover in the human body is well established, but measurement data for tritium turnover in organic compounds are limited, particularly for long-term biokinetic components.

Animal studies have shown a non-uniform distribution of OBT among soft tissues of the body. Also, within a single organ, tritium is distributed non-uniformly among the various organic molecules (ICRP, 1989). However, other than for the special case of DNA precursors (see section 6.5.6), it appears that any non-uniformity of distribution within cells will be small, and in any case will be reflected in RBE values.

Several studies have investigated the distribution of OBT within cells and the bodies of test animals. These have helped produce dosimetry models of energy deposition within cells. Section 5.3.3 provides more details on dosimetry aspects, but the work by Chen (2006) warrants discussion here as it estimates an RBE for tritium. Chen (2006) ran a Monte Carlo simulation of beta radiation energy tracts from tritium bound to radiosensitive sites with varying spherical diameters (10 nm to 2 μm) and compared this to the energy distribution of HTO that was homogeneously distributed throughout the body. As expected, the "dose mean linear energies" of OBT were higher than that of the HTO by a factor of 1.7, which was close to the value found by Straume and Carsten (1993). However, as the AGIR (HPA, 2007) points out, "the extent of any increase will depend on the extent that OBT does preferentially localize within critical targets"; that is, if the OBT were homogenously distributed, then the added effect would be much lower.

About 70% of the hydrogen in the human body is in the exchangeable form, with about 95% of this hydrogen forming water molecules. Non-exchangeable hydrogen forms covalent bonds with carbon, and is found in components such as protein, lipids and carbohydrates. Several factors determine the distribution of OBT in the body resulting from tritium in the diet. These include the ratio of OBT to HTO in the dietary items, daily intakes of carbohydrates, fats and proteins, oxidation rates of the dietary constituents, the gut absorption factors for organic precursors (namely monosaccharides, fatty acids and amino acids), the retention of organic precursors, and HTO and OBT excretion rates (Richardson *et al*, 1998).

Physiological models of OBT biokinetics have been proposed by Richardson (2001), Richardson and Dunford (2003) and Melintescu *et al* (2007). They provide sex-differentiated biokinetics and dose coefficients for males and females. Richardson *et al* (2001) present sex differences in dose coefficients based on the ICRP model, which stem from daily carbon intake rate that differs between females (228 g carbon) and males (303 g carbon). The resulting biological half-life of carbon is 51 days for female adults and 40 days for male adults. Richardson and Dunford (2003) consider the differing water and organic contents of tissues and organs, as well as differing biokinetics for their organic components, as presented in the non-ICRP "HCNO Model" (Richardson and Dunford, 2003). Table 6.11 shows dose-per-unit intake values for

adults from these studies and the values as published by the ICRP for its HTO and OBT models. It can be seen that dose coefficients from the various studies in Table 6.11 are within a factor of 2 of the ICRP (1996) values, with the highest one from Richardson and Dunford (2003). It should be noted that Richardson and Dunford (2003) also provide dose coefficients for tritiated nutrients, with the highest value for tritiated protein at 8.4×10^{-11} Sv/Bq, which is twice the ICRP (1996) value for OBT.

Richardson *et al* (1998) conducted a literature review of studies on OBT exposure and found that there exists significant amount information on intakes of tritiated food from animal experiments, but very little data from human intakes. The review also found there is sparse information on the exchangeable and non-exchangeable forms of OBT in diet. This, in turn, may have introduced uncertainties in current dosimetric models for tritium in the diet. Based on this literature review, Richardson (2001) proposed a biokinetic model based on the overall catabolic reactions of foodstuffs, the Principal Nutrient Metabolic (PNM) model. This model accounts for the non-unifiorm deposition of organically bound trtium in tissues and organs, but, as with the ICRP model, does not include compartments representing the long-term retention of structural proteins and fat as adipose tissue.

It can be seen from Table 6.11 that taking gender differences into account increases the dose coefficient by up to about 25% for HTO and up to 50% for OBT. Accounting for the non-uniform distribution of organically bound tritium increases the dose by up to 80%.

Table 6.11: Adult Dose Coefficients from Physiologically-Based OBT Biokinetic Models

Biokinetic Model	Dose coefficient (Sv/Bq)
Ingestion of HTO:	
ICRP (1996)	1.8×10^{-11}
Richardson *et al* (2001)	1.8×10^{-11} (males) 2.2×10^{-11} (females)
Melintescu *et al* (2007)	1.6×10^{-11} (males) 2.3×10^{-11} (females)
Ingestion of OBT:	
ICRP (1996)	4.2×10^{-11}
Richardson *et al* (2001)	4.2×10^{-11} (males) 6.1×10^{-11} (females)
Richardson (2001)	7.6×10^{-11} (adults, PNM model)
Richardson and Dunford (2003)	7.4×10^{-11} *
Melintescu *et al* (2007)	4.7×10^{-11} (males) 7.0×10^{-11} (females)

** For "Reference Man" diet (ICRP, 1975)*

6.5.6 Biokinetics of Tritiated DNA Precursors

Tritium may be incorporated into DNA or RNA for the purpose of experiments studying cell kinetics. This section examines the biokinetics of such compounds. The nucleic acid precursors thymidine and deoxycytidine are most commonly labelled with tritium for this purpose. Uridine and adenine are most commonly labelled with tritium for work involving RNA (HPA, 2007).

After tritiated thymidine (^{3}HTdR) is administered to humans or animals, it is incorporated into DNA during the synthesis stage of the cell cycle. Following ingestion of ^{3}HTdR, about 2% of the tritium is incorporated into DNA (Lambert, 1969), and the remainder appears as HTO. Tritiated thymidine is available for only a short time after intake and primarily for uptake by rapidly cycling cells such as bone marrow or gut. Chronic exposure to ^{3}HTdR will also label slowly cycling cells. Hence, the rate of turnover of these cells will determine the retention rate of this tritium.

The NCRP (1979) examined the dose resulting from ingestion of ^{3}HTdR based on considerations that are mainly theoretical. In the case of acute intakes by ingestion, it was concluded that tritium ingested as thymidine is 8.6 times more hazardous than that ingested as HTO. It also suggests this may need revision as more precise data on stem cells and ^{3}HTdR distribution and incorporation rates become available. Conclusions regarding chronic intakes are similar. In the cases of other tritium-labelled DNA and RNA precursors, the recommendation is to apply exposure limits for ^{3}HTdR until more data on the radiation effects of these other compounds become available. ^{3}HTdR is unstable above -4°C and therefore may degrade once released into the environment.

The NCRP (1979) states: *"Because DNA is metabolically stable, in contrast to RNA, label bound to RNA precursor will be distributed, as a function of time, with increasing preference to DNA. Hence, for cells with a long lifespan, it is finally the rate of cellular proliferation that defines the biological half-life of the radionuclide incorporated in the cell nucleus, irrespective of whether it was initially bound to RNA or DNA. On this basis, the dose to the stem cell nucleus from ^{3}H-thymidine is about 50 times higher than from the same amount administered as ^{3}HOH". Furthermore, the same report states "…it appears justified to estimate the long-term hazard from labeled RNA precursors … to be not larger than that from the same amount of equally labeled thymidine. Until more experimental evidence is available, late hazards from labeled RNA precursors should be considered similar to those from equally labeled thymidine".*

Komatsu *et al* (1990) examined the dose resulting from tritium bound to DNA, as a result of ingesting HTO and OBT. These investigators fed HTO and food to mice for 22 days. Equilibrium was reached by the 16th day of chronic intake. In the group of mice fed tritiated food, the highest ratio of OBT to HTO was found to be 2.2 in the liver. Liver DNA was found to have a lower specific activity than that of liver OBT. This was attributed to tritiated DNA containing little, if any, exchangeable OBT, which has a high specific activity. Comparing the specific activities of DNA-bound tritium in both groups of mice (those fed HTO and those fed tritiated food) the specific activity of DNA-bound tritium in the tritiated food group was found to be 4.6 times that of the HTO group. The study also suggests that the ratio of the specific activity of DNA-bound tritium to HTO may be higher in embryos than in adults.

Tritium bound to DNA was found to contribute little (less than 1%) to the total dose as a result of chronic exposure to either HTO or food. The total doses for both exposure groups were found to be similar for chronic intakes. In the case of acute intakes of HTO, DNA-bound tritium was found to contribute about 20% to the total dose from intakes of HTO and about 40% to the total dose from intakes of tritiated food. The total dose resulting from the ingestion of tritiated food was found to be about double that from the ingestion of HTO.

More recently, Melintescu *et al* (2007) reported that tritium can be strongly bound in the hydration shell, mostly in DNA. This tritium, referred to as buried tritium, represents about 5% of the OBT concentration in plants and 20% of that in fish. Buried tritium contributes to the total dose resulting from tritium intake. Melintescu *et al* (2007) report that effects due to buried tritium are included in the assessment of the RBE and radiation weighting factor, so dose from buried tritium does not need to be added to the total tritium dose calculation.

Arguments have been presented suggesting that tritiated DNA and histone precursors present a significantly greater risk than that resulting from HTO (Müller, 2008a, b). The author indicates such tritiated compounds may be 1,000 to 5,000 times more effective than HTO because of their heterogeneous distribution in the body. The author attributes this mainly to the short range of tritium's beta particles, which causes their energy to be deposited in the cell nucleus. The authors also note that it remains to be proven that no significant risk exists from tritium bound to DNA as a result of releases of HTO to the environment (from HTO taken up by plants and animals, converted into OBT by these plants or animals, ingested by humans and incorporated into human cell nuclei).

Bridges (2008a, b) responded to both articles by Müller (2008a, b) by stating that the approximate thousandfold difference in effects is based on units of activity (such as becquerels) in the medium, rather than in terms of the dose to the cell or the nucleus. Also, the work referred to by Müller was carried out on *in vitro* systems, while *in vivo* results are quite different. Almost all ingested thymidine is broken down in the gut, and there is evidence that the effectiveness of ^{3}HTdR in adult mammals is only slightly greater than that expected from HTO. Furthermore, free ^{3}HTdR is unstable in the environment and therefore unlikely to be a source of exposure to tritiated thymidine. Available information indicates that the amount of tritium incorporated into DNA in *in vivo* systems is too small to cause the RBE to increase.

