Health Protection Agency

Review of Risks from Tritium

Report of the independent Advisory Group on Ionising Radiation

The cover shows the sun over a nuclear power station.
Tritium is generated by nuclear fusion reactions in the sun and would be generated in terrestrial nuclear fusion power production. It is also produced as part of the fuel cycle in current nuclear fission power production and has several uses in industry.

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Foreword

The Radiation Protection Division of the Health Protection Agency (HPA) undertakes research to advance knowledge about protection from the risks of ionising and non-ionising radiations. It provides laboratory and technical services, runs training courses, and provides expert information. It also has a statutory responsibility for advising UK government departments and those with regulatory responsibilities for ionising and non-ionising radiation in the fields of medical, public and occupational exposure.

The HPA Radiation Protection Division was formed when the National Radiological Protection Board (NRPB) merged with the HPA on 1 April 2005. In 1995 the Director of the NRPB had set up the Advisory Group on Ionising Radiation (AGIR) that had as its terms of reference:

> 'to review work on the biological and medical effects of ionising radiation relevant to human health in the occupational, public health, medical and environmental fields and advise on research priorities'

In addition, the AGIR was given the task of helping the NRPB, where appropriate, to deal with any urgent request for advice or work from the Department of Health or other government departments. The AGIR was reconstituted in 1999 as an independent body and reported directly to the Board of the NRPB; since April 2005 it reports to the HPA Board Subcommittee on Radiation, Chemical and Environmental Hazards. The remit of the AGIR is restricted to the provision of scientific judgements and does not include the development of specific recommendations relating to radiation protection policy. These are matters for the HPA and its Board. For details of the current work of the AGIR, see the website at www.hpa.org.uk. The AGIR has, to date, issued four reports that consider

- heterogeneity in response to radiation,
- guidance on the promotion of further optimisation of medical exposures,
- epidemiology of second cancers,
- UK population risks for leukaemia.

In July 2001, the then Environment Minister, Michael Meacher MP, announced the establishment of a group with the remit 'to consider present risk models for radiation and health that apply to exposure to radiation from internal radionuclides in the light of recent studies and to identify any further research that may be needed'. The Working Group thus formed, which became known as CERRIE, commenced its work in December 2001 and its completed report was sent to the Committee on Medical Aspects of Radiation in the Environment (COMARE) in 2004 for consideration.

In its response to the CERRIE report, COMARE made a recommendation that:

> '... the NRPB be asked to carry out a review, with the widest possible consultation, of internal tritium dosimetry paying particular attention to tritiated water and organic compounds containing tritium'

The NRPB considered that this recommendation could be best satisfied by a subgroup of the AGIR. Accordingly, approval was given for the formation of an AGIR subgroup on internal tritium dosimetry at the December 2004 meeting of the NRPB Board.

The terms of reference given to the Subgroup were:

> '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.'

This report compiled by the AGIR Subgroup on Tritium Internal Dosimetry addresses these issues. Notably, the Subgroup conducted a consultation seminar to elicit a range of views on the subject before preparing the report.

Review of Risks from Tritium

HAS BEEN PREPARED BY THE

Subgroup on Tritium Internal Dosimetry of the Advisory Group on Ionising Radiation

CHAIRMAN
Professor B A Bridges OBE
University of Sussex

MEMBERS
Professor A T Elliott
Glasgow Western Infirmary

Dr M A Hill
Medical Research Council Radiation and Genome Stability Unit, Harwell

Dr B E Lambert
St Bartholomew's Medical College, London *(retired)*

Dr M P Little
Imperial College Faculty of Medicine, London

Professor R Waters
Cardiff University

SECRETARIAT
A W Phipps
Health Protection Agency, Chilton

HPA REPRESENTATIVE
Dr J W Stather
Health Protection Agency, Chilton

OBSERVER
Dr H Walker
Department of Health, London

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Advisory Group on Ionising Radiation

CHAIRMAN
Professor B A Bridges OBE
University of Sussex

MEMBERS
Professor D T Goodhead OBE
Medical Research Council, Harwell

Professor P Hoskin
University College London Hospitals

Dr M P Little
Imperial College Faculty of Medicine, London

Professor T McMillan
Lancaster University

Professor J Little
University of Ottawa

Dr M Spittle OBE
University College London Hospitals

Professor N Wald
Wolfson Institute of Preventive Medicine, University of London

SECRETARIAT
Dr S Bouffler
Health Protection Agency, Chilton

HPA REPRESENTATIVE
Dr J W Stather
Health Protection Agency, Chilton

OBSERVER
Dr H Walker
Department of Health, London

Review of Risks from Tritium

Report of the independent Advisory Group on Ionising Radiation

Chairman: Professor B A Bridges OBE

This report from the independent Advisory Group on Ionising Radiation reflects understanding and evaluation of the current scientific evidence as presented and referenced in this document.

Executive Summary

The Advisory Group on Ionising Radiation (AGIR) is a body that advises the Health Protection Agency on the biological and medical effects of ionising radiation relevant to human health. The AGIR set up a subgroup on tritium, with a remit to take into account a wide range of views and provide a scientifically sound consensus on the doses and risks resulting from internal exposure to tritium.

Tritium (^{3}H) is a radioactive isotope of hydrogen. It decays by beta decay, emitting an electron with a range of energies up to a maximum energy of 18.6 keV (mean energy of 5.7 keV), and has a physical half-life of 12.3 years. Tritium can be formed by the action of cosmic rays on the atmosphere, in nuclear reactors and in accelerators. It is discharged to the environment from nuclear reactors (both fission and fusion), nuclear fuel reprocessing plants, and other processing plants, such as those concerned with the manufacture of nuclear weapons. In addition, it is used in medicine and research as well as in some luminous products. Tritium mainly exists in the environment as tritiated water or in organic molecules (organically bound tritium, OBT).

Workers at nuclear sites and at facilities that manufacture tritium-labelled compounds for use in medicine can be exposed to tritium. Members of the public can be exposed following ingestion of contaminated foodstuffs. However, radiation doses to both groups are relatively low.

A number of factors combine to create a good deal of interest in tritium doses to both workers and members of the public. Tritium is ubiquitous in environmental and biological systems and is very mobile due to its occurrence as water. Tritium can become incorporated in many organic compounds with very different behaviour in both the environment and the human body. The high ionisation density along the short track length of the tritium beta particle in tissue means that track-structure considerations are also of some interest. These and other issues are explored in detail in this report.

There are a variety of theoretical reasons that have led to the general expectation of a relative biological effectiveness (RBE) of about two for tritium compared with gamma radiation. Interpretation of published experimental studies is complicated by the fact that the reference radiations varied, and doses and dose rates were frequently much higher than those normally received by people. The few available animal carcinogenicity studies gave RBE values close to one, but we have reservations about the relevance of most of them. In a wide variety of cellular and genetic studies RBE values for tritiated water have generally been observed in the range from one to two when compared with orthovoltage X-rays and in the range from two to three when compared with gamma rays. We recommend that high energy gamma rays should be the preferred choice for reporting RBE values and that (pending a published international consensus) an RBE value of two should be used in epidemiological studies and individual retrospective risk assessments. The selection of the value of two was guided largely by an analysis of the available experimental data with rounding and biophysical considerations; fractional values were not considered appropriate. We further suggest that consideration be given to the use of a value of two for radiation weighting factor (w_R) in routine radiation protection assessments for tritium.

We have reviewed the available studies of cancer and other adverse health effects in workforces and members of the general public exposed to tritium. The usefulness of the information is often impaired by a lack of dosimetric data, low doses and small numbers of cases. A number of workforce studies have been identified in which tritium-specific individual doses have been estimated, although none of them enables reliable inferences to be made on risks associated with exposure to tritium. In general, the available epidemiological studies on the offspring of radiation workers or on pregnancy outcome in areas subject to releases of tritium do not contain enough detail to estimate risks from tritium exposure. A number of workforces have the potential for epidemiological study including the five main tritium-exposed workforces in the UK, as well as a number abroad. These have groups who are relatively highly exposed, with apparently good dosimetry, and which could be used as the basis of further study. Considerable effort has already been expended in calculating tritium-specific doses from urinalysis monitoring results for tritium workers in the UK and we believe that this work should be completed to produce a comprehensive database of tritium-specific individual doses. We recommend that the possibility of international collaboration be explored with a view to achieving a study of reasonable statistical power.

We have reviewed a wide range of biokinetic data from both animal and human studies and concluded that the information available generally provides support for the current internationally accepted models. In some cases special models have been developed – for example, for OBT in flounders taken from the Cardiff Bay area, and the model has been applied to critical group calculations by regulatory bodies. A new model for tritiated water is under development by the ICRP. This will have little impact on calculated doses for members of the public but could significantly affect some calculations of intake and dose based on urine samples provided by workers. Tritiated nucleic acid precursors can present a unique hazard because of the possibility of their incorporation in DNA. However, in practice the relatively few people using such compounds and the safety procedures in modern laboratories mean the risks to workers and the general population are low.

Tritium that is incorporated into the DNA of oocytes is a special case since most of it is likely to remain there until fertilisation. A calculation has been undertaken for the critical group ingesting fish from the Cardiff Bay area. We have assumed an RBE value of two for tritium, and the ICRP figure for severe hereditary effects based on extrapolation from irradiated male mice. A probability of around one in a million is indicated for severe hereditary effects in this critical group. Tritium doses to oocytes from current exposures, and from any reasonably foreseeable future exposure, pose a very small risk of severe hereditary effects when compared to natural rates. We therefore see no need for special protection of females. However, existing evidence does not enable account to be taken of any effects there might be on pregnancy outcomes resulting from bystander effects or genomic instability phenomena.

1 Introduction

This report presents the views of the Subgroup on Tritium Internal Dosimetry of the Advisory Group on Ionising Radiation (AGIR), fully endorsed by the AGIR. The Subgroup was formed by the National Radiological Protection Board (now the Radiation Protection Division of the Health Protection Agency) in response to a recommendation from the Committee on Medical Aspects of Radiation in the Environment (COMARE). The Subgroup on Tritium Internal Dosimetry was given the remit:

> '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.'

To facilitate the gathering of a wide range of views on the dosimetry of tritium following uptake into the human body, a consultation seminar was held in conjunction with the first meeting of the Subgroup. Invitations were sent to individuals who had published material on dosimetric aspects of the risk from tritium exposure. A wide range of views was canvassed and those who attended are listed in Appendix A. In addition, written views were available from one individual on the tritium risk to oocytes. All these views were considered.