6.6 Summary and Conclusions

While current ICRP models for intake of HTO, HT and OBT are reasonably consistent with experimental results, further work related to HT and OBT biokinetics is suggested in this section.

HTO behaviour is well understood, and the current ICRP model appears to accurately predict HTO body burden and urinary excretion. The ICRP is considering adopting a revised biokinetic model for HTO (Taylor, 2003). Although the Taylor (2003) model for HTO has a dose coefficient similar to that of the current ICRP model, it treats OBT differently by considering the long-term retention of tritium. It has been proposed that the ICRP adopt the Taylor model, so there are

significant changes expected in the interpretation of bioassay results at long times following unusual HTO intakes. However, given the variation in the limited data on which the Taylor model was based, it would be beneficial to assess it against further human data. Moreover, it would be of interest to compare the Taylor model's predicted contribution of OBT to dose with the work of Trivedi *et al* (1997b; 2000), which studied OBT contribution to dose in actual human HTO exposure cases. Finally, the Taylor model applies only to adults; an expansion to various age groups is needed to satisfy the requirements of public dose assessments.

When elemental tritium gas is inhaled, the dose to the cells of the respiratory tract's AI region should be considered when the exposure is predominantly to HT.

The ICRP's OBT model appears to be generally consistent with experimental results. However, it does not account for the differentiated deposition of OBT between various organs and tissues. The use of physiologically based OBT models, such as the one proposed by Richardson and Dunford (2003), should be encouraged when significant doses are expected (such as in non-routine or accidental exposures). The validation and incorporation of these models in computer codes would facilitate their use in OBT dose assessments. Furthermore, it would be valuable to expand this type of model to include age dependency for all age groups, including the nursing infant.

The NCRP (1979) presented a review and interpretation of data on the distribution of radionuclides incorporated in genetic material. A review of recent work on this topic would allow this information to be updated. Finally, Komatsu *et al* (1990) concluded that the total dose resulting from the ingestion of tritiated food is about twice that from the ingestion of HTO. This suggests that current OBT dose coefficients account for the binding of tritium to DNA.

Annual doses to members of the public residing near nuclear power plants are in the order of a few μSv, and annual tritium doses to persons residing near tritium processing facilities are less than 0.1 mSv (CNSC, 2009). Therefore, improvements to models discussed above would not have a large impact on the estimated doses, and current dose estimates do not significantly underestimate risks, which are very low.

Recap: Section 6

- Current ICRP models describing the behaviour of HTO and OBT in the human body are reasonably consistent with experimental results.
- Radiation doses from tritium are estimated by measuring the tritium in bioassay samples (i.e., urine) or through environmental monitoring, and then using biological models to estimate the concentration of tritium in the various organs and tissues in the body.
- The ICRP recommends two main metabolic models to estimate the dose from tritiated compounds:
  - The ICRP HTO model used to estimate the dose resulting from intakes of tritiated water or other tritiated compounds that partially convert to HTO after being taken into the body. Tritiated water by far results in the most important doses from intakes of tritiated compounds by workers and the public.
  - The ICRP OBT model used to estimate the dose resulting from intakes of various tritiated organic compounds. It is used for the estimation of doses to the public resulting from dietary intakes of organically bound tritium, i.e., tritium bound to nutrients. Organically bound tritiated compounds yield doses per unit intake of about twice that of tritiated water, but the overall amount of OBT in the body is much lower than the amount of HTO.
- A new model (Taylor, 2003) has recently been proposed for HTO which varies from the ICRP model in the way it treats the OBT formed in the body after tritiated water is inhaled or ingested. It has the advantage over the ICRP model that it accounts for tritium that is retained for long periods of time in the body (biological half-life of about one year). However, this model applies only to adults and would need to be expanded to account for various age groups before it could be used for estimating doses to members of the public.

7 OPTIONS FOR ASSESSING AND CONTROLLING RISKS ASSOCIATED WITH TRITIUM EXPOSURE

The ICRP's principles and recommendations have generally been adopted both in Canada and internationally, in order to protect radiation workers and members of the public from radiation. These are based on reviews of national and international committees — including that of the ICRP and others such as UNSCEAR, the U.S. National Council on Radiation Protection and Measurements, the U.K. Health Protection Agency and the U.S. National Academy of Sciences/ National Research Council — on what is known about the sources and effects of ionizing radiation. As the leading group in radiation protection, the ICRP has formulated what it believes to be a practical, working system of radiation protection that is scientifically based with straightforward assumptions. The ICRP's 2007 recommendations set out in ICRP 103 did not change substantially from the 1991 version.

With respect to controlling exposures to tritium radiation, the ICRP approach has been criticized for assigning a weight of 1 to all low-LET radiations, including tritium's beta radiation despite the considerable evidence suggesting that the RBE for cancer induction is more than that — and possibly more than twice as much (see Section 5.2). The radiation weighting factor w_R is a factor by which an absorbed dose (in gray) is weighted for the purpose of determining the equivalent dose (in sievert). The w_R for a specified type and energy of radiation has been selected to be representative of values of the RBE of that radiation (e.g. tritium beta radiation) in causing stochastic effects (e.g. cancer) at low doses. Using a w_R for tritium to reflect the RBE value (e.g. 2.2 relative to gamma radiation would best reflect the radiation risk for tritium.

The ICRP has argued that w_R is one of the simplifying assumptions used to assign doses to reference individuals for the purpose of summing doses from external and internal exposures to different radionuclides in order to compare them with dose limits, constraints and reference levels that relate to representative workers or members of the public independently of sex and age.

This section outlines the ICRP approach and the implications of changing the radiation weighting factor w_R of tritium from a value of 1.

7.1 The ICRP's Approach to Radiation Protection From Internal Emitters

The ICRP approach to radiation protection is to provide:

"an appropriate standard of protection for man without unduly limiting the beneficial practices giving rise to radiation exposure."

"This aim of providing an appropriate standard of protection, rather than the best possible standard regardless of costs and benefits, cannot be achieved on the basis of scientific concepts alone. Members of the Commission and its Committees have the responsibility for supplementing their scientific knowledge by value judgments about the relative importance of different kinds of risk and about the balancing of risks and benefits. The Commission believes that the basis for such judgments should be made clear, so that readers can understand how the decisions have been reached." (ICRP 103, 2007; ICRP.org)

The ICRP aimed to devise risk-related quantities that would allow all types of radiation exposures to an individual to be summed, considering the differences in effectiveness of various radiations in causing stochastic effects, and different contributions of organs and tissues to total detriment from stochastic effects.

The ICRP protection quantities of equivalent and effective dose use the sievert (Sv) and are calculated from the absorbed dose (Gy). The protection quanities of equivalent and effective dose are risk-related quantities that can be compared with limits, constraints and reference levels, and used when optimizing radiation protection. The protection system includes assigned doses for radionuclide intakes and extremities (i.e., hands, feet).

The principal quantities used by ICRP (*1991; 2007*) are:

(i) the mean absorbed dose in an organ or tissue, D_T, given in terms of energy absorbed per unit mass (joules/kg). It is called the gray (Gy)

(ii) the equivalent dose in an organ or tissue, H_T, obtained by weighting absorbed dose using defined radiation weighting factors, w_R, to take account of the relative effectiveness of different radiation types, per unit absorbed dose, in causing stochastic effects at low doses. The equivalent dose, H_T, in tissue or organ T is given by:

$$H_T = \sum_R w_R D_{T,R}$$

where w_R is the radiation weighting factor for radiation, R. The unit is given the special name the sievert (Sv). The choice of radiation weighting factors is informed by available information on RBE for cancer related end-points at low doses and dose rates.

(iii) the effective dose, E, obtained as the sum of equivalent doses to each organ or tissue, weighted using defined tissue weighting factors, w_T, to take account of the contribution of the individual organs and tissues to overall detriment from cancer and hereditary effects:

$$\begin{aligned} E &= \sum_T w_T H_T \\ &= \sum_T w_T \sum_R w_R D_{T,R} \end{aligned}$$

where H_T is the equivalent dose in tissue or organ, T, w_T is the weighting factor for tissue T and $\Sigma w_T = 1$. The unit is also called the sievert (Sv).

The protection quantities of equivalent and effective dose are intended for use as defined by the ICRP within its recommended system of protection. Therefore, other applications (such as, epidemiology studies and incidences with high intake of radioisotopes) should use absorbed dose (grays). Risk estimates to individuals for special or specific investigations (such as a very large exposure) should use the best available information on RBE relating to the stochastic effect(s) under consideration, and should use age- and sex-specific risk estimates (see ICRP, 2007, pp 252–3).

The calculations of equivalent and effective dose are not specific to individuals, but rather are calculated for "reference individuals" in occupational and public settings (in the public settings, the reference individuals include those of different ages). Therefore, in the ICRP's protection system, individual-specific data such as breathing rate and gender, are not included in routine dose assessments. However, the ICRP recommends using this information in epidemiological studies and where dose/risk assessments are needed for specific tissues or organs (such as when a radiation dose has been received far in excess of the dose limits). In these special cases, it is recommended to use absorbed doses (in grays) and appropriate RBEs and risk estimates. Effective and equivalent dose are to be used with dose limits, constraints and dose optimization. They provide a specified and universal means to assess and control dose from internally deposited radionuclides and external irradiations. The ICRP (2007) believes that practical radiation protection would not be improved by separate dose calculations for males and females or age-specific parameters. It follows that the beta-radiation-specific weighting or tissue weighting factors would not necessarily provide more protection and could imply a greater precision than actually existed.

7.1.1 Change the Radiation Weighting Factor (w_R)

Radiation that has sufficient energy to ionize molecules is called ionizing radiation. This term encompasses a wide variety of radiation including:

- soft dental X-rays
- high-energy gamma rays
- heavy particles
- protons
- neutrons
- alpha particles
- electrons

All these types of radiation may pose health risks by depositing their kinetic energy within living tissue. The pattern of the deposition of that energy, the LET varies according to radiation's type and amount of energy. Different tissues and organs also have different levels of sensitivity to radiation.

From a radiobiological perspective, the relative biological effectiveness (RBE) provides the ratio of the absorbed doses of two types of radiation that produce the same specified effect. However, for radiation protection purposes, a radiation weighting factor is used to account for the effects of radiations of different qualities and to permit an overall dose to be calculated by adding the doses from those different radiations (ICRP, 2003). The ICRP published radiation weighting factors in its 1990 recommendations and assigning a w_R of 1 to photons and electrons of all energies. Its ICRP 92 publication (2003) reviewed the RBE, the quality factor (Q) and the w_R in some detail and recommended retaining this weighting factor. The ICRP confirmed this in its recommendations issued in 2007 (ICRP, 2007).

Radiation weighting factors are chosen as a simple representation of the effectiveness of different radiations in causing stochastic effects at low doses and dose rates. They do not consider, for example, observed differences between low-LET radiations (such as photons of different energies) or different alpha-particle RBE values for various cancer types (such as solid tumours and leukemia) (Harrison and Day, 2008).

The ICRP uses broad judgments to smooth over and simplify many of the experimental differences in RBE values by using generic radiation weighting factors, including a w_R of 20 for all high-LET alpha particle radiations and a w_R of 1 for all low-LET radiations (ICRP, *1991*; 2007). It is clear that this is a broad brush simplification for radiological protection purposes and is defended on the grounds of simplicity, practicality and transparency, provided that it can be shown that this simplification will not unduly affect the operational outcome. For example: if doses are estimated for comparison with regulatory limits and the use of generic radiation weighting factors leads to estimated effective doses well below levels requiring intervention, then scientifically more rigorous calculation methods would not necessarily improve the level of protection.

The AGIR (HPA, 2007) report, which thoroughly reviewed the effects of tritium and estimations of its RBE, suggested that the ICRP consider using a w_R of 2 for tritium for prospective assessments (worker and public dose estimates), in the context of optimization and dose limitation. B. Bridges, the Chair of the AGIR report, further explored implementing a w_R of 2 in an editorial (Bridges, 2008c). It is apparent that the concern of the AGIR report was for workers with tritium exposures at or near the dose limit. Bridges stated that:

To compensate for an RBE of 2 for tritium, the investigation level for tritium workers would need to be set a factor of at least 2 below the annual limit of intake (ALI) and certainly a factor of 2 below the investigation level for workers exposed to gamma radiation if they are to have the same degree of protection. Of course, if the investigation level is but a small fraction of the ALI then the consequence of assuming a w_R of 1 rather than an RBE of 2 becomes academic.

However, the report then said that:

The AGIR noted that the ICRP had some good reasons for deciding on a w_R of 1 for all photon radiations. Nevertheless, AGIR suggested to ICRP that the possibility should be considered of using a w_R of 2 for prospective assessments also, i.e., in the determination of equivalent and effective dose. Following this advice might remove a concern of some RPOs [radiation protection officers] *in industry that tritium workers are less well protected than gamma radiation workers, and at the same time help to dispel any misguided public perception that ICRP is trying to play down the risk from tritium.*

Raising the w_R for tritium radiation to 2 would double the assigned effective doses to workers handling tritium and to members of the public exposed through environmental pathways. In some cases, this could draw more attention to these doses and lead to better efforts to reduce those doses. As far as public doses due to tritium in Canada currently stand, the estimated tritium doses to the most exposed “critical group” are all well under 0.1 mSv/year year, or

less than 10% of the public dose limit and are under than 0.01 mSv/year in the vicinity of nuclear power plants (CNSC, 2009). Even if the dose estimates were doubled, all doses to critical groups would remain below 20% of the public dose limit.

Nuclear energy workers have average doses from tritium that range from 0.1 to 1 mSv/year, with some individual workers occasionally approaching 5 mSv. Where other types of radiation exposure such as gamma radiation are included, the tritium dose can make up 10–50% of the total dose (CNSC, 2009). The doubling of these dose estimations would certainly draw more attention to those workers, but whether that added attention would result in improved radiological protection is not certain, but may result in the requirement that licensed conduct additional ALARA analyses.

The ICRP (2007) system includes the concepts of dose constraints (see glossary) and optimization of protection. In controlling doses from tritium, the regulatory body could apply a constraint specifically to tritium doses that would require investigations and remedial actions when it was exceeded. Current CNSC regulations do not require constraints as per the ICRP concept, but they are similar to the Action Level requirement in the CNSC *Radiation Protection Regulations*. However, the use of constraints to account for the higher RBE of tritium is less transparent than increasing the RBE value to 2.

As shown by Table 7.1, the w_R values used by the ICRP are radiation specific and form part of the definition of equivalent dose.

Table 7.1: Recommended Radiation Weighting Factors (ICRP, 2007)

Radiation Type	Radiation Weighting Factor (w_R)
Photons	1
Electrons and muons	1
Protons and charged pions	2
Alpha particles, fission fragments, heavy nuclei	20
Neutrons	A continuous function of neutron energy is recommended (see Figure 1 and Equation 4.3 in ICRP (2007).

The designation of a radionuclide-specific w_R, such as changing the w_R to 2 for tritium, would be a marked change from the ICRP's approach since the ICRP does not assign specific w_R values to any radionuclides. Other examples where the RBE value differs from the w_R are for very "soft" x-rays (less than 100 keV) and low-energy electrons emitted by atoms (Auger electrons). These radiations also become more biologically effective as their energy decreases, likely due to the same mechanism described in section 5.3.6 for tritium. However, the ICRP does not make an exception for these radiations in its weighting table either.

The ICRP commented (ICRP, 2007; Cox *et al*, 2008) on the use of a single w_R value of 1 for all low-LET radiation, stating that it is one of many simplifying assumptions that allow doses from several radiation types to be summed and that the use of this single value does not compromise the intended use of the protection quantities for dose limitations. Strictly, changes to the ICRP's methodology would mean that the calculated quantities should not be called equivalent and effective doses. "The ICRP makes clear that for applications outside the system of protection, including the assessment of health risks to individuals, absorbed doses should be used, together with the best available information on RBE and risk factors. In such applications, it is likely that uncertainties will also be considered and that these will be substantially greater than factors of 2 to 3, particularly for low dose exposures (ICRP, 2007)."

7.2 Summary and Conclusions

Concern has been expressed about the adequacy of the ICRP's radiation protection system, notably that it does not accurately reflect radiological risks of tritium exposures. In this light, two options were discussed: retaining the current ICRP system in its entirety, or modifying the system by changing the w_R for tritium.

Modification of the tritium weighting factor used in the calculation of the effective and equivalent dose (in sieverts) would be a significant departure from the ICRP framework.

The ICRP has designed the sievert (Sv) as the unit to give a measure of dose for all ionizing radiations. It does this by applying weighting factors (w_R) for the different types of radiation (i.e., alpha, beta and gamma) and for the radiation sensitivities of different organs and tissues. The use of the sievert has these implications:

- The sievert is strictly a unit for radiation protection purposes.
- It provides a single unit for dose from all ionizing radiations for optimization and to compare against the dose limit.
- Due to simplifications, the w_R loosely reflects the biological effectiveness of the type of radiation and is therefore only an approximate indicator of the risk.
- All electrons (beta radiation) and photons have a weighting factor of one.
- The w_R is not based upon the source of the radiation (for example, x-ray machines or specific radioisotopes).
- Doses are gender neutral; equivalent and effective doses are calculated for a "representative person" based on a population of male and females, ethnicity and age.
- The sievert should not be used for assessing doses in instances where individual risk assessments are required. These would be special instances where large intakes are suspected or in epidemiological studies. In those cases, tissue weighted absorbed doses with appropriate RBE values should be used. As well, characteristics specific to the individual should be taken into account.

Application of a different radiation weighting factor for tritium to reflect the RBE value would be more reflective of the radiation risk. However these considerations must be taken into account for this approach:

- Occupational and public doses are already low and there is a continuous effort to reduce these further.
- It would be inconsistent with the ICRP system of radiological protection which is currently the international standard approach. Specifically:
  a) There are no other isotope-specific w_R
  b) Use of the sievert unit would not be appropriate
  c) It would be difficult to compare radiation protection practices nationally and internationally

A decision to change from the current ICRP framework should consider that doses to workers and members of the public are relatively low. From the information on health effects reported here (see Chapter 3), one would not expect to observe any increase in disease in either population. Similarly, epidemiological studies of populations with known exposures to tritium have not demonstrated any excess disease.

Recap: Section 7

- In Canada and internationally, radiation protection for nuclear workers and members of the public is based on the principles and recommendations of the ICRP.
- With respect to controlling exposures to tritium, a criticism of the ICRP approach is that it weighs all low linear energy transfer (LET) radiations—including tritium's beta radiation—as one, although there is much evidence to suggest that the RBE for cancer induction by tritium is possibly more than twice as much.
- While the ICRP system of protection is risk-based, equivalent and effective dose relate to "reference persons" and do not take account of age, size and sex differences in risk factors.
- One alternative to the ICRP approach would be the use of a specific radiation weighting factor for tritium. However, this could possibly lead to a false impression of the accuracy with which we understand low dose risks and would not necessarily improve protection.
- Another option that would be consistent with the ICRP's recommendations would be the setting of dose constraints on tritium exposures. The constraints would be in addition to dose limits and the dose optimization (ALARA) process.
- Nonetheless, the current system is adequately protective; epidemiological studies of populations with known exposures to tritium have not demonstrated any excess disease.