Four principal issues of concern were identified, as follows.

a What is the effectiveness of tritium beta radiation compared to X-radiation or gamma radiation?

b What proportion of tritium entering the body is retained as organically bound tritium?

c What risk does tritium pose to non-dividing oocytes?

d What special measures are needed for estimating the risk from tritiated DNA precursors?

The present review covers these areas and includes additional material sufficient to provide a comprehensive report on the issues addressed. Other organisations have published reports that deal with these and other aspects of tritium doses and risks (ICRP, 1989, 1991, 2003; UNSCEAR, 1993, 2000, 2001). This review concerns itself solely with the consequences of the uptake of tritium into the human body and does not deal with the fate of tritium in the environment prior to its uptake (although this is recognised as an area where there is incomplete understanding).

Chapter 2 gives a short summary of the important physical properties of tritium, identifies the main sources of tritium in the UK, and notes the magnitude of doses based on current models and parameters. The relative biological effectiveness (RBE) of tritium is explored from physical and chemical standpoints and the important experiments that report values for tritium RBE are described in Chapter 3. A review of the studies of doses and effects in exposed human populations is an important part of the report and these are covered in some length in Chapter 4. The evidence which underlies the current ICRP biokinetic models for tritium is given in Chapter 5 and Chapter 6 deals with the question of possible effects on female germ cells. The report ends with conclusions and recommendations.

2 Physical Properties, Sources and Doses

Tritium (^{3}H) is a radioactive isotope of hydrogen. It decays solely by beta decay, emitting an electron with a range of energies up to a maximum energy of 18.6 keV (mean energy of 5.7 keV), along with an electron anti-neutrino. The physical half-life of tritium is 12.3 years (see, for example, ICRP, 1986).

$$^3\mathrm{H} \rightarrow {}^3\mathrm{He}^+ + \mathrm{e}^- + \bar{\nu}_\mathrm{e}$$

Both the average track length of 0.56 μm in water and the maximum track length of 6 μm in water (Carsten, 1979) of the emitted electrons are small compared to the average size of a cell (10–20 μm).

Tritium can be formed in a number of ways:

a through the interaction of cosmic ray neutrons with ^{14}N and ^{16}O in the upper atmosphere (cosmogenic tritium),

b during the fission of heavy atomic nuclei such as ^{235}U in nuclear reactors and weapons,

c by capture of a neutron by a deuteron (a ^{2}H nucleus) such as occurs in heavy water moderated reactors,

d in tritium manufacture achieved by the capture of neutrons by ^{6}Li nuclei positioned within a nuclear reactor or in a blanket surrounding a reactor,

e by production in a particle accelerator by bombarding ^{3}He with neutrons.

Tritium is released into the environment directly from any of the above sources, and during reprocessing of irradiated nuclear fuel, and it should be noted that fusion power reactors using tritium as a fuel may well become widely used in coming years. In addition, tritium is used in the manufacture of radionuclide-labelled materials for application in medicine, research and industry, and can be released from such manufacturing plants (notably that in Cardiff, UK, operated by GE Healthcare) and in the use and disposal of these materials. Tritium has also been used in luminous paint employed in some wristwatches and compasses, and in emergency exit signs, gun-sights, and 'Trimphones'. Releases can occur during the manufacture of these items, their use, the recovery of tritium from disused items and from their disposal. Discharges can be in the form of tritiated water, liquid or vapour (HTO), tritiated hydrogen gas (HT), or organically bound forms which are often referred to by the generic abbreviation OBT.

2.1 Environmental discharges, measurements and doses

In the UK, the greatest discharge to the environment of tritium arises from the nuclear fuel reprocessing plant and associated facilities at Sellafield, which discharged about 1600 TBq in liquid forms and 90 TBq in gaseous forms in 2005 (EA et al, 2006). In the same year the combined discharges from UK nuclear power stations were about 2300 TBq (99% of which was in liquid form), while the tritium production plant at Chapelcross discharged about 300 TBq (almost entirely gaseous) and the GE Healthcare laboratories at

Cardiff some 330 TBq (90% gaseous). The Cardiff liquid discharges are of particular interest since they include various tritium-labelled organic compounds resulting from the production of such compounds for use in pharmaceutical and life sciences research and development. In addition, the discharges into the English Channel from the reprocessing plant at La Hague in France are of relevance to UK exposures. In 2003 discharges from La Hague amounted to about 12,000 TBq. There is increased interest in this source of tritium since discharges rose by about a factor of three during the 1990s (EC, 2003).

The Royal Navy submarine flotilla now consists exclusively of vessels powered by pressurised water reactors (PWRs) which gives rise to activation products, including tritium, within the primary coolant circuit. The routine maintenance, servicing and refitting of submarines produce a range of radioactive wastes, all of which may be contaminated by tritium. In addition to the operations of present generation vessels, the Ministry of Defence also has responsibility for dealing with the decommissioning and eventual disposal of earlier generations of nuclear powered submarines. Nevertheless, discharges to the environment are substantially lower than from the main tritium-discharging civil sites. Thus, in 2005 the Devonport and Faslane dockyards discharged 155 and 115 GBq, respectively, to the sea (EA et al, 2006).

Significant discharges have occurred in a number of other countries which may or may not have an impact on UK exposures – for example, from Marcoule in France and from Savannah River in South Carolina, USA, where atmospheric discharges peaked in the early 1960s, at about 8440 TBq, and liquid discharges peaked in the early 1970s, at about 930 TBq (Grosche et al, 1999). In 2005 Ontario Power Generation in Canada discharged about 1200 TBq of tritiated water and 800 Bq of tritium gas; other Canadian sites discharge lower activities of tritium.

Results of measurements of tritium concentrations in foodstuffs during 2005 are given in the RIFE 11 report (EA et al, 2006). At many sites tritium concentrations are reported as below about 5 Bq kg^{-1} or have not been measured. However, measurements in marine fish and shellfish taken from the Cardiff Bay area are higher, ranging from 1 to 11 kBq kg^{-1}, with up to 90% of the activity being in organic forms. Furthermore, earlier measurements in the Cardiff Bay area gave significantly higher values – generally in the range 20–50 kBq kg^{-1}, but with some values up to 120 kBq kg^{-1} (Williams et al, 2001). Some samples of fish and shellfish from the Irish Sea near Sellafield had concentrations in 2005 of up to about 200 Bq kg^{-1}, with an organic fraction of about 100% (EA et al, 2006)*.

Although the discharges noted above appear large, the weak beta emission of tritium and its comparatively short retention in the body mean that doses calculated using standard assumptions are low. Thus UNSCEAR (2000) gives annual doses from intakes of cosmogenic tritium to be 0.01 μSv, and doses to wearers of radioluminous timepieces are reported to be below 10 μSv y^{-1} (Watson et al, 2005).

The annual committed effective dose to a critical group consuming fish and shellfish from the Cardiff Bay area during the highest years of discharge has been estimated to be in the range 53–133 μSv (Lambert,

* Given that discharges from the Sellafield site are believed not to contain OBT to any significant extent, it is not clear to the Subgroup that current models can account for such a high organic fraction. In addition, data from a freshwater lake at Chalk River, Canada, show that OBT concentrations are generally slightly lower than HTO concentrations (ratio 0.8) for both omnivorous and piscivorous fish species (EMRAS Tritium/C14 Working Group, 2006) which is at odds with the measurements on samples from the Irish Sea. We draw this observation to the attention of COMARE who may wish to seek further clarification.

2001), taking into account uncertainty in biokinetic models (Chapter 5) and RBE (Chapter 3). Since then the operator of the Cardiff plant (GE Healthcare) has introduced measures to remove a large fraction of the organic activity from the discharge (Bonnett et al, 2007) and critical group doses have decreased accordingly. For example, the annual committed effective dose in 2005 to adults in the critical group has been calculated as 20 μSv (EA et al, 2006) by applying a special dose coefficient for organically bound tritium in marine foodstuffs in the Cardiff Bay area (Hodgson et al, 2005; see also Section 5.4.1). These doses may be compared with the average annual dose to members of the UK population from natural sources of radiation of about 2000 μSv.

However, a number of factors combine to create a good deal of interest in tritium doses to both workers and members of the public. Tritium is ubiquitous in environmental and biological systems and is very mobile due to its occurrence as water. While many radionuclides are likely to be encountered in only a few common forms, tritium can become incorporated in many organic compounds with very different behaviour in both the environment and the human body. The high ionisation density along the short track length of the tritium beta particle in tissue means that track-structure considerations are also of some interest. These and other issues are explored in detail later in this report.

2.2 Occupational doses

A review of the numbers of people occupationally exposed and their estimated doses is given in Appendix B. A brief summary is given here; mean cumulative or lifetime doses are reported to be in the region of a few mSv. It should be borne in mind that pessimistic assumptions are often adopted for general radiation protection purposes, thus the reported doses are likely to have been overestimated to some extent at some sites.

At the BNFL sites of Sellafield, Chapelcross and Capenhurst, 1758 workers have been monitored for exposure to tritium. The highest tritium exposures at Sellafield occurred in the late 1950s and early 1960s when tritium was produced by irradiation of lithium in reactors and then extracted in a specifically designed plant. Of the 1758 total, 911 were Sellafield tritium workers, where the mean cumulative tritium dose was 2.1 mSv (maximum 127 mSv). Excluding those workers in the low dose group (<0.1 mSv), for whom dose estimates are not as reliable, the mean cumulative dose was 4.1 mSv. Details of doses at Capenhurst and Chapelcross are not currently available.

At the UKAEA sites of Harwell, Winfrith and Dounreay, 2373 workers have been monitored for exposure to tritium, as a result of the operation of heavy water reactors at these establishments. Tritium-specific doses are not yet available for all workers known to have been exposed. For those workers with tritium doses calculated, the mean lifetime dose is about 0.7 mSv (maximum 11 mSv), while for those exposed only after 1985 (when measurements are more reliable) the mean is 0.3 mSv (maximum 7 mSv).

At the Atomic Weapons Establishment (AWE), Aldermaston, approximately 3800 workers have been monitored for exposure to tritium from 1956 to the present. The mean lifetime dose is 2.4 mSv (maximum 125 mSv). There are about 200 workers with lifetime tritium doses greater than 10 mSv.

Doses from tritium exposures at sites operated by GE Healthcare (formerly Amersham plc) have been recorded in a variety of forms (paper records, computer files, etc) but a numerical summary is not currently available.

Exposure to tritium will also occur to some extent during the operation, maintenance and decommissioning of naval propulsion reactors, although details of consequent doses are currently unavailable. Other places of work which could give rise to tritium doses include universities, research establishments and some industries, notably valve manufacturers. In addition, some companies are involved in occasional contract work at licensed nuclear sites. Tritium doses at luminising plants have decreased to insignificant levels in recent years.

The expected use of nuclear fusion reactors in electricity power generation has led to some interest in assessing possible doses from exposure to tritium resulting from the operation of such reactors. Macheta et al (1999) have demonstrated the potential for significant exposure of workers during maintenance operations of the Joint European Torus (JET) fusion tokamak, and Hodgson et al (2004) have studied the dissolution of tritium-loaded carbon particles produced during the experimental operation of JET.

Significant occupational exposures to tritium have also occurred in a number of other countries. In the USA operations at a number of nuclear sites, notably the Savannah River Site in South Carolina (Cragle et al, 1988), would have resulted in tritium exposures, and the extent of potential tritium exposures at American establishments may be appreciated from the details of the dose reconstruction programme (NIOSH, 2007). In Canada the extensive use of heavy water reactors for power generation leads to tritium doses being received by workers (Zablotska et al, 2004); in the annual report for 2005 from the Canadian National Dose Registry (Health Canada, 2006) 22,470 nuclear power workers had an average dose of 0.88 mSv, and 17% of this was due to intakes of tritium. Many workers in specific jobs have up to 40% of their doses from tritium, and several acute doses greater than 1 mSv every year are experienced.

In Russia tritium was produced for weapons at the Mayak plant in the Southern Urals from the early 1950s, using reactors designed specifically for that purpose (Kruglov, 2002). Heavy water moderated reactors were also operated at Mayak from the early 1950s. Both these operations would have led to the exposure to tritium of the personnel involved, possibly at high levels owing to the difficult nature of the operations (particularly in the early years). It is likely that tritium production continues at Mayak today.

In France, tritium exposures will have occurred during clock- and watch-making as well as in nuclear programmes. During the last 15 years annual doses at the French sites have been generally less than 1 mSv, although some doses up to 1.5 mSv have been received during cleaning operations (L Lebaron-Jacobs, CEA, Fontenay-aux-Roses, personal communication). In other countries, such as China, India and Korea, it is likely that exposures will also have occurred, although details are not currently available.

We understand that tritium is produced for commercial purposes, eg radioisotope labelling, in Canada, Russia, South Africa, Switzerland, and possibly other countries. Clearly there is scope for workers to receive doses at tritium production facilities in these countries.

3 Relative Biological Effectiveness

The data from extensive experimental studies both in animals and with *in vitro* cell cultures clearly show that different types of radiation or radiations of different energies have different efficiencies in the production of biological effects per unit absorbed dose and that this is related to the differences in ionisation densities of the radiation tracks. These differences are generally expressed as the relative biological effectiveness (RBE), which is defined as the ratio of the absorbed dose of the reference radiation to the absorbed dose of the test radiation that is required under similar conditions to produce an identical level of biological response in a particular animal or cellular study. The value of RBE depends not only on the type of radiation but also on the biological endpoint, biological system and conditions of the experiment, along with dose and dose rate. Typically the RBE for high linear energy transfer (LET) radiation will increase to a maximum value (RBE_M) at low dose and dose rates due to the curvilinear response of acute doses of the low LET reference radiation compared to the linear response for high LET (see also Section 3.2).

Risk estimates for radiation-induced cancers are mainly derived from studies of the Japanese atomic-bomb survivors who were exposed predominantly to low LET radiation. In order for these risk estimates to be applied to a range of different radiation qualities the ICRP has adopted the quantity *equivalent dose* (SI unit sievert, Sv) (ICRP, 1991). The equivalent dose is calculated by multiplying the average absorbed dose by a radiation weighting factor (w_R) to take into account differences in biological effectiveness of different radiation types at inducing malignancy or genetic damage (ICRP, 1991). While RBE values are derived experimentally and for a particular radiation type and will typically have a range of values for different measured endpoints, the w_R is a value judged by the ICRP to be the most appropriate for a given radiation type for the purpose of calculating equivalent dose for radiation protection purposes.

For X-rays, gamma rays and electrons of all energies the ICRP in Publication 60 assigned a w_R of one (ICRP, 1991). The implicit assumption is that low energy beta particles or X-rays are equally efficient in causing stochastic effects as are high energy gamma rays. Many of the current risk estimates are based on studies of the Japanese atomic-bomb survivors, who received doses from such high energy gamma rays (predominately in the 2–5 MeV range). However, both theoretical expectations and experimentally derived RBE values for a range of biological endpoints indicate that lower energy electrons (such as those produced by tritium) or photons are expected to be biologically more effective than higher energy gamma rays. Although the ICRP recognised that there was evidence for a significant variation in RBE values for low LET radiation (for example, increasing RBE with decreasing photon energy), it was argued that a more detailed description was not necessary for the purposes of radiation protection, thus a value for w_R of one was chosen for practical reasons to apply to all electrons and photons (ICRP, 1991).

3.1 Track-structure considerations

Ionising radiations, such as electrons, deposit their energy in the form of highly structured tracks of ionised and excited molecules. These interactions can result in DNA damage either directly by ionisation of its constituent atoms, indirectly by reactions with free radicals (principally hydroxyl radicals) produced by interactions of the radiation with the surrounding water molecules, or by combinations of these two. The free radicals produced will typically only diffuse a few nanometres, due to the high reactivity of the cellular environment, thus the spatial structure of the tracks is largely preserved. Ionising radiation can induce a range of different types of molecular damage in DNA, such as base damage, single strand breaks (SSB), double strand breaks (DSB), DNA–protein cross-links, and combinations of all of these. Since the pattern of damage is determined by the structure of the radiation tracks, ionising radiation has the ability to produce clustering of damage over the dimensions of the DNA helix and larger. The probability of clustered DNA damage, together with the degree of complexity, has been shown to increase with ionisation density (LET) of radiation (Nikjoo et al, 2001, 2002). The ultimate biological consequence is dependent on how this damage is subsequently processed by the cell, whether the damage is repaired and, if so, with what fidelity. It has been shown in a number of model systems that other forms of clustered DNA damage also compromise the DNA repair pathways and can lead to an increase in mutation frequency (Gulston et al, 2004; Pearson et al, 2004).

Tritium decay results in the production of a very low energy beta particle (average energy 5.7 keV) of short range (average track length 0.56 μm), as a result the average ionisation density (and LET) produced by the emitted beta particle is significantly higher than that produced by higher energy beta particles or photons, such as ^{60}Co gamma rays (see Table 3.1). Lower energy photons or electrons similar to those produced by tritium decays show a significant shift in microdosimetric energy deposition patterns towards higher lineal energy (y) compared to higher energy photon or electron fields. Spectra of energy deposition in low pressure proportional counters over a range of simulated tissue site sizes for tritium, 250 kVp X-rays and ^{60}Co gamma rays were measured by Ellett and Braby (1972). The results were then interpreted using the earlier site model of the Kellerer-Rossi theory of dual radiation action (see, for example, Kellerer and Rossi, 1971) to estimate the RBE for limiting low doses. The dual radiation action model simply assumes that biological effect is proportional to the square of the energy deposited in some small volume, often taken to be about 1 μm in diameter. Ellett and Braby reported theoretical RBE values for tritium of 3.75 compared to ^{60}Co gamma rays and 1.5 compared to 250 kVp X-rays (half value layer, HVL 1.8 mm Cu) assuming a critical site size of 1 μm.

TABLE 3.1 Track average LET in water for various radiations based on a cut-off energy of 100 eV (ICRU, 1970)

Radiation	Track average LET in water (keV μm^{-1})
^{60}Co gamma rays	0.22
200 kV X-rays	1.7
^{3}H beta particles	4.7
50 kV X-rays	6.3

On the nanometre scale also, analysis of the energy deposition patterns of tritium beta particles has shown tritium to be more effective in producing larger sized clusters of ionisations which can be enfolded within a 2.3 nm diameter sphere compared with photons with energies above 100 keV (Moiseenko et al, 1997). This represents ionisation events on the dimensional scale of DNA. A joint Task Group of the ICRU and ICRP suggested a relationship between what the Task Group called a quality factor, $Q(y)$, and lineal energy, y, determined in 1 μm diameter spherical tissue volumes (ICRU, 1986). The relationship was based in part on general observations and theoretical considerations, with special consideration given to the experimental data on chromosome aberrations in human lymphocytes. The value of $Q(y)$ obtained for tritium beta particles was approximately two compared to orthovoltage X-rays. This is supported by theoretical calculations performed by Bigildeev et al (1992) based on similar microdosimetric quantities on the micrometre scale.

Morstin et al (1993) calculated the lineal energies of tritium beta particles for spherical sites of diameters from 1 nm to 10 μm and showed that the values decreased by more than an order of magnitude over this range. Then, when they applied the assumptions of the site model of dual radiation action theory, they found that the predicted RBE of low doses of tritium beta particles relative to 250 kVp X-rays rose from a value of less than 1.1, for assumed 10 nm sensitive sites, to a peak of around 1.5 for 1 μm and then decreased to around 0.6 for 10 μm. The corresponding predicted RBE of tritium relative to ^{60}Co gamma rays was around 1.5 for 10 nm sites, 2.9 for 1 μm and 1.6 for 10 μm. Morstin et al (1993) pointed out limitations of the dual radiation action approach and they also considered the possibility of two different pathways of radiation damage related to two different target sizes. They produced bidimensional correlated distributions of lineal energy for spherical sites of 10 nm (also 20 nm) diameter (to represent DNA DSB formation) within a gross sensitive volume of 1 μm diameter. By then 'assuming arbitrarily (by somewhat questionable analogy to the DRA [dual radiation action] theory)' a squared dependence of RBE on the product of the lineal energies for the large and small sites, they obtained estimated theoretical RBE values for tritium compared to 250 kVp X-rays of 1.6 for the 10 nm sites, and 1.8 for the 20 nm sites, within the 1 μm gross sensitive volumes.