8 CONCLUSIONS

This report aimed to:
- conduct an independent review of scientific literature to assess health risks to workers and the public from exposure to tritium
- assess Canadian and international dosimetry practices for tritium intakes
- review the approaches for limiting exposures to tritium

In response to those objectives, this report provides:
- an overview of tritium's physical, chemical and radiological properties
- a detailed analysis of the adverse health effects of tritium radiation, including reviews of laboratory and epidemiological studies
- a review of experimental studies that estimate the relative biological effectiveness (RBE) of tritium radiation
- a description of biokinetic models and dosimetry of tritium
- a review of the ICRP's approach for protection from tritium and possible modification of the radiation weighting factor for tritium

The review of the physical, chemical and radiological properties of tritium highlights its unique properties:
- It can replace the stable form of hydrogen in water molecules and organic compounds.
- It has one of the lowest energies of the beta-particle emitters, and much more tritium per unit mass of tissue is generally required to generate the same absorbed dose as other radioisotopes.

In laboratory studies, tritium radiation has been shown to induce both stochastic and deterministic health effects, consistent with the effects induced by other types of ionizing radiation. As with other radiations, the occurrence and severity of deterministic effects are proportional to dose. Effects, such as teratogenic and reproductive injury, require intakes of 1 GBq or higher. It is assumed that tritium exposure can also induce stochastic effects, such as cancer; however, there has been no epidemiological evidence of tritium-induced cancer in humans to date. Laboratory studies indicate that the lowest dose necessary to induce cancer in mice is in the range of 1 GBq per gram of body weight or a milligray per day, an amount far in excess of the intakes by workers in Canada and tritium concentrations of 100 Bq/L or less in Canadian public drinking water supplies. Hereditary effects have not yet been demonstrated in humans for any radiation exposure, although the ICRP recommends a risk estimate of 5×10^{-6} per mGy for severe hereditary effects, since it is highly unlikely that humans are immune to germ line mutations and associated transgenerational effects.

The risk from organically bound tritium (OBT) should intuitively be greater than that from HTO, but studies looking specifically at OBT-related health effects are few, with most of them using DNA precursors, such as thymidine. While most OBT produced in the environment would not be DNA precursors, the organic compounds into which it is incorporated will have a longer residence time in the body, thereby posing a greater risk. Biokinetic models appear to account for this difference reasonably well, but new, improved models continue to be developed.

A review of the relative biological effectiveness (RBE) of tritium radiation indicates a fairly wide range of values. Based upon arguments presented by the ICRP, the most appropriate choice for the reference radiation is gamma radiation. An appropriate biological endpoint for an RBE would be cancer, as it represents the greatest risk in occupational and environmental settings. Although there have been very few suitable laboratory studies using cancer as their endpoint, the weight of the evidence points to an RBE factor of 2 or more.

Current ICRP models for intake of HTO, HT and OBT are reasonably consistent with experimental results. While improved models are under development, they will only apply to adults, so an expansion to various age groups, would be required for use in public dose assessments.

Recent studies have indicated that the effective dose resulting from the ingestion of OBT may in some cases be close to twice that predicted by the current ICRP model. In terms of the incorporation of tritium into genetic material, there is evidence that current OBT dose coefficients do account for the binding of tritium to DNA. However, the current ICRP model does not account for differentiated deposition of OBT between organs and tissues. To account for these differences, the use of physiologically based OBT models, such as the one proposed by Richardson and Dunford (2003), should be encouraged when doses are expected to be significant.

In Canada, tritium concentrations in the environment (such as those in air, water, vegetation, animals and milk) are monitored to estimate the annual dose to members of the public living around nuclear facilities. This information is used to confirm that releases from these facilities result in doses below the public dose limit of 1 mSv, as established in the CNSC's *Radiation Protection Regulations*. In 2006, the tritium concentrations in air in the vicinity of nuclear facilities varied between 0.38 Bq/m^3 and 35.66 Bq/m^3 and the corresponding radiation doses varied between 0.00045 mSv and 0.00236 mSv per year. Tritium doses to members of the public around processing facilities were also very low (0.00001 to 0.0145 mSv per year) (CNSC, 2009). All these doses are well below the regulatory dose limit of 1 mSv per year for a member of the public and the exposures attributed to natural background radiation. Given the extremely low doses to the public from tritium emissions — and that these doses are much lower than those known to cause health effects — it is highly unlikely that ecological or analytical health studies of members of the public would be able to produce any meaningful results regarding tritium risk.

Radiation doses to Canadian nuclear energy workers are typically less than 10% of the regulatory dose limit of 50 mSv per year and 100 mSv in five years (cumulatively). In 2006, occupational doses from tritium exposures ranged from 0.07 to 0.26 mSv for workers in nuclear generating stations, and from 0.30 to 0.90 mSv for workers in processing and research facilities. In all cases, the doses received by workers were far less than the CNSC annual occupational regulatory dose limit (CNSC, 2009).

The lack of current evidence of excess risk among these populations suggests that any tritium-specific risk would be low. Available studies of cancer and other adverse health effects in workforces are not always useful, due to data that is not tritium specific, it involves low doses

and small numbers, and the simultaneous higher exposures from other radiation exposure in the workplace. It is thus very difficult to use current epidemiological studies for an adequate assessment of tritium-related health risks. There is a need for individual studies and pooled analyses of workers with relatively high tritium exposures and good-quality dosimetry data to assess these risks accurately and appropriately.

Doses from tritium are currently kept low through the protective framework recommended by the ICRP. The ICRP has developed a radiation protection system that considers the differences in effectiveness of different types of cancer-causing radiation, variations in the radiosensitivity of tissues, and contributions to the total detriment from stochastic effects. The ICRP has devised the protection quantities of equivalent and effective dose, in order to sum the doses from several types of radiation, to compare them to limits and constraints and to provide points of reference for optimization. A perceived shortcoming of this framework is that it requires some of the assumptions to be simplified in order to calculate dose. This report reviewed the discussion on the appropriateness of using a w_R of 1 for all beta and all photon radiation, when available scientific data suggest that a w_R of 2 or more would be more in line with an RBE for tritium beta particles. Furthermore, as explained by the ICRP, the system of protection is risk based, but its equivalent and effective dose relate to reference persons and so the system should be recognized as only rough correlates of risk to individuals. The protection quantities do not consider age and sex differences in risk factors, but base protection on limits and constraints that apply to all workers or members of the public. Setting constraints below limits and optimizing protection below constraints are central to the ICRP system.

The scientific information considered in this report provides the basis for consideration of appropriate protection standards and approaches for tritium. One option is to consider setting constraints on tritium doses, which would be in line with ICRP recommendations. Another option is to recommend a radiation weighting factor of 2 for tritium beta particles which would be a departure from ICRP recommendations. In any case and including the status quo, the current system of radiation protection with a focus on optimization has been effective in keeping exposures of workers and members of the public very low. Tritium doses are well below doses at which increase risk of cancer has been observed.

9 GLOSSARY

Absorbed dose: The energy deposited by ionizing radiation to a suitably small volume of matter divided by the mass of that volume. The unit of measurement is the gray (Gy).

Absorption (from the respiratory tract): Movement of material from the respiratory tract to blood. Materials are classified into three categories depending on their rate of absorption from the respiratory tract to blood:

- Type F materials are readily absorbed into blood from the respiratory tract (fast absorption rate).
- Type M materials have intermediate rates of absorption into blood from the respiratory tract (moderate absorption rate).
- Type S materials are relatively insoluble in the respiratory tract (slow absorption rate).

Acetylcholinesterase: An enzyme that degrades (through its hydrolytic activity) the neurotransmitter acetylcholine, producing choline and an acetate group.

Activity: The rate at which nuclear disintegrations occur in a radioactive material. Used as a measure of the amount of a radionuclide present. The unit of measurement is the becquerel (Bq). 1 Bq = 1 disintegration per second.

Action level: A specific dose or other parameter that, if reached, may indicate a partial loss of control of the radiation protection program.

Acute exposure: An exposure received within a short period of time. Normally used to refer to exposures of sufficiently short duration (for example less than an hour) that the resulting doses can be treated as instantaneous.

Age-adjusted rate: The summary rate of disease or death in a population where the age specific rates are weighted by the age structure of a standard population. This allows rates to be compared over time as the population age distribution changes.

Aggregate mean: The mean for all values in all samples combined, as opposed to the mean values of the individual samples.

ALARA (As Low As Reasonably Achievable): A concept (or optimization tool) in radiation protection used to keep individual, workplace and public dose limits As Low As Reasonably Achievable, with social and economic factors taken into account. ALARA is not a dose limit, but a practice that aims to keep dose levels, as far below limits as possible.

Alpha particles: Positively charged particles consisting of two protons and two neutrons that are emitted by the nuclei of radioactive (unstable) elements as they decay. Alpha particles are relatively large and can be stopped by skin or a sheet of paper. An alpha particle is a helium nucleus.

Amino acid: An organic molecule containing both an amino group (NH_3) and a carboxyl group (COOH).

Annual limit on intake (ALI): The activity of a radionuclide that, when taken into the body, results in a committed effective dose of 20 mSv.

Apoptosis: A form of cell death also referred to as programmed cell death, in which a "suicide" program is activated within the cell, leading to fragmentation of the DNA, shrinkage of the cytoplasm, membrane changes and cell death without lysis or damage to neighbouring cells. It is a normal phenomenon that occurs frequently in multicellular organisms.

Atom: A unit of matter consisting of a single nucleus surrounded by a number of electrons equal to the number of protons in the nucleus. The atom is the smallest portion of an element that can combine chemically with other atoms. All atoms other than Hydrogen-1 also have neutrons.

Atomic mass: The unit of measurement for the mass of an isotope of an element. The atomic mass is expressed in atomic mass units, which are defined as one-twelfth the mass of an atom of Carbon-12. An atomic mass of 1 is equivalent to approximately 1.66×10^{-27} kg.

Atomic number: The number of protons in the nucleus of an atom. The symbol used is Z.

Auger emitter: An atom that has had an electron ejected from a core level, leaving a vacancy that is filled by an electron from a higher energy level and causing a release of energy. This energy is released in the form of an emitted photon or it can be transferred to another electron, which is ejected from the atom. This second ejected electron is called an Auger electron.