In a recent theoretical study by Chen (2006), microdosimetric simulations were performed to compare differences in energy deposition between tritium uniformly distributed within a cell (as expected with HTO) and a non-uniform distribution based on the assumption that all OBT was bound uniformly within biologically critical sites of dimensions from 10 nm to 2 μm. The dose mean lineal energies within these critical targets were calculated to be a factor of 1.7 higher for OBT bound to the critical site compared to HTO over a wide range of target dimensions. This effect would be in addition to any increase in effectiveness resulting from a localised increase in dose to the critical target due to a non-uniform distribution of energy within the cell. However, the extent of any increase will depend on the extent that OBT does preferentially localise within critical targets.

Most of the above theoretical calculations of RBE are based on the assumptions of uniform interaction between pairs of elementary biological 'sub-lesions' within sensitive sites of approximately 1 μm. However, a number of experimental investigations have indicated that the biological effectiveness of radiation at low doses is determined predominantly by patterns of energy deposition over much smaller distances down to nanometre dimensions and therefore micrometre-sized simulated volumes typically will not provide an adequate description of these patterns (Geard et al, 1980; Goodhead, 1982; Griffin

et al, 1998; Kellerer et al, 1980). The earlier site model of the Kellerer-Rossi theory of dual radiation action (Kellerer and Rossi, 1971) assumed interaction of sub-lesions within a uniform sensitive site of a given size which was typically fitted to be of approximately 1 μm diameter. The site model was subsequently superseded by the distance model [generalised theory of dual radiation action (Kellerer and Rossi, 1978)] which assumes that the probability for interaction of sub-lesions varies as a function of distance apart. Fitting to experimental data required that low dose (single-track) effects were dominated by very-short-ranged interactions (from ≪1 μm down to sub-nanometre), while high dose (two-track) interactions extended well beyond 1 μm across the entire cell nucleus (Brenner and Zaider, 1984; Goodhead, 2007; Goodhead and Charlton, 1985; Zaider and Brenner, 1984). The developments in the theory of dual radiation action have been critically discussed by Goodhead (1982, 1983, 1987, 2006) and Rossi and Kellerer (1983) and compared with alternative possible mechanisms of radiation action.

The effectiveness of low energy electrons, similar to those produced by tritium, can be studied using ultrasoft X-rays (0.1–5 keV) which interact in the cell to produce low energy electrons. Data from a range of laboratories around the world, with few exceptions, show ultrasoft X-rays to have increased effectiveness for a wide range of biological endpoints compared to equal doses of conventional X-rays or gamma rays (Goodhead and Nikjoo, 1990; Goodhead, 1994; Hill et al, 2001; Hill, 2004), with RBE values typically increasing with decreasing ultrasoft X-ray energy down to C_K X-rays (0.28 keV; producing a single photoelectron with a range less than 7 nm). RBEs greater than unity were also found for Ti_K and Cu_K X-rays with energies (4.5 and 8.0 keV, respectively) similar to the average energy of the emitted beta particle from tritium. The range of endpoints studied includes cellular inactivation for a range of cell types in addition to chromosome aberrations, mutation, transformation and DNA DSB induction. Not only is there an increase in DSB induction with decreasing electron energy (RBE for DSB induction rising from 1.4 for 4.5 keV X-rays to 2.7 for 0.28 keV X-rays compared to ^{60}Co gamma rays) but there is also an increase in complexity of DNA damage. Monte Carlo calculations indicated that the fraction of DSBs that are complex (if defined as a DSB with at least one additional strand break within ten base pairs) increases from around 20% for high energy electrons to 32% for 1 keV electrons (Nikjoo et al, 2002), rising to around 60% if the definition of a complex DSB also includes having at least one base damage associated with a simple DSB (Nikjoo et al, 2001). It has been concluded that critical damage can result from isolated, highly localised clusters of energy deposition over nanometre distances, with an increase in ionisation density leading to an increase in effectiveness due to greater clustering of damage on DNA within a few base pairs. In general, ultrasoft X-rays show all the characteristic features of low LET radiation (Goodhead et al, 1981), including similar rejoining kinetics for DNA DSB to ^{60}Co gamma rays apart from an indication of a slightly higher residual unrejoined fraction of these DNA breaks for ultrasoft X-rays (Botchway et al, 1997; deLara et al, 2001).

The percentage of absorbed dose deposited by low energy electrons (0.1–5 keV) is around 33% for ^{60}Co gamma rays and 49% for 220 kV X-rays, rising to around 78% for tritium beta particles (Nikjoo and Goodhead, 1991) – these are similar to the low energy electrons produced by ultrasoft X-rays. It has been inferred that these low energy secondary electron track ends produced by low LET radiation are the predominant cause of DSB induction, cell inactivation and other cellular effects, with isolated sparse ionisations and excitations apparently having little biological effect (Botchway et al, 1997; Goodhead and Nikjoo, 1990). The contribution to absorbed dose of these low energy electrons is substantial for tritium

beta particles compared to orthovoltage X-rays or gamma rays and therefore the ultrasoft X-ray data would predict an increase in biological effectiveness as a result of greater clustering of ionisation events on the nanometre (DNA) scale, leading to an increase in the number of DSBs per unit absorbed dose, along with a slight increase in complexity of the breaks due to additional associated damage within a few base pairs.

Both theoretical considerations and experimental data (see Section 3.5) suggest that the low energy beta particles produced by tritium decays are more biologically effective than hard X-rays and gamma rays per unit absorbed dose. This is a result of the average ionisation density along the track of the tritium beta particle being significantly higher than that produced by much higher energy photons. Theoretical calculations based on track-structure considerations suggest an RBE of approximately two, relative to ^{60}Co gamma rays.

3.2 Relationship between RBE and DDREF

In studies aimed at deriving a value of RBE for tritium there is the potential for the value obtained to depend upon the total dose and rate at which doses from both tritium and the reference radiation are delivered. In the case of tritium, the dose is expected to be protracted in time since the dose rate is dictated by the rate of radiological decay and rate of loss from the body. Experiments using X-rays or gamma rays, however, often deliver dose in a single acute exposure because this is more convenient. It is generally accepted that the same dose delivered in a protracted manner can have a lower effect than would an acute dose, due to the greater opportunity for DNA repair in the protracted case (ICRP, 1991; NCRP, 1980; NRC, 2006; UNSCEAR, 1993, 2000).

To allow for differences in the effectiveness of low LET radiation, such as X-rays or gamma rays, for the induction of stochastic effects when delivered at high doses and dose rates compared with exposures at low doses and dose rates the ICRP introduced a *dose and dose rate effectiveness factor* (DDREF) in Publication 60 (ICRP, 1991). This is used for general radiation protection when extrapolating from risks derived at high dose rates, most notably from the Japanese atomic-bomb survivors, to low dose rate exposures typical of current environmental and occupational situations. The currently recommended value of DDREF for radiation protection is two (ICRP, 1991, 2007a), although both dose dependence and dose rate factors have been found to vary widely in different animal or cellular systems and in epidemiological studies (ICRP, 2005; NCRP, 1980; UNSCEAR, 1993, 2000). Recently the US BEIR Committee proposed a dose rate factor of 1.5, based mainly on human epidemiological studies (NRC, 2006), while in the draft of the new ICRP recommendations (ICRP, 2007a) a DDREF value of two is retained.

The rationale for adopting a DDREF is illustrated in Figure 3.1 which shows the form of dose–response relationships for low LET radiations assumed for radiation protection purposes. The practical system of radiation protection recommended by the ICRP in 2007 indicated that it will continue to be assumed that at doses below around 100 mSv a given increment in dose will produce a directly proportionate increment in the probability of incurring cancer or hereditary effects attributable to radiation. This dose–response model is usually referred to as a linear non-threshold or LNT dose–response. This is in

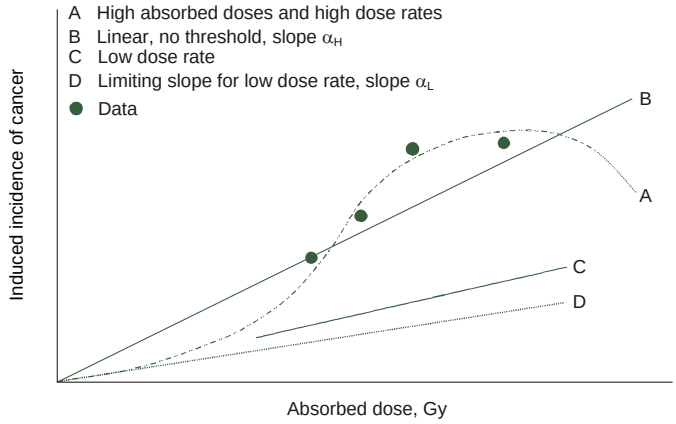

Figure 3.1 Forms of dose–response for tumour induction

accord with advice by UNSCEAR (2000), NCRP (2001) and NRC (2006). By contrast, a recent report from the French National Academy of Sciences (2005) argues in support of a practical threshold for radiation cancer risk. UNSCEAR (2000) has also reported that for some tumour types there may be a threshold for tumour response. Other dose–response relationships are also possible as described in the CERRIE report (2004).

However, from an analysis in Publication 99 (ICRP, 2005) the ICRP concluded that the adoption of an LNT model combined with a judged value of a DDREF provided a prudent basis for the practical purposes of radiation protection.

The data points shown in Figure 3.1 are representative of data for low LET radiation and will normally be available for medium to high dose/dose rate exposures. It is generally assumed, on the basis of an LNT response at low doses, that at high dose rates the dose–response for stochastic effects can be represented by a linear-quadratic (L-Q) function, at least up to doses at which cell killing starts to occur (curve A). The incidence, *I*, of an effect can thus be related to the dose, *D*, by an expression of the form:

$$I(D) = \alpha D + \beta D^2$$

where α and β, the coefficients for the linear and quadratic terms fitted to the radiation response, are constants and will be different for different endpoints. At higher doses terms describing cell killing would need to be included. If a threshold existed in the dose–response, again additional terms would be needed.

For exposures at low doses and low dose rates, the response is expected to become linear as predicted from an L-Q response. However, sufficient data in this region are seldom available from experimental or epidemiological studies and the response needs to be inferred. The data points available at high doses and high dose rates can be extrapolated to obtain estimates of the risk at low doses in a number of ways:

a by a simple linear fit to the data, line B, of slope α_H,

b using curve A, based on fitting a linear-quadratic (L-Q) dose–response relationship,

c from line D, which represents the extrapolated linear portion of curve A, in the limit, with slope α_L,

d from line C, which represents the slope of the linear fit to the available low dose and low dose rate data.

An assessment of the effects of exposure to ionising radiation at low doses will thus depend upon how the extrapolation to low doses is made. The simple linear fit to the data, line B, would be expected to overestimate risks at low doses. For radiation protection purposes the ICRP therefore recommends that the ratio between the slopes of the best fit to the data obtained at high doses (α_H, line B) and the limiting slope of curve A (α_L, line D) should be taken to be two (ie assuming $\alpha_H/\alpha_L = 2$). As described earlier, the ICRP has therefore adopted a DDREF of two for assessing risks at low doses and low dose rates of low LET radiation from epidemiological studies where data are obtained generally at higher doses and dose rates.

The exact form of any specific dose–response relationships for low LET radiations will vary and thus curve A would be expected to differ for X-rays and gamma rays and for any particular biological endpoint. It will also depend upon the dose rate used in any particular study. Similar considerations will apply to the shape of the dose–response for exposures to tritium. The RBE determined for tritium in any particular study will thus depend upon the shape of the dose–response curve for the endpoint of concern and the extent of the data available for both tritium and the reference low LET radiation to which the comparison is made.

Most of the lower values for the RBE of tritium reported in the literature are from studies which have used higher doses and dose rates, particularly from the reference radiation. This trend can be explained by the high dose rate of the reference radiation reducing the apparent relative effectiveness of the tritium doses. A review of some tritium RBE studies was carried out by Ujeno (1983) which illustrates this phenomenon. Those studies which included external reference radiation showed a tendency for an inverse relationship between dose rate and RBE. The author concluded that use of a RBE of one would be reasonable for assessing the dose from very large intakes of tritium but that a figure larger than one would be more appropriate for environmental exposure situations. Therefore, the differences in the RBE with photon/electron energy can be viewed as differences in the DDREF assuming that the response at high acute doses is less dependent upon or is independent of photon/electron energy.

3.3 Other proposed reasons for expecting an RBE greater than one

As noted in Section 3.1, track-structure considerations indicate that more of the ionisations caused by tritium are at a relatively high density and are thus more likely to lead to damage that is more difficult to repair. In addition, there are two further theoretical reasons why an RBE greater than one might be expected. These are:

a possible effects of transmutation to helium,

b accumulation of tritium in the hydration shell of DNA.

3.3.1 Possible effects of transmutation to helium

A special consideration of the biological effects of tritium is the transmutation effect. This is the local effect resulting from the conversion of the parent atom into helium but the critical problem in assessing the relative role of transmutation is the identification of this chemical transmutation relative to the emitted radiation, recoil and excitation energy as well as the concurrent acquisition of a positive charge by the resultant compound.

During the transmutation of a tritium atom a maximum recoil energy of 3 eV is given to the helium nucleus – this has not been considered sufficient for bond breaking and may be ignored (Kacena, 1967). Feinendegen and Bond (1971) have concluded that the biological effects of the tritium transmutation are primarily due to the production of helium, which leads to the formation of a positively charged carbonium ion. In complex molecules the effect of this conversion is difficult to distinguish because of the proximity to the deposition of energy and associated ionisation events from the beta emission.

This phenomenon has been approached by varying the position of the tritium atom in the molecule as exemplified in the work of Feinendegen (1967), Feinendegen and Bond (1971), Krisch and Zelle (1969) and Person et al (1976). It has been found that the effects seen can be largely accounted for on the basis of the beta particle dose absorbed in the immediate volume. There are exceptions to this, which were in mutagenic studies with bacteria which had incorporated ^{3}H-uridine and ^{3}H-uracil. When these two compounds were incorporated as cytosine into DNA, decays at the 5-carbon position were seven times as effective as decays at the 6-position. Person et al (1976) showed that the excess mutations induced by tritium at the 5-position of cytosine were almost entirely due to the C to T coding change, the mechanism being a substitution of a T–A pair for the original C–G pair. These effects have been further studied (Teebor et al, 1984) by investigating the presence of 5-hydroxymethyl-2'-doxyuridine (HMdu), a radiation-induced derivative of thymine, in HeLa cells irradiated with tritiated thymidine. Teebor et al concluded that 5-methyl-^{3}H-thymidine was considerably more effective in the production of HMdu than 6-^{3}H-thymidine and that was due to the transmutation of ^{3}H to ^{3}He in the methyl group of thymine. This demonstration of mutation complements the observations of Person et al (1976), Krasin et al (1976) and Cleaver (1977) who showed in *Escherichia coli* and Chinese hamster cells that labelling with 6-^{3}H-thymidine was mutationally two to three times more effective than 5-methyl-^{3}H-thymidine. It is noteworthy that Cleaver (1977) concluded that transmutation did not increase the frequency of SSBs. However, in a later study Tisljar-Lentulis et al (1983) estimated that, in human T1 cells, 31% of SSBs (but not DSBs) could be associated with transmutation of tritium in DNA labelled with 6-^{3}H-thymidine. The mutagenic, but not lethal, effects of transmutation were further emphasised by the work of Korolev and Ivanov (1985) using yeast labelled with 8-^{3}H purines.

The possibility of such effects being manifested in humans after intake of either tritiated water or food has been explored by Carsten (1979) based on the premise that only 2% of the DNA hydrogen is located at the 5-position of the cytosine ring. The risk was considered to be sufficiently small to be of no practical hazard in relation to the predicted effects of the emitted beta radiation. This conclusion was also reached after a comprehensive review by Feinendegen and Bond (1971). They concluded that 'the effects of intracellular tritium are overwhelmingly due to beta irradiation of the nucleus' and that

'transmutation effects do not produce a measurable effect'. In any case, experimental studies of the RBE of tritium would take account of such effects, if they occurred.

3.3.2 Accumulation of tritium in the hydration shell of DNA

Intracellular discrimination between tritium and hydrogen atoms due to isotopic differences (in particular, a mass ratio of three) has been considered in the past (see, for example, Carsten, 1979, and Mathur-de Vre and Binet, 1984) and concluded to be of little consequence for the risk of tritium. At the preliminary consultation seminar (Appendix A), however, it was suggested that tritium might become enriched in the hydration shell of DNA and thus result in more radiation damage to DNA than would be expected. While this should in principle be taken into account in the experimental determination of the RBE for tritium, it was decided to pursue it further.

Contrary to the traditional view of 'organically bound tritium' in biomatter, recent experiments that employed denaturing agents have clearly shown that a significant form of such tritium should be designated as 'buried tritium', an exceedingly tightly bound tritiated water (Baumgartner and Donhaerl, 2004). In such a fraction the 'buried tritium' in biomacromolecules, such as native proteins, is in bridge positions where the exchange rates are reduced from microseconds to days, months or even years as a consequence of the three-dimensional structure that arises upon the 'folding' of these native biomacromolecules. The hydrogen bridges between the molecules of water are stronger than between organic configurations, resulting in accumulation of tritons both inside the biopolymers and within their primary hydration shields. There is an enrichment of tritium in the newly identified buried hydrogen bonds compared to the free water in the cell. In most biomacromolecules, eg proteins, the enrichment may be 1.4-fold but in DNA, where the hydration shell consists of 11 molecules per nucleotide and is not readily permeable to ions, the enrichment in the water trapped in the core may be two-fold.

While this will certainly result in slightly more beta tracks originating from tritiated water within and around the DNA, it remains true that the vast majority of beta tracks encountered by the DNA will have originated from tritiated water outside the DNA since that is where most of the tritiated water is situated. The effect on radiation dose to the DNA will therefore be small and, as stated above, should be seen as one of the factors tending to increase the RBE in experimental determinations.

3.4 Difficulties caused by using different reference radiations in studies of RBE

The original reference radiation for the weighting factor in radiation protection was stated to be gamma rays from radium (ICRP, 1951). However, in 1955, the ICRP defined the reference radiation as X-rays with an average specific ionisation of 100 ion pairs per μm of water (ICRP, 1955) with 200 kVp X-rays typically used. A number of conventions have subsequently been used.

In the literature a range of reference radiations have been used for determination of RBE values and it is important when stating RBE values that the reference radiation is also specified. This is due to significant

differences between LET values for typical reference radiations, such as ^{60}Co gamma rays and 200 kVp X-rays (see Table 3.1). Therefore the RBE values obtained can differ depending on which radiation was taken as the reference.

Many experimental data over the years have shown that not all low LET radiations have the same effectiveness, especially at low doses. Orthovoltage X-rays are typically found to be twice as effective as high energy gamma rays at low doses (Section 3.1), this difference is consistent with biophysical calculations (Ellett and Braby, 1972; Kellerer, 2002). Additionally differences have been observed for X-ray sets operated at the same potential but with different filtration. For 220 kVp X-rays, a linear dose–effect coefficient to the fitted data for the induction of dicentric chromosome aberrations in human lymphocytes of 0.040 ± 0.003 Gy^{-1} for lightly filtered X-rays (4.05 mm Al + 0.5 mm Cu) was observed compared to 0.022 ± 0.004 Gy^{-1} for heavily filtered X-rays (2.0 mm Al + 3.35 mm Cu), which gave maximum low dose RBE values of 3.7 ± 1.5 and 2.1 ± 0.9, respectively, compared to ^{60}Co gamma rays (Bauchinger et al, 1983; Schmid et al, 1984). Similarly, the experimental values obtained for the RBE of tritium indicate differences in the biological effectiveness with reference to X-rays and gamma rays. In general, the values obtained when the reference radiation was ^{60}Co gamma rays were greater than the values obtained when the reference radiation was orthovoltage X-rays.

There is currently no internationally agreed standard for the reference radiation. For a number of reasons a high energy gamma-ray source such as ^{60}Co would be the preferred choice for the reference radiation (ICRP, 2003).

a Data for the atomic-bomb survivors represent the main source of information on radiation risks and these individuals were mainly exposed to high energy gamma rays.

b Most experimental animal studies of cancer induction have been carried out with gamma rays, including those at low dose rates.

c High energy gamma rays have the lowest values of LET.

d There is a more uniform distribution of energy deposition for large fields compared to X-rays.

e The LET and therefore the biological effectiveness of X-irradiations can depend on the filtration used.