Becquerel: The SI unit of radioactivity, equal to one transformation (decay) per second. The becquerel supersedes the non-SI unit *curie* (Ci). 1 Bq = 27 pCi (2.7×10^{-11} Ci) and 1 Ci = 3.7×10^{10} Bq.

Beta particles: High-energy negatively charged electrons or positively charged positrons that are ejected by radioactive (unstable) elements as they decay. A beta particle is identical in mass and charge to an electron. Beta particles are relatively small and can be stopped, for example, by a sheet of aluminum a few millimetres thick.

Bioassay: Any procedure used to determine the nature, activity, location or retention of radionuclides in the body by direct (*in vitro*) measurement or by *in vitro* analysis of material excreted or otherwise removed from the body.

Biological half-life: The time required in a given radionuclide for its activity to decrease, by biological clearance and radiological decay, to half its original activity.

Biokinetic model: A mathematical description of the behaviour of radionuclides in the metabolic processes of cells, tissues, organs and organisms. It is most frequently used to describe distribution of radionuclides among tissues and excretion.

Blotter effect (or capillary action): The ability of a material to draw liquid into it.

Buried tritium: Molecules of tritium that are strongly bound in the hydration shell, mostly in DNA.

CANDU: The CANDU (CANada Deuterium Uranium) reactor is a Canadian-invented, pressurized heavy water reactor that uses heavy water (deuterium oxide) for moderator and coolant and natural uranium for fuel.

Carcinogen: Any agent, such as a chemical or a form of radiation that can cause cancer.

Carcinoma: Cancer of epithelial cells; the most common form of human cancer.

Case control study: A study designed to determine whether people with a disease or condition (cases) differ in exposure to certain agents and factors than do a similar group of people who do not have the disease (controls). A variation of this type of study is a nested case-control study, where the cases of a disease are identified from the original cohort and are matched to controls selected from the same cohort who have not developed the disease by the time of disease occurrence in the case.

Catabolism: A general term for the enzyme-catalyzed reactions in a cell by which complex molecules are degraded to simpler ones with release of energy.

Cataract: A disease, affecting the crystalline lens of the eye or its envelope, causing impairment of vision (blurred vision) or blindness.

CBA/H strain of mice: A strain of mice developed in 1920 by L.C. Strong at Cold Spring Harbor, NY, by crossing the Bagg albino with the DBA mouse (the oldest of all inbred strains). CBA mice are a superior animal model because they have low spontaneous leukaemia incidence (0.1 to 1%), develop acute myeloid leukaemia after exposure to radiation or benzene, and have cytogenetic, molecular, and histopathological characteristics that are comparable to those seen in human acute leukaemia. CBA/H mice are one of several inbred strains of CBA mice.

Cell: The structural and functional unit of all known living organisms. It is the smallest unit of an organism that is classified as living.

Chi-squared (χ^2) test: A statistical test that is used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more groups.

Chromatid: One copy of a chromosome formed by DNA replication that is still joined at the centromere to the other copy. The two identical chromatids are called sister chromatids.

Chromatid aberration: Damage to chromatids that can result from chromatic and isochromatid breaks, gaps, single fragments, and chromatid exchanges.

Chromosome: Structure composed of a very long DNA molecule and associated proteins that carries part (or all) of the hereditary information of an organism.

Chromosome aberration: Damage to chromosomes that can result from dicentrics, centric rings, acentric rings, and terminal deletions.

Chronic exposure: Exposure persisting in time. The adjective "chronic" relates only to the duration of exposure, and does not imply anything about the magnitude of the doses involved. It normally refers to exposures persisting from days to many years as a result of long-lived radionuclides in the environment.

Chronic lymphocytic leukaemia (CLL): The most common type of leukaemia, involving a particular subtype of white blood cells — a lymphocyte called a B-cell. B-cells originate in the bone marrow, develop in the lymph nodes, and normally fight infection.

Cohort study: A study designed to follow a group of people (a cohort) over time to determine whether their exposure to certain factors, as measured at the beginning and over time, influence whether they develop a certain disease or condition.

Committed effective dose: A dose of radiation, received by an organ or tissue from a nuclear substance:

- during the 50 years after the substance is taken into the body of a person 18 years old or older

or

- during the period beginning at intake and ending at age 70, after it is taken into the body of a person less than 18 years old.

Compton scattering: The interaction of a photon with an orbital electron results in transfer of energy from the photon to the essentially unbound electron.

Confidence interval: A range of values for a variable of interest, with a specified probability (such as 90%, 95%, or 99%) including the true value of the variable. The specified probability is called the confidence level, and the upper and lower ranges of the confidence interval are called the confidence limits.

Confidence limit: Interval estimates for the mean that give an indication of the uncertainty there is in the estimate of the true mean. Interval estimates are often desirable because the estimate of the mean varies from sample to sample. Instead of a single estimate for the mean, a confidence interval generates a lower and upper limit for the mean. A narrower interval indicates a more precise estimate.

Confounding factor: A factor associated with both the disease and the exposure. A confounding factor may mask an actual association or falsely demonstrate an apparent association between study variables where no real association exists. Confounding factors should be measured and considered to avoid bias in a study's conclusions.

Congenital anomaly (abnormality): A health problem present at birth (not necessarily genetic).

Corpora lutae (corpus luteum): Forms at the site of ovulation on the ovary, and produces progesterone.

Cosmic rays: High-energy charged particles originating in outer space, which travel at nearly the speed of light and strike the Earth from all directions.

Covariate: A variable that is possibly predictive of the outcome under study. A covariate may be of direct interest to the study or may be a confounding factor or effect modifier. Examples include maternal age, birth weight, birth order and sex.

Critical toxic value: The lowest concentration of a substance that will cause a certain adverse effect for each assessment endpoint.

Decay (radioactive): The transformation of a radioactive nuclide into a different nuclide by the spontaneous emission of radiation such as alpha, beta, or gamma rays, or by electron capture. The end product is a less energetic, more stable nucleus. Each decay process has a definite half-life.

Deoxyribonucleic acid (DNA): The molecular compound in the nucleus of a cell that forms the blueprint for the structure and function of the cell. DNA has a three dimensional structure in which two DNA chains are held together by hydrogen bonding between the bases, forming a helix.

Derived air concentration (DAC): The concentration of a radionuclide in air that, when inhaled at a breathing rate of 1.2 m^3 per hour for 2,000 hours per year, results in the intake of 1 ALI.

Descriptive/ecological study: A study concerned with and designed only to describe the existing distribution of variables, such as health status, without establishing cause and effect. Unlike analytic studies, which usually attempt to identify risk factors that cause disease, descriptive studies do not test hypotheses. The units of analysis are populations or groups of people, rather than individuals.

Deterministic effects: Changes in cells and tissues that are certain to occur after an acute dose of radiation (above a threshold value of at least 1000 mSv), below which the radiation effect is not detected. The severity of health effects — such as skin reddening, burns, and hair loss — increases with the radiation dose received.

DNA damage: Can be due to either environmental factors or normal metabolic processes inside the cell. DNA damage occurs often, but the cell has the ability to repair itself. The vast majority of DNA damage affects the primary structure of the double helix; that is, the bases themselves are chemically modified. These modifications can be as severe as to break one side of the double helix (single strand break) or both sides (double strand break).

DNA precursors: Compounds that may eventually be incorporated into DNA or RNA.

Dopamine: A monoamine neurotransmitter found in the brain and essential for the normal functioning of the central nervous system.

Dose: A general term for a measure of the energy deposited by radiation in a unit mass. See the more specific terms absorbed dose, equivalent dose, effective dose and collective dose.

Dose and dose rate effectiveness factor (DDREF): The ratio between the risk per unit effective dose for high doses and dose rates and low doses and dose rates.

Dose coefficient: The committed effective dose to a person as a result of taking 1 Bq of a radionuclide into the body.

Dose constraint: Part of the ICRP radiation protection framework. It is considered to be the most fundamental level of protection for the most exposed individuals from a single source within a class of exposure. In planned situations (practices), the dose constraint will be less than the limit and will depend upon local knowledge of the working environment. In emergency or existing exposure situations, it represents the level of dose/risk where action is almost always warranted, although the chosen value of the constraint will depend upon the circumstances of the exposure. Constraints may be used to set investigation levels.

Dose limit: The value of the effective dose or the equivalent dose to individuals from controlled practices that shall not be exceeded. Section 13(1) of the *Radiation Protection Regulations* states that a Nuclear Energy Worker shall not exceed an effective dose limit of 50 mSv over a one-year dosimetry period and 100 mSv over a five-year dosimetry period. The limit for a pregnant worker is defined as 4 mSv for the balance of the pregnancy, once declared. The limit stipulated for members of the public is 1 mSv in one calendar year.

Dose mean lineal energies: The average or mean energy released by a radiant particle along its path, used to calculate the absorbed dose in Grays.

Dose rate: A dose delivered over any unit of time (an annual dose is technically a dose rate).

Dosimetric model: (1) For intakes of radionuclides into the body, a model that estimates the dose in various organs and tissues per disintegration of a radionuclide in a specified source organ (site of deposition or transit in the body). (2) For external exposure, a model that estimates the dose rate in organs and tissues per unit activity concentration of a radionuclide in an environmental medium.

Dosimetry: A scientific subspecialty in radiation protection and medical physics that focuses on calculating internal and external doses from ionizing radiation.

Edema: Swelling caused by the entry of fluid and cells from the blood into the tissues, which is one of the cardinal features of the process of inflammation.

Effective dose: An ICRP radiation protection unit of dose designed to reflect the amount of radiation detriment. It is obtained by multiplying the equivalent dose of each tissue or organ by an appropriate tissue weighting factor and summing the products. The unit of measurement is the sievert (Sv).

Electron capture: A radioactive decay process in which an orbital electron is captured by and merges with the nucleus. After the process, the mass number is unchanged, but the atomic number is decreased by one because a proton is converted to a neutron.

Electron: A stable elementary particle having a negative electric charge of 1.6×10^{-19} coloumbs and a mass of 9.1×10^{-31} kg.

Electron volt (eV): A unit of energy = 1.6×10^{-12} ergs = 1.6×10^{-19} J; 1 eV is equivalent to the energy gained by an electron in passing through a potential difference of 1 V; 1 keV = 1,000 eV; 1 MeV = 1,000,000 eV.

Elements: Specific types of atoms that have the same number of protons in their nucleus and therefore have the same atomic number. The number of neutrons may differ.

Embryo: A fertilized egg from conception to the eighth embryonic week.

Energy: A thermodynamic quantity equivalent to the capacity of a physical system to do work. The unit of measurement is the joule (J).

Enzymatically catalyzed reaction: A specific biochemical reaction or a chemical change in another substance that is facilitated by a protein.

Epidemiology: The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to control health problems in populations.

Equivalent dose: A measure of the dose to a tissue or organ designed to reflect the amount of harm caused to the tissue or organ. Obtained by multiplying the absorbed dose by a "radiation weighting" factor to allow for the biological effectiveness of the various types of radiation in causing harm to tissue. The unit of measurement is the sievert (Sv).

Estimated no-effects value: Derived by dividing the critical toxic value (CTV) by an application factor. An application factor is used to account for the uncertainties inherent in extrapolating between measurement and assessment endpoints, including variables such as the difference between laboratory animals and species found in the wild; fluctuations in environmental parameters, such as temperature, which may cause different effects; or other environmental stresses that organisms may face in their natural habitat.

Excess Odds Ratio (EOR): The probability that an event will occur divided by the probability that it will not occur i.e., the odds ratio minus one (one, representing the background risk).

Excess risk: The difference between the incidence of a specified stochastic effect observed in an exposed group to that in an unexposed control group.

Excess relative risk (ERR): The ratio of the excess risk of a specified stochastic effect to the probability of the same effect in the unexposed population; i.e., the relative risk minus 1 (with 1 representing the background risk). The excess relative risk is normally used in the context of observed numbers of effects.

Fertilization: Fusion of sperm and egg.

Film badge: A dosimeter used for monitoring cumulative exposure to ionizing radiation. The badge consists of a photographic film and a holder. The film is removed and developed to measure exposure.

Fission (nuclear fission): The division of a heavy nucleus into two (or, rarely, more) parts with masses of equal order of magnitude; usually accompanied by the emission of neutrons and gamma radiation.

Fission product: A radionuclide produced by nuclear fission. Used in contexts where the radiation emitted by the radionuclide is the potential hazard.

Foetus: A term used to refer to a baby during the period of gestation between eight weeks and term.

Follicle: One of the cell types that surround a developing oocyte or egg.

Fusion: A nuclear reaction in which nuclei combine to form a larger nucleus with the simultaneous release of energy.

Gamete: Specialized haploid cell, either a sperm or an egg, serving for sexual reproduction.

Gamma rays: Penetrating electromagnetic radiation emitted by an atomic nucleus during radioactive decay; a wave form of ionizing radiation.

Gastrointestinal death: Bleeding or perforation of the GI, occurs in the range of 1000–5000 cGy from the loss of gastrointestinal mucosa, leading to a terminal loss of electrolytes and water through the denuded intestine.

Granulosa cell tumours: Granulosa cell tumours are tumours that produce granulosa cells. A granulosa cell is a somatic cell (any cell other than a sex cell) of the sex cord that is associated with the developing female gamete (the oocyte, or egg) in the ovary of mammals.

Gray (Gy): The SI unit of absorbed radiation dose, corresponding to the absorption of 1 joule of radiation energy per kg of material. Radiation damage depends on the absorption of radiation energy and is approximately proportional to the concentration of absorbed energy in tissue. For gamma and beta radiations, the gray is numerically equal to the sievert.

Haematopoietic: Any developmental series of cells that derives from hematopoietic stem cells and results in the production of mature blood cells.

Healthy Worker Effect: A phenomenon observed initially in studies of occupational disease: workers often exhibit lower overall death rates than the general population, because persons who are severely ill and chronically disabled are ordinarily excluded from employment or leave employment early. Death rates in the general population may be inappropriate for comparison if this effect is not taken into account. Similar effects are known for military personnel, migrants, and other groups.

Haemorrhage: Heavy bleeding. A subdural haemorrhage occurs in the brain.

Health indicator: A variable that can be directly measured and that reflects the state of health of persons in a community. Examples include infant mortality rates, incidence rates based on notified cases of disease, disability days, etc.

Hemangiosarcoma: A type of cancer that begins in the cells that line blood vessels.

Hematoma: A localized swelling, outside of the blood vessels, filled with blood. Usually caused by some form of trauma.

Hereditary effect: A radiation-induced health effect that occurs in a descendent of the exposed person.

Histone: One of a group of small abundant proteins, rich in arginine and lysine, four of which form the nucleosome on the DNA in eukaryotic chromosomes.

Hydrogen: The simplest and most common element, it has three isotopes; protium, deuterium, and tritium. Protium (H-1), by far the most abundant isotope, contains only a proton in its nucleus, deuterium (H-2) contains a proton as well as a neutron, and tritium (H-3) has a proton and two neutrons. Tritium is the only radioactive isotope of hydrogen.

Immersion: Submergence, sinking until covered completely with water.

Incidence: The number of new cases of disease appearing in a population in a specific time period, usually within a year.

Incidence rate: The number of new cases of disease appearing in a time period divided by the number of people at risk of developing that disease.

Inorganic: Material derived from non-living material; non carbon based compounds.

Internal emitter: A radioactive substance that has entered the body through ingestion, inhalation, absorption.

Intraperitoneal: Injection of a substance into the peritoneum (body cavity or abdominal cavity).

In vitro: Latin for *"within the glass"*, a term used to describe an experiment performed not in a living organism, but in a controlled environment, such as in a test tube or Petri dish.

In vivo: Latin for "within the living", a term used to describe an experiment using a whole, living organism as opposed to a partial or dead organism, or an *in vitro* controlled environment.

Ion: An atom, molecule, or fragment of a molecule that has acquired an electrical charge through the loss or capture of electrons.

Ionizing radiation: Radiation capable of producing ion pairs in biological materials, for the purpose of radiation protection. Examples are alpha particles, gamma rays, x-rays and neutrons.

Irradiation: Exposure to ionizing radiation.

Isotopes: Various forms of atoms of the same chemical element, which are distinguished by the number of neutrons in the nucleus. The number of protons remains the same, but the number of neutrons differs. For example, uranium has 16 different isotopes.

Isotropic effect: The difference in physical properties and chemical reactivity due to the difference in mass between isotopes of the same element.

Joule: One joule is the energy expended when 1 unit of force is applied to move an object a distance of 1 m.

Justification: The concept that there has to be more good than harm. The ICRP defines justification as the process of determining whether the benefits to individuals and to society from introducing or continuing a practice outweigh the harm (including radiation detriment) resulting from that practice.

Kinetic energy: The energy possessed by an object because of its motion; equal to one half the mass of the body times the square of its velocity.

Lag time: The time elapsed between initial exposure to radiation, and the onset of the disease, when symptoms and signs are first apparent. Also referred to as a latency period.

LD 50: Dose that causes 50% of the population to die post irradiation.

LD 50/30: Dose that causes 50% of the population to die in the first 30 days post irradiation.

Linear no-threshold (LNT) model: The hypothesis that the risk of stochastic effects is directly proportional to the dose for all levels of dose and dose rate (below those at which deterministic effects occur).

Linear energy transfer (LET): A measure of energy deposited over a distance as energy is transferred from radiation to the exposed matter. A high value of linear energy transfer indicates that energy is deposited within a small distance; for example in Joules/μm.

Leukaemia: Cancer of the white blood cells (leukocytes). Myeloid leukaemia is a type of leukaemia affecting myeloid tissue (bone marrow). Aleukaemia is a type of leukaemia in which the circulating white blood cells are normal or decreased in number.

Lipid (fats): Organic compounds including the fats, oils, waxes, sterols, nucleic acids, and triglycerides. Lipids are characterized by being insoluble in water, and account for most of the fat present in the human body.

Lymphoma: Tumours of the lymphocytes that grow in lymphoid and other tissues, but do not enter the blood in large numbers. There are many types of lymphoma, which represent the transformation of various developmental stages of B or T lymphocytes.

Malignant: Term to describe cancerous tumours, which tend to grow rapidly and that can invade and destroy nearby normal tissues and spread throughout the body.

Mass: See atomic mass.

Meta-analysis: A statistical technique that involves combining and analyzing the data of a number of independent studies.

Metabolic model: A mathematical description of the behaviour of radionuclides in the metabolic processes of cells, tissues, organs and organisms. It is most frequently used to describe distribution of radionuclides among tissues and excretion.

Metabolize: A term for the way cells chemically change food so that it can be used to store or use energy and make the proteins, fats, and sugars needed by the body.

Microbial degradation: Change of a chemical compound to a less complex compound as a result of action by bacteria.

Microcephaly: Condition of abnormal smallness of the head, sometimes associated with mental defects.

Microphthalmus: Abnormal smallness of one or both eyes; congenital, and almost always hereditary (usually recessive, but may also be dominant).

Millisievert (mSv): One one-thousandth of a sievert.

Molecule: A group of atoms chemically bonded to each other.

Monoamine oxidase: An enzyme that catalyzes the oxidation of many body compounds (for example, epinephrine, norepinephrine, and serotonin).

Morbidity: The frequency of disease, illness, injuries, or disabilities in a given population.

Mutation: A chemical change in the DNA in the nucleus of a cell. Mutations in sperm or egg cells or their precursors may lead to inherited effects in children or later generations. Mutations in body cells may lead to effects such as cancer.

National Dose Registry (NDR): Canada's central repository for occupational radiation doses. Managed by Health Canada, it publishes annual reports on occupational dose information and trends, according to job type.