3.5 Experimental studies of RBE

3.5.1 Studies of carcinogenesis

In this section we survey the experimental animal studies on the RBE of tritium, in particular those of Gragtmans et al (1984), Johnson et al (1995), Seyama et al (1991) and Revina et al (1984). A feature of all of these studies, in particular those of Gragtmans et al (1984), Seyama et al (1991) and Revina et al (1984), is the high background incidence, so that in many cases what is measured is acceleration of onset rather than excess incidence. As with many animal studies, these are of genetically inbred populations, and so the question of relevance to the more genetically heterogeneous human population is not clear.

As we shall see, the analysis of all datasets is suboptimal, so we have attempted re-analysis whenever possible. This analysis and further discussion is presented at more length in Appendix C.

3.5.1.1 Gragtmans et al (1984): breast cancer in Sprague-Dawley rats

The study of Gragtmans et al (1984) involved treatment of female Sprague-Dawley rats with 200 kVp X-irradiation given at either low/moderate dose rate (total doses of 0.29, 0.57, 1.1 or 2 Gy over ten days) or at high dose rate (total doses of 0.57 or 1.78 Gy over one hour). Other animals were injected (four times at two-day intervals) with HTO in saline solution (total doses of 0.46, 0.92, 1.63 and 3.85 Gy). There were about 120–130 animals in each of these dose groups. There was also a control (unirradiated) group of about 200 animals. Animals were followed for breast cancer. As generally with this strain of rat, the underlying incidence of breast cancer was very high, so that by the end of the study 63% of controls had developed cancer. Thus the experiments are essentially looking at earlier occurrence rather than lifetime incidence, but they effectively demonstrate this. Interestingly, HTO contributed 10–30 times the dose of OBT in these experiments.

As can be seen from Appendix C, the estimates of tritium RBE that we derive are consistent with those estimated by Gragtmans et al (1984), and are all statistically consistent with an RBE of one. Values of RBE much greater than 1.5 are inconsistent with the data. Thus, for enhancement by tritium of tumour appearance as a function of time, there is nothing to suggest that tritium possesses an RBE much greater than one. There must, however, be reservations about the relevance of these values, coming as they do from data describing the earlier occurrence of a cancer which has developed in the majority of the controls by the end of the experiment.

3.5.1.2 Johnson et al (1995): myeloid leukaemia and other cancers in CBA/H mice

The study of Johnson et al (1995) involved treatment of male CBA/H mice with low/moderate dose rates (total doses of 1.06, 1.98 and 2.64 Gy over ten days) of 200/150 kVp X-irradiation. The first X-ray tube (operating at 200 kVp) failed part way through the experiment and subsequent irradiations were carried out with a 150 kVp tube equipped with an ISO filter designed to produce an X-ray spectrum with an average energy of 104 keV, approximately equal to the average energy of the spectrum from the 200 kVp set and therefore a similar average LET (Myers and Johnson, 1990). The X-ray dose rate was reduced by 45% every two days to parallel the expected reduction in dose rate from injected HTO. Another group of mice were injected with a single intraperitoneal injection of HTO (total doses of 0.85, 1.86 and 3.04 Gy). There were generally between 730 and 750 animals in each of these groups. There was also a control (unirradiated) group of 747 animals. Animals were principally followed for myeloid leukaemia, although the paper gives brief details of various other cancers that developed (3768 in all, compared with 279 myeloid leukaemias). There are insufficient details given on these other cancers to allow much analysis of them. Acute myeloid leukaemia (AML), the principal endpoint used, has a spontaneous incidence in CBA/H mice that is essentially zero. Johnson et al (1995) used doses which appeared to saturate the effect at the lowest dose (1–2 Gy) of both radiations – the authors comment on the fact that the effect has a plateau from 1 Gy (this can also be observed in Figure C2).

As can be seen from Appendix C, the estimates of tritium RBE that we derive are generally consistent with those estimated by Johnson et al (1995), and are generally all statistically consistent with an RBE of one –

that is to say, most 95% confidence intervals include one. Values of RBE much greater than three are inconsistent with the data. The indication that the response in this study may have been saturated at the lowest dose used is somewhat atypical, since in this system saturation is normally found after doses that are two or three times higher. Thus there is no useful measure of the low dose slope of the induction curves so that the RBE cannot be determined for the incidence of myeloid leukaemia as a function of dose.

3.5.1.3 Seyama et al (1991): all tumours in female rodents

The study of Seyama et al (1991) involved treatment of female mice from three related strains, C57BL/6N x C3H/He, BCF_1 and C57BL/6N, with gamma doses at high dose rate (0.27 or 2.7 Gy from a ^{60}Co source at a dose rate of 0.47 Gy min^{-1}), or to moderate dose rates from a 'tritium simulator' (0.27 or 2.7 Gy from a ^{137}Cs source at progressively reducing dose rates, which were initially 5.9 10^{-5} Gy min^{-1} for the 0.27 Gy dose, and 5.3 10^{-4} Gy min^{-1} for the 2.7 Gy dose). The dose rate reduction regime is not specified in the paper, but presumably matches the reduction in dose rate from tritium. A group of C57BL/6N x C3H/He mice were also exposed to fission neutrons (0.27 or 2.7 Gy from a ^{252}Cf source at a dose rate of 2.7 Gy min^{-1}). Another four groups of BCF_1 mice were injected with single intraperitoneal injections of varying concentrations of HTO (3.75, 7.5, 15 and 20 mCi, resulting in total doses of 1.97, 3.95, 7.90 and 10.53 Gy, respectively). A further four groups of C57BL/6N x C3H/He mice received four weekly injections of 5 mCi* (total 20 mCi) or 3.75 mCi (total 15 mCi). For purposes of comparison with the fission-neutron-irradiated and gamma-irradiated animals, two further groups of C57BL/6N x C3H/He mice were given single intraperitoneal injections of HTO (1.9 10^8 and 1.9 10^7 Bq, equivalent to doses of 2.7 and 0.27 Gy, respectively). Animals were followed for a variety of tumours, and a total of 905 tumours developed. The most numerous tumours were ovary (263), pituitary (141), reticulum cell neoplasm (73), lipoma (65), leukaemia (63), liver (62) and lung (58).

As noted in Appendix C, the quantitative information that can be derived from this study is limited. The effect (incidence of tumours) seems to have nearly saturated at the lowest dose point, so that this study effectively measures acceleration of the appearance of tumours rather than excess incidence. In the long-term experiments the total incidence of tumours was similar at 500 days in all groups. As with the previous study, no RBE can be calculated for the incidence of cancer as a function of dose.

3.5.1.4 Revina et al (1984): all cancer and leukaemia in Wistar rats

This report describes experiments conducted in Wistar rats, in which 45 rats were administered 37 10^4 Bq per gram HTO of animal weight intragastrically (group II), five times a week during six months, 39 rats were chronically exposed to gamma radiation of ^{137}Cs in daily doses comparable with the tritium-exposed animals (group III), and 140 were controls (group I). A significant problem with this study is the large doses (about 25 Gy), although this was mitigated by the long period over which the doses were administered. The methodology for estimating 'probabilities' of tumour mortality, and with it RBE, is also problematic (see Appendix C), as is the very high rate (78%) of malignant tumour development in controls (although the leukaemia rate is substantially lower). It is noteworthy that the RBEs derivable from

* The curie (Ci) is an old unit of radioactivity equivalent to 3.7 10^{10} Bq. A convenient sub-multiple is the millicurie (mCi), ie 3.7 10^7 Bq.

these data are higher than those in other animal studies (for example, Gragtmans et al, 1984, and Johnson et al, 1995) and towards the upper end of the biological data that we review (see Table 3.2). Common radiobiological thinking would lead to the expectation that radiation quality effects would be less obvious at high doses than at low (UNSCEAR, 1993), so the result is unlikely to be exaggerated on this score. For this reason it is likely that the 'true' RBE values would be expected to be somewhat greater than those derived by Revina et al (1984). Notwithstanding these considerations, this study is of little use for estimating the limiting low dose RBE, since there is only one dose point in both tritium-exposed and gamma-exposed animals. Using the leukaemia endpoint, arguably the most reliable (because further from saturation than all malignant tumours), an RBE of about 2.49 (95% confidence interval (CI) 2.00, 2.98) can be derived from this study.

In summary, taken at face value these experimental animal carcinogenesis studies imply fairly modest tritium RBEs, with central estimates generally in the range 0.8–2.5, and an upper 97.5 percentile value of no more than about three. However, the experimental design and statistical analysis of many of these studies leave a lot to be desired, so that despite their obvious relevance to cancer, their findings should be treated with caution. Interpretation of the studies is complicated by the fact that in two of them cancer incidence is nearly saturated at the lowest doses, or in the controls, and in a third there is only a single dose point.

3.5.2 Other experimental studies

Values of RBE for genetic endpoints including chromosome aberrations and micronuclei in mammalian cells as well as genetic endpoints are presented in Table 3.2. The information available suggests that for these endpoints RBEs for HTO generally range from one to two for orthovoltage X-rays and are in the range from two to three when compared with ^{60}Co or ^{137}Cs gamma rays. The values of RBE for OBT are broadly the same as those for HTO.

A further series of studies summarised in Table 3.2 relates to the development of chromosome aberrations in human lymphocytes using HTO with exposures carried out *in vitro*. Dose–response curves for this biological endpoint have been shown to be particularly reproducible, especially at moderate and high doses and, therefore, may be considered to provide good estimates of RBE. Nonetheless, variability occurs due to differences in data analysis methods and actual scoring or response differences within a given cytogenetics laboratory. For example, Bocian et al (1977) exposed human lymphocytes to HTO giving doses ranging from 0.28 to 2.5 Gy and compared results with acute exposures to 180 kVp X-rays. They reported an RBE of 1.17 (95% CI 1.13, 1.21) in this dose range. However, upon revaluation of the data by Prosser et al (1983) it became clear that it was not possible to derive an accurate maximum limiting RBE from the Bocian et al results due to the lack of sufficient data at low doses. RBEs could only be calculated over the dose range used; at the lowest dose (0.28 Gy), the RBE was 1.91 (95% CI 0.64, 3.18) (Prosser et al, 1983). The Prosser et al dose–response curve for tritium has been used to estimate the dose received as a consequence of an accidental human intake of tritium and the resulting dose estimate was very close to that obtained from urine measurements (Lloyd et al, 1986a,b).

A subsequent HTO study again using dicentrics in human lymphocytes was reported by Prosser et al (1983). In that study, the dose–response following 24-hour exposure to HTO was compared with that from exposure to 1 Gy min^{-1} 250 kVp X-rays. The RBE calculated at low doses (ratio of α coefficients) was 1.13 (95% CI 0.78, 1.48). Straume and Carsten (1993) re-evaluated an RBE from the Prosser et al (1983) tritium data but based instead on 250 kVp X-ray results obtained at very low doses (Lloyd et al, 1988). On this basis the RBE was approximately two. It was noted that the Lloyd et al results were pooled from six cytogenetic laboratories including that of the National Radiological Protection Board (NRPB), and so the re-evaluation by Straume and Carsten (1993) based on it should be treated with extreme caution. Other methods of analysis using the same data gave an RBE of 1.48 (95% CI 0.93, 2.03), and a value of 3.42 (95% CI 2.17, 4.67) was obtained when using the earlier ^{60}Co gamma-ray data of Lloyd et al (1975) as comparison radiation, and 3.78 (95% CI 1.35, 6.21) when based on the more recent gamma-ray data of Lloyd et al (1986a). The re-evaluation by Straume and Carsten (1993) based on these results should similarly be treated with caution.

Lambert (1969) studied the death of spermatogonia in mice having specifically matched the exponentially decreasing dose rate to the mouse testes (over four days) from a single injection of either HTO or tritiated thymidine with the same dose rate from X-rays, and reported an RBE of 2.3–2.4 for HTO and 1.3–1.6 for tritiated thymidine (also in Table 3.2a). Rusinova et al (1989) assessed reduction of thymus weight in animals exposed to HTO and a comparison group exposed to ^{137}Cs at exponentially decreasing dose rate (a tritium simulator). Thymus mass varied substantially over the period of the study in both groups, with typically an initial reduction in mass followed by some recovery. At low doses (0.75 Gy HTO, 1.4 Gy gamma) little effect on the thymus mass was observed. Nevertheless Rusinova et al estimated a tritium RBE in relation to reduction of thymus mass integrated over the damage period of 2.9 for 2.77 Gy HTO exposure and 2.1 for 12.72 Gy HTO exposure. The RBEs with respect to the thymus mass reduction rate were 3.95 and 1.24 for HTO doses of 0.75 and 12.72 Gy, respectively. The RBEs with respect to the half-time, $T_{1/2}$, of thymus mass reduction were 6.5 and 1.4 for HTO doses of 0.75 and 12.72 Gy, respectively. The main problem with this study is the relatively high doses required to induce an effect, so the information that it can provide on limiting low dose RBE is very limited. The method of analysis is also very unclear.

Kozlowski et al (2001) compared the induction of stable chromosome aberrations in bone marrow cells from female mice and their offspring after exposure to X-rays and beta emissions from tritium (as HTO) at either 7 or 14 days of pregnancy. Similar levels of damage were seen in the offspring and their mothers, for both X-rays and tritium (doses of about 0.5 Gy in both cases), showing no evidence of greater *in utero* sensitivity. The RBEs are generally in the range 0.5–1.0 (Table 3.2). In interpreting these RBE estimates account must be taken of the acute X-ray source used for reference. It would be expected that a chronically delivered X-ray reference would have been somewhat less effective, resulting in an elevation of these RBE estimates, by a factor of two or so.

TABLE 3.2 Summary of information on tritium RBE
(a) *In vivo* experiments

Study	Effects studied and species	Radiations	Reference radiation	Dose range (Gy)	Tritium RBE (and 95% CI where indicated)
Gamma radiation reference					
Dobson and Kwan (1976, 1977)	Oocyte survival in mice	HTO and chronic γ	^{60}Co γ (tritium simulator)	~0.07–~0.88[a], 0.22–1.25[b]	2.8
Carr and Nolan (1979)	Testes weight loss in mice	HTO and chronic γ	^{60}Co γ (tritium simulator)	0.14–0.58[a], 0.58[b]	1.43 (1.06, 1.80)
Carr and Nolan (1979)	Testes weight loss in mice	^{3}HTdR and chronic γ	^{60}Co γ (tritium simulator)	~0.03–~0.70[a], 0.58[b]	2.07 (1.58, 2.56)
Revina et al (1984)	Leukaemia in rats	HTO and chronic γ	^{137}Cs γ (tritium simulator)	25.3[a], 24.8[b]	2.49 (2.00, 2.98)
Zhou et al (1986)	Dominant lethal mutations in female mice	HTO and chronic γ	^{60}Co γ (tritium simulator)	0.04–0.91[a], 0.53–2.70[b]	2.94 (2.00, 4.28)
Ijiri (1989)	Survival of small intestinal cells in mice	HTO and chronic γ	^{137}Cs γ (tritium simulator)	0–0.2[a], 0.0–0.4[b]	1.6 (1.2, 2.0)
Ijiri (1989)	Survival of descending colon cells in mice	HTO and chronic γ	^{137}Cs γ (tritium simulator)	0–0.2[a], 0.0–0.4[b]	1.4 (1.2, 1.6)
Rusinova et al (1989)	Thymus weight loss in rats	HTO and chronic γ	^{137}Cs γ (tritium simulator)	0.15–12.72[a], 0.64– 19.60[b]	1.24–6.5
Satow et al (1989a)	Teratogenic effects in rats	HTO and chronic γ	^{137}Cs γ (tritium simulator)	~2.0–~6.0[a], 1.75–6.80[b]	1.01 (0.57, 1.78)[d]
Satow et al (1989b)	Oocyte survival in mice	HTO and chronic γ	^{137}Cs γ (tritium simulator)	0.04–0.25[a], 0.06–0.21[b]	1.1–3.5
Zhou et al (1989)	Dominant lethals (oocyte, spermatogonia), dominant skeletal mutations (spermatogonia), oocyte + spermatogonial survival at 0.2 Gy, exponentially decreasing dose rate in mice	HTO and chronic γ	^{60}Co γ (tritium simulator)	0.2–0.6[a], 0.74–2.07[b]	2.99 (1.64, 4.34)
Zhou et al (1989)	Chromosome aberrations in spermatocytes, oocyte + spermatogonial survival at 0.2 Gy, constant dose rate in mice	HTO and chronic γ	^{60}Co γ (tritium simulator)	0.2–0.6[a], 0.43–2.07[b]	2.65 (0.91, 4.35)
Seyama et al (1991)	Cancer in mice	HTO and chronic γ	^{137}Cs γ (tritium simulator)	0.27, 2.7[a b]	2.5[c]

Study	Effects studied and species	Radiations	Reference radiation	Dose range (Gy)	Tritium RBE (and 95% CI where indicated)
X-radiation reference					
Lambert (1969)	Spermatogonial survival in mice	HTO and chronic X-rays	200 kVp X-ray	0.003–0.24[a], 0.05–0.50[e]	2.3–2.4
Lambert (1969)	Spermatogonial survival in mice	^{3}HTdR and chronic X-rays	200 kVp X-ray	0.019–1.50[a], 0.05–0.50[e]	1.3–1.6
Gragtmans et al (1984)	Mammary tumours in rats	HTO and chronic X-rays	200 kVp X-ray	0.46–3.85[a], 0.29–2.00[e]	1.17 (0.82, 1.52)
Chopra and Heddle (1988)	Chromosome aberrations in peripheral blood in mice	HTO and chronic X-rays	250 kVp X-ray	1.5–6.0[a e]	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[a e]	1.21 (0.8, 1.9)
Johnson et al (1995)	Leukaemia in mice	HTO and chronic X-rays	200 kVp X-ray initially, 150 kVp after failure of first X-ray tube	0.85–3.04[a], 1.06–2.64[e]	1.24 (0.63, 1.85)
Kozlowski et al (2001)	Chromosome aberrations in bone marrow in mice: HTO and X-ray	HTO and acute X-rays	250 kVp X-ray	0.7[a], 0.5[e]	0.43 (0.20, 0.81)
Kozlowski et al (2001)	Chromosome aberrations in bone marrow in mice: tritiated cress and X-ray	HTO and acute X-rays	250 kVp X-ray	0.4[a], 0.5[e]	0.84 (0.41, 1.55)
Kozlowski et al (2001)	Chromosome aberrations in bone marrow in mice: offspring and X-ray	HTO and acute X-rays	250 kVp X-ray	0.4–0.7[a], 0.5[e]	0.64 (0.28, 1.37)
Kozlowski et al (2001)	Chromosome aberrations in bone marrow in mice: mothers and X-ray	HTO and acute X-rays	250 kVp X-ray	0.4–0.7[a], 0.5[e]	0.49 (0.17, 1.09)
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[a], 0.5[e]	0.56 (0.31, 0.96)

Notes
(a) Tritium dose. (b) Gamma dose. (c) Computed at 500 days, 2.7 Gy. (d) Wald-based confidence interval. (e) X-ray dose.