Natural radiation: Natural background radiation is constantly present in the environment and is emitted from a variety sources. These sources include cosmic rays, terrestrial sources (radioactive elements in the soil), ambient air (radon), and internal sources (food and drink). The annual global per caput effective dose due to natural radiation sources is 2.4 mSv (UNSCEAR, 2000).

Neonate: A fertilized egg, from conception to approximately 4 weeks of age.

Neoplasia: An abnormal cell growth that may progress to cancer.

Neutron: An elementary particle found in the nucleus of atoms having no electrical charge, with a mass of about 1.6×10^{-27} kg.

Neutron capture: A type of nuclear reaction in which an atomic nucleus absorbs a free neutron and the two merge to form a heavier nucleus. Neutrons can react with an atomic nucleus in several ways each ending with a different product.

Non-human biota: All living organisms, excluding humans.

Non-ionizing radiation: Radiation that does not possess sufficient energy to produce ions. Examples are ultraviolet (UV), visible light, infrared, and radio waves.

Non-zero (positive) average dose: Average dose determined using the subset of data containing only the non-zero (positive) values. Zero dose readings, which include both zero and below measurable threshold readings, are not included in this subset.

Norepinephrine: A neurotransmitter (and a hormone) found mainly in areas of the brain that are involved in governing autonomic nervous system activity, especially blood pressure and heart rate.

Nuclear energy worker: A person who is required, in the course of the person's business or occupation in connection with a nuclear substance or nuclear facility, to perform duties in such circumstances that there is a reasonable probability that the person may receive a dose of radiation that is greater than the CNSC's prescribed limit for the general public (1 mSv/year).

Nucleic acid: RNA or DNA, a macromolecule consisting of a chain of nucleotides joined together by phospholipid bonds.

Nucleoside: The precursor of nucleic acids, consisting of an organic base and a sugar.

Nucleus (of an atom): The positively charged central portion of an atom that contains protons and neutrons.

Nuclide: A species of atom characterized by the number of protons and neutrons and the energy state of the nucleus.

Odds Ratio: The probability that an event will occur divided by the probability that it will not occur.

Oocyte: The developing egg. It is usually a large and immobile cell.

Oogenesis: Formation and maturation of oocytes in the ovary.

Optimization: The process of determining what level of protection and safety makes exposures, and the probability and magnitude of potential exposures, as low as reasonably achievable (ALARA), with economic and social factors being taken into account, as recommended by the International Commission on Radiological Protection's system of radiological protection.

Ordinary Least squares: Technique for estimating the unknown parameters in a linear regression model.

Organic compound: Any compound containing carbon atoms covalently bound to other atoms.

Organogenesis: The formation of organs during development.

Orthovoltage X-rays: x-rays produced by x-ray tubes operating at voltages in the 200–500 kVp range (i.e., peak voltage), and thus possessing energy up to 200–500 keV, although there is a spectrum of energies with a peak much less than the peak tube voltage.

Osteosarcoma: A malignant tumour of the bone that usually develops during the period of rapid growth during adolescence.

Ovary: Contains the egg cells necessary for reproduction, and also produces estrogen and progesterone.

Ovum: The mature female gamete in sexually reproducing organisms. It is usually a large and immobile cell. Also referred to as the egg.

Oxidation (verb oxidize): Loss of electrons from an atom, as occurs during the addition of oxygen to a molecule or when a hydrogen is removed.

Pair production: The simultaneous production of an electron and a positron by an interaction of a photon or a fast-charged particle with the electronic field of a nucleus or other particle.

Percutaneous: Passage or absorption of substances into the body through unbroken skin.

Photoelectric effect: The interaction of a photon with an atom, resulting in the absorption of the incident photon and the release of a bound electron from that atom with energy equal to the photon energy minus the electron binding energy.

Photon: A quantum (smallest possible amount) of electromagnetic radiation.

Photon absorption: Occurs when the photon, an electromagnetic wave of energy, traveling at the speed of light is absorbed into the matter through which it may pass. This phenomenon can occur as a photoelectric effect, Compton scattering or pair production.

Pleural cancer: Cancer of the pleura, which are the membranes that surround the lungs and line the inside of the chest cavity.

Poisson regression: A technique used to describe the occurrence of small number of counts (or events) as a function of a set of predictor variables. Among its numerous applications, Poisson regression has been applied to compare the occurrence of selected diseases in exposed and unexposed cohorts.

Polysaccharides: Linear or branched polymer of monosaccharides. They include glycogen, starch, hyaluronic acid, and cellulose.

Positron: A stable elementary particle having a positive electric charge of 1.6×10^{-19} coulombs and a mass of 9.1×10^{-31} kg (similar to an electron, but positively charged).

Positron emission: In those instances where the neutron-to-proton ratio is too low and alpha emission is not energetically possible, the nucleus may, under certain conditions, attain stability by emitting a positron.

Protein: The major macromolecular constituent of cells. A linear polymer of amino acids linked together by peptide bonds in a specific sequence.

Proton: A stable elementary particle found in the nucleus of atoms with a positive electric charge of 1.6×10^{-19} kg.

Quality factor: A number by which the absorbed dose in a tissue or organ is multiplied to reflect the relative biological effectiveness of the radiation, the result being the dose equivalent. Superseded by radiation weighting factor in the definition of equivalent dose ICRP 60, but still defined as a function of linear energy transfer for use in calculating the dose equivalent quantities used in monitoring.

Radiation: Energy travelling through space in the form of waves or particles. Ionizing radiation (such as alpha particles, beta particles, gamma rays, x-rays, and neutrons) has the ability to remove electrons from the matter it encounters. The term radiation, as used in this document, implies ionizing radiation.

Radiation effectiveness factor (REF): Represents the biological effectiveness of different radiation types, relative to high-energy Cobalt-60 gamma rays, for the purpose of estimating cancer risks and probability of causation of radiogenic cancers in identified individuals.

Radiation weighting factor (w_R): The factor by which the absorbed dose is weighted for the purpose of determining the equivalent dose. The radiation weighting factor for a specified type and energy of radiation has been selected to be representative of values of the relative biological effectiveness (RBE) of that radiation in inducing stochastic effects at low doses. The RBE of one radiation compared with another is the inverse ratio of the absorbed doses producing the same degree of a defined biological end point (ICRP Publication 60).

Radioactive: Exhibiting radioactivity; emitting or relating to the emission of ionizing radiation or particles such as alpha and beta particles, neutrons or gamma rays.

Radiogenic: A radiogenic nuclide is one that is produced by the process of radioactive decay.

Radioisotope: Form of an atom with an unstable nucleus that emits radiation as it decays.

Radiological half-life: Time required to spontaneously reduce the activity of a radionuclide to half of the original amount.

Radionuclide: A radioactive nuclide.

Radiosensitive: A qualitative term to differentiate cells, tissues, and organs that are more sensitive to radiation damage than others.

Radon: A chemical element with symbol Rn and atomic number 86. Radon is a colorless, odorless, tasteless, naturally occurring, radioactive noble gas that is formed from the decay of radium. It is one of the heaviest substances that remains a gas under normal conditions and is a health hazard.

Radon decay products (or radon progeny): A term used to refer collectively to the immediate products of the Radon-222 decay chain. These include Polonium-218, Lead 214, Bismuth-214, and Polonium-214. They have an average combined half-life of about 30 minutes. Also called radon progeny and radon daughters.

Rate ratio: A relative measure of comparison based on the ratio of two measures of disease frequency.

Record Linkage: The collection of two or more different sources of information to form a combined record for statistical and research purposes. Record linkage is a potentially important source of valuable statistical information, for example, to shed light on the effectiveness of certain cancer screening methods.

Relative biological effectiveness (RBE): A relative measure of the effectiveness of different radiation types in inducing a specified health effect. It is expressed as the inverse ratio of the absorbed doses of two different radiation types, the denominator being the reference radiation that would produce the same degree of a defined biological end point.

RBE_{MAX} (or RBE_M): The maximum RBE value determined at low dose and dose rates.

Reference man: An idealized human with characteristics defined by the International Commission on Radiological Protection for radiation protection purposes (ICRP, 2002).

Relative risk: The ratio between the incidence of a specified stochastic effect observed in an exposed group and that in an unexposed control group.

Regression coefficient (β): When the regression line is linear ($y = \beta x + b$) the regression coefficient is the constant (β) that represents the rate of change of one variable (y) as a function of changes in the other (x); it is the slope of the regression line.

Ribonucleic acid (RNA): Polymer formed from covalently linked nucleotide monomers. Each nucleotide consists of a nitrogenous base, a ribose sugar, and a phosphate. RNA molecules transcribe information from DNA molecules and use that information for protein synthesis.

Risk: A multiattribute quantity expressing hazard, danger or chance of harmful or injurious consequences associated with actual or potential exposures.

Risk coefficient: (1) Probability of a cancer (fatal cancer or cancer incidence) per unit radiation dose; or (2) probability of a cancer per unit activity intake of a radionuclide or per disintegration per unit volume, area or mass of a radionuclide in the environment.

Scattered radiation: Radiation that, during passage through matter, is changed in direction and the change is usually accompanied by a decrease in energy.

Sievert (Sv): The SI unit of absorbed radiation dose in living organisms modified by radiation type and tissue weighting factors. The sievert is the unit of dose measuring the equivalent dose and effective dose. It replaces the classical radiation unit, the rem. Multiples of sievert (symbol Sv) used in practice include the millisievert (mSv) and the microsievert (μSv).

Socioeconomic status (SES): An individual's comparative status in social and economic standing within a community, based on factors such as social class, level of education, income, and type of job.

Solid cancer: Cancers occurring in "solid" organs such as the breast or prostate, as opposed to cancers occurring in the blood for example, which is liquid.

Specific activity: The amount of radioactivity per unit mass of that substance, i.e., Bq/g that is radionuclide specific.

Spermatid: An immature gamete produced by a spermatocyte; develops into a spermatozoon (or sperm).

Spermatogenesis: Development of sperm.

Spermatogonia: Precursor cell from which sperm mature.

Spermatozoa (plural, singular is sperm or spermatozoon): The mature male gamete in animals. It is motile and usually small compared with the egg.

Standardized incidence ratio (SIR): The ratio of the observed number of new cases of a disease or condition in a population to the expected number of new cases (observed/expected). The expected number is determined by applying the sex and age specific incidence rates of a standard population, such as Ontario or Canada, to a population of the study population, such as Port Hope. An SIR of 1.0 indicates that there is no difference between the study and standard population. An SIR greater than 1.0 means that there are more new cases of disease in the study population than in the standard population. An SIR less than 1.0 means that incidence is lower in the study population.

Standardized mortality ratio (SMR): The ratio of the observed number of deaths from a disease or condition in a population to the expected number of deaths (observed/ expected). The expected number is determined by applying the sex- and age-specific death rates of a standard population, such as Ontario or Canada, to a population of the study population, such as Port Hope for the study period. An SMR of 1.0 indicates that there is no difference between the study and standard population. An SMR greater than 1.0 means that there are more deaths from the disease in the study population than in the standard population. An SMR less than 1.0 means that there are fewer deaths in the study population.

Starch: Polysaccharide composed exclusively of glucose units, used as an energy storage material in plant cells.

Standardized registration rate (SRR): see Standardized Incidence Ratio (SIR). The registration of cancer is synonymous with the incidence of cancer.

Statistically significant: A statistical property of an observation or an estimate that is unlikely to have occurred by chance alone.

Statistical power: The ability of a study to demonstrate an association if one exists. The statistical power of a study is greatly affected by the frequency of the condition under study, the sample size, the study design, and the magnitude of the effect.

Steady state: Constant in time.

Stochastic effects: A term used to group radiation-induced health effects that have a statistical risk, such as cancer or inheritable diseases. For these diseases, the probability of their occurrence increases proportionally to the radiation dose received: the lower the dose, the lower the probability of occurrence. However, at no time, even for high doses, is it certain that cancer or genetic damage will result.

Stratification: The process of or result of separating a sample into several subsamples according to specified criteria, such as age groups, socioeconomic status, etc. The effect of confounding variables may be controlled by stratifying the analysis of results.

Sugar: Small carbohydrates with a monomer unit of general formula $(CH_2O)n$. Examples are the monosaccharides glucose, fructose and mannose, and the disaccharide sucrose (composed of a molecule of glucose and one of fructose linked together).

Teratogenic: A radiation-induced health effect in the exposed unborn embryo/foetus.

Thermoluminescent dosimeter (TLD): A type of radiation dosimeter that measures gamma and beta radiation dose by measuring the amount of visible light emitted from a crystal in the detector when the crystal is heated. The amount of light emitted is dependent upon the radiation exposure.

Threshold limit value: A level to which it is believed a worker can be exposed to a chemical agent day after day for a working lifetime without adverse health effects.

Tissue weighting factor: The factor by which the equivalent dose is weighted for the purpose of determining the effective dose. The tissue weighting factor for an organ or tissue represents the relative contribution of that organ or tissue to the total detriment due to effects resulting from uniform irradiation of the whole-body (ICRP Publication 60).

Top-down approach: an approach to a problem that begins at the highest conceptual level and works down to the details.

Track structure: The energy disposition characteristics of a radiant particle as it interacts with molecules. It may also include the shape of the path (such as linear or circular).

Transmutation: The conversion of one element to another through radioactive decay.

Tritium: A radioactive isotope of the element hydrogen (symbol T or ^{3}H). The nucleus of tritium (sometimes called a triton) contains one proton and two neutrons. Tritium atoms can replace hydrogen atoms in water molecules to form tritiated water (HTO), in organic molecules to form organically bound tritium (OBT), in air to form tritiated gas (HT). Tritium also exists in many other compounds such as tritiated hydrocarbons, tritiated particulates, tritiated thymidine (^{3}HTdR), and metal tritides (tritium bearing metals).

Toxic: as defined in Section 64 of the *Canadian Environmental Proection Act*:
A substance is toxic if it is entering or may enter the environment in a quantity or a concentration or under conditions that:

(a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or
(b) constitute or may constitute a danger to the environment on which life depends, or
(c) constitute or may constitute a danger in Canada to human life or health.

Two-stage clonal expansion: a stochastic model of stem cell kinetics and mutation, corresponding to the initiation, promotion, malignant conversion, and progression paradigm of carcinogenesis.

Uranium:
Natural Uranium: Refers to Uranium with the same isotopic composition as found in nature. It contains approximately 0.7% Uranium-235, 99.3% Uranium-238, and a trace of Uranium-234, by weight. In terms of amount of radioactivity, approximately 2.2 % comes from Uranium-235, 48.9% from Uranium-238, and 48.9% Uranium-234.
Enriched Uranium: Refers to Uranium that has been processed to increase the concentration of fissionable Uranium-235 isotope to prepare it for use in some types of reactors. Natural uranium is about 0.7 % U-235. Enriched uranium is about 3% U-235.

X-ray: Ionizing electromagnetic radiation emitted by an atom when it has been bombarded with electrons. X-rays differ from gamma rays in that they are emitted from the orbiting electrons, not the nucleus, and they have a much wider energy range, or spectra. A “soft x-ray” is one of low energy, generally below 100 KeV

Zygote: Diploid cell produced by fusion of a male and female gamete. A fertilized egg.

10 ABBREVIATIONS

A-bomb: Atomic bomb
AECB: Atomic Energy Control Board
AECL: Atomic Energy Canada Limited
AGIR: Advisory Group on Ionizing Radiation
AI: Alveolar-interstitial
ALARA: As Low As Reasonably Achievable
ALI: Annual Limit on Intake
AWE: Atomic Weapons Establishment
β: Regression coefficient
β: Tritium dose
BEIR: Biological Effectiveness of Ionizing Radiation
Bfs: German Federal Office for Radiation Protection
BNFL: British Nuclear Fuels Limited
BW: Body weight
BWR: Boiling Water Reactor
C_F: Concentration foetus
C_M: Concentration mother
CANDU: Canadian Deuterium Uranium
CEPA: Canadian Environmental Protection Act
CERRIE: Committee Examining Radiation risk from Internal Emitters
CI: Confidence interval
CLL: Chronic lymphocytic leukaemia
CNSC: Canadian Nuclear Safety Commission
CNS: Central nervous system
COMARE: Committee on Medical Aspects of Radiation in the Environment
CTH_3: tritiated methane
D_0: dose required to reduce the population
DAC: Derived Air Concentration
DDREF: Dose and Dose Rate Effectiveness Factor
DNA: Deoxyribonucleic acid
DRHD: Durham Region Health Department
DSB: Double strand break
E. coli: *Escherichia coli*
EOR: Excess odds ratio
ERR: Excess relative risk
γ: Gamma dose
GCCR: German Childhood Cancer Registry
GI: Gastro-intestinal
H_2O: Chemical symbol for water, also seen as HOH
HCNO: Hydrogen carbon nitrogen oxigen
HPA: Health Protection Agency
HSE: Health and Safety Executive
HT: Tritiated gas

^{3}HTdR:	Tritiated thymidine
HTO:	Tritiated water
KiKK:	Kinderkrebs in der Umgebung von Kernkraft werken – Childhood cancer in the vicinity of nuclear power plants
KKK:	Krümmel nuclear power plant
IARC:	International Agency for Research on Cancer
ICRP:	International Commission on Radiological Protection
ICRU:	International Commission on Radiological Units and Measurements
LD:	Lethal dose
$LD_{50/30}$:	Lethal dose that kills 50% of the population in 30 days
LDEF:	Low dose effectiveness factor
LET:	Linear energy transfer
LHNHL:	All leukaemia and non-Hodgkin's lymphoma
N:	Number
NCRP:	National council on radiation protection
NDR:	National Dose Registry
NGS:	Nuclear Generating Station
NHL:	Non-Hodgkin's lymphoma
NPP:	Nuclear Power Plant
NRCT:	National Registry of Children's Tumours
NRRW:	National Registry for Radiation Workers
OBT:	Organically bound tritium
O/E:	Observed/expected
OH:	Hydroxyl
OPG:	Ontario Power Generation
OR:	Odds ratio
PNM:	Principal nutrient metabolic
PSL:	Priority substance list
PWR:	Pressurized water reactor
Q:	Quality factor
RBE:	Relative biological effectiveness
$RBE_{MAX/M}$:	Maximum relative biological effectiveness
REF:	Radiation effectiveness factor
RPO:	Radiation protection officer
RR:	Relative risk
SES:	Socioeconomic status
SIR:	Standardized incidence ratio
SIR_i:	SIR installation regions
SIR_c:	SIR control regions
SMR:	Standardized mortality ratio
SRR:	Standardised registration rates
SRS:	Savannah River Site
SSB:	Single strand break
SSK:	German Commission on Radiological Protection
Type F,M,S:	Type fast, medium, slow, absorption rates

UK:	United Kingdom
UKAEA:	United Kingdom Atomic Energy Authority
UNSCEAR:	United Nations Scientific Committee on the Effects of Atomic Radiation
US:	United States
w_R:	Radiation weighting factor
w_T:	Tissue weighting factor
X:	X-ray dose
χ^2:	Chi squared

11 UNITS

Bq: becquerel
cm: centimetre
d: day
g: gram
GBq: gigabecquerel
Gy: gray
h: hour
kBq: kilobecquerel
keV: kiloelectron volts
kg: kilogram
km^2: kilometre squared
kV: kilovolt
Kvcp: kilovolt constant potential
kVp: kilovolt peak
L: litre
MBq: megabequerel
m: metre
m^2: metre squared
m^3: metre cubed
mGy: milligray
mL: millilitre
mm: millimetre
mSv: millisievert
R: röntgen
Sv: sievert
µSv: microsievert
µm: micrometre
y: year

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