TABLE 3.2 ***continued***
(b) ***In vitro*** **experiments**

Study	Effect	Radiations	Reference radiation	Dose range (Gy)	Tritium RBE (and 95% CI where indicated)
Gamma radiation reference					
Ueno et al (1982)	Cell survival in mammalian cells	HTO and chronic γ	^{60}Co γ	~1.0–~11.0[a], ~0.5–~11.0[b]	1.3–1.6
Ueno et al (1982)	Micronuclei in mammalian cells	HTO and chronic γ	^{60}Co γ	~1.0–~8.0[a], ~2.0–~9.0[b]	1.8–2.3
Ueno et al (1982)	Mutation in mammalian cells	HTO and chronic γ	^{60}Co γ	~1.5–~5.0[a], ~2.0–~6.0[b]	1.8
Yamada et al (1982)	Mouse embryo cell survival	HTO and chronic γ	^{60}Co γ	~0.6–~16.3[a,b]	1.09–1.70
Matsuda et al (1986)	Chromosome aberrations in mouse zygotes	HTO and chronic γ	^{60}Co γ	0.09–0.34[a], 0.05–0.30[b]	1.62 (1.30, 2.07)
Tanaka et al (1994)	Chromosome aberrations in human lymphocytes: dicentrics	HTO and chronic γ	^{60}Co γ	0.14–2.10[a], 0.05–4.0[b]	2.39 (2.20, 2.59)[c]
Tanaka et al (1994)	Chromosome aberrations in human lymphocytes: centric rings	HTO and chronic γ	^{60}Co γ	0.14–2.10[a], 0.05–4.0[b]	3.14 (2.56, 3.86)[c]
Tanaka et al (1994)	Chromosome aberrations in human lymphocytes: dicentrics and centric rings	HTO and chronic γ	^{60}Co γ	0.14–2.10[a], 0.05–4.0[b]	2.52 (2.33, 2.72)[c]
Tanaka et al (1994)	Chromosome aberrations total in human bone marrow cells	HTO and chronic γ	^{60}Co γ	0.13–1.11[a], 0.25–2.0[b]	1.30 (0.96, 1.76)[c]
Tanaka et al (1994)	Chromatid aberrations total in human bone marrow cells	HTO and chronic γ	^{60}Co γ	0.13–1.11[a], 0.25–2.0[b]	4.96 (3.73, 6.59)[c]

Study	Effect	Radiations	Reference radiation	Dose range (Gy)	Tritium RBE (and 95% CI where indicated)
X-radiation reference					
Bocian et al (1977)	Chromosome aberrations in human lymphocytes	HTO and acute X-rays	180 kVp X-ray	0.28–2.55[a], 0.5–3.0[d]	1.91 (0.64, 3.18)[e]
Vulpis (1984)	Chromosome aberrations in human lymphocytes	HTO and acute X-rays	250 kVp X-ray	0.25–7.0[a], 0.05–9.0[d]	8.0 (0.2, 15.8)
Little (1986)	Transformation in mouse cells	HTO and acute X-rays	220 kVp X-ray	~0.25–~5.0[a], ~0.5–~4.0[d]	<1–2
Kamiguchi et al (1990a,b)	Chromosome-type aberrations in human sperm	HTO and acute X-rays	220 kVp X-ray	0.14–3.74[a], 0.23–1.82[d]	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	0.14–3.74[a], 0.23–1.82[d]	2.17 (1.73, 2.73)
Kamiguchi et al (1990a)	Chromosome breakage aberrations in human sperm	HTO and acute X-rays	220 kVp X-ray	0.14–3.74[a], 0.23–1.82[d]	1.47 (1.33, 1.62)
Kamiguchi et al (1990a)	Chromosome exchange aberrations in human sperm	HTO and acute X-rays	220 kVp X-ray	0.14–3.74[a], 0.23–1.82[d]	1.96 (1.49, 2.62)

Notes
(a) Tritium dose. (b) Gamma dose. (c) Wald-based confidence interval. (d) X-ray dose. (e) Based on recalculation by Prosser et al (1983).

3.5.3 Summary of RBE studies

Straume and Carsten (1993) summarised the information then available on radiobiological knowledge of carcinogenic, genetic, developmental and reproductive effects associated with exposures to tritium. They used the data to develop values of RBE for the data available compared with effects of X-rays or gamma rays. The data have been further reviewed, updated, and in some cases reanalysed and are presented in Table 3.2, together with information as to whether the delivery of the comparison radiation was acute or chronic. Details of the updating and re-analysis of data are in press (Little and Lambert, 2008).

It is thought that the *in vivo* data are more appropriate because for practical radiation protection purposes the average organ dose will have been calculated following intake of tritium compounds and compared with that from an external radiation source. In general, RBEs for *in vivo* data would be expected on theoretical grounds to be less than those for *in vitro* data. Track structures become more similar as radiation penetrates deeper into tissue, so that as more dose is due to 'deeper' tracks more of the dose is due to that from track ends (energy deposition at ends being less LET dependent). There are indications of this in Table 3.2. The experiments with chronically delivered comparison radiation are also more appropriate given that tritium delivers dose in this way.

It should be noted that the studies in Table 3.2 are all [with the exception of the AECL report of Chopra and Heddle (1988)] in the peer-reviewed literature. We have excluded various other studies that have appeared in conference proceedings, in particular those of Kashima et al (1985), Nakamura et al (1985), Morimoto et al (1989), Suzuki et al (1989) and Ueno et al (1989); these (and others) were included in the review by Straume and Carsten (1993). We have excluded some other studies considered by Straume and Carsten (1993) that did not have adequate concurrent controls – for example, the studies of Carsten and Commerford (1976), Russell et al (1979), Prosser et al (1983) and Furuno-Fukushi et al (1987). Some of the calculations of RBE conducted by Straume and Carsten (1993) [eg the tritium experiments of Prosser et al (1983) combined with the ^{60}Co experiments of Lloyd et al (1975)] are based on non-concurrent experiments, and so should not be considered reliable; these are not reported in the table. Five studies (Gragtmans et al, 1984; Johnson et al, 1995; Little, 1986; Revina et al, 1984; Seyama et al, 1991) provided information on RBEs for carcinogenesis or cell transformation endpoints, which included mammary tumours in rats, leukaemia and other tumours in mice, and cell transformation studies on cells in culture. They concluded that the most well-defined RBEs appeared to be those for the acceleration of the appearance of mammary tumours in Sprague-Dawley rats (Gragtmans et al, 1984) and for induction of myeloid leukaemias in CBA/H mice (Johnson et al, 1995). [The studies of Revina et al (1984) and Seyama et al (1991) were not considered by Straume and Carsten (1993).] The table shows tritium RBEs in the range from one to two for carcinogenesis endpoints, using orthovoltage X-rays as the comparison radiation.

When comparing the distribution of RBEs among the nine studies in which X-rays were used as the comparison, the RBE distribution was highly skewed with most values in the range from one to two. In contrast, RBEs among the 14 studies for which gamma rays were used as the comparison were approximately normally distributed, with most values in the range from two to three. A more rigorous critical analysis of a restricted number of studies considered closest to being optimal has yielded an

aggregate RBE estimate of 2.19 (95% CI 2.04, 2.33) with respect to chronic gamma radiation and 1.17 (95% CI 0.96, 1.39) with respect to chronic X-irradiation (Little and Lambert, 2008).

The RBEs summarised in the table were obtained using radiations delivered at higher doses and dose rates than those generally received by workers or the public. Thus the average RBE values presented and the RBE distributions could, if anything, somewhat underestimate the actual RBEs most relevant for human risk assessment.

Many of these data have been reviewed in a report by Kocher et al (2005), which described tritium RBEs using a log-normal distribution with a geometric mean of 2.4 and geometric standard deviation of 1.4.

3.6 Conclusions for RBE

a A variety of theoretical and experimental studies with radiation of LET similar to that of tritium beta particles has led to the general expectation of an RBE of at least two for tritium compared with gamma radiation.

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

c Experimentally determined RBE values can vary significantly depending on the choice of reference radiation. It is recommended that high energy gamma rays, should be the preferred choice for reporting RBE values. Where lower energy X-rays and gamma rays have been 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 including a description of anything that may modify the energy spectrum, such as filtration.

d Interpretation of RBE experiments is complicated by the fact that dose rates are rarely comparable and the reference radiation may itself be more effective than hard gamma rays.

e In a wide variety of cellular and genetic studies RBEs for tritiated water have generally been observed in the range from one to two when compared with orthovoltage X-rays and in the range from two to three when compared with gamma rays.

f For developmental endpoints the RBEs for HTO were similar to those obtained for cellular and genetic studies.

g Whole animal carcinogenesis studies have yielded RBEs with central estimates generally in the range 0.8–2.5. However, we have several reservations about 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; the crucial low dose parts of the dose–response curves therefore cannot be compared.

h There are grounds for thinking that published RBEs could somewhat underestimate the actual RBEs 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 We consider that the most likely RBE relative to chronically delivered hard gamma rays is between two and three and consider a value of two is most appropriate, based largely on an analysis of the available experimental data with rounding and biophysical considerations; fractional values were not considered appropriate.

4 Epidemiology

Clearly the most appropriate source of information for deriving risks to health from exposures to tritium would be from epidemiological studies if sufficient high quality data were available. Epidemiological studies of radiation-exposed groups such as the Japanese atomic-bomb survivors (Preston et al, 2003, 2004) and various medically irradiated groups, whether treated for malignant conditions (eg Boice et al, 1985, 1988; Little et al, 1999) or benign conditions (eg Howe, 1995; Howe and McLaughlin, 1996; Little et al, 1999; Little and Boice, 1999; Weiss et al, 1994, 1995), have historically been employed by bodies such as the ICRP (1991), the BEIR Committee (NRC, 2006) and UNSCEAR (2000) to estimate radiation risk. However, the usefulness of such information is often impaired by a lack of dosimetric data, low doses and small numbers of cases, and this is particularly so for exposure to tritium. This chapter reviews some of the more informative studies involving exposure to tritium, although all have limitations. The epidemiological data are reviewed at somewhat greater length by Little and Wakeford (2008).

4.1 Studies of radiation workers

4.1.1 United Kingdom Atomic Energy Authority (UKAEA) workers

The study of Beral et al (1985) involved mortality follow-up of 39,546 UKAEA workers (of whom about 52% were classified radiation workers), from 1946 to 1979. The study of Atkinson et al (2004) involved mortality follow-up of a somewhat larger cohort, of 51,367 UKAEA workers (of whom about 51% were classified radiation workers), extending follow-up to the end of 1997. There was a statistically significant elevation in prostate cancer mortality in comparison with national rates in the cohort of 1418 workers monitored for tritium in the study of Beral et al (1985): the standardised mortality ratio (SMR) was 8.89 (2-sided $p<0.001$), based on 6 deaths; there were no statistically significantly elevated SMRs for nine other endpoints. There are no data given on tritium doses to this group (nor for doses from any other internally deposited radionuclide). There was a statistically significant (2-sided $p<0.001$) increasing trend of prostate cancer mortality with film-badge dose in the full cohort (tritium and non-tritium workers) of Beral et al (1985). Atkinson et al (2004) did not separately analyse the UKAEA tritium workers, but the findings did not substantiate those of Beral et al (1985). In particular, the trend of prostate cancer with dose failed to be statistically significant (2-sided $p=0.13$), although it remained so for those workers followed up until 1979 (2-sided $p<0.01$). In the absence of tritium-specific doses it is difficult to infer very much about risk from tritium in these two studies.

The study of Rooney et al (1993) involved follow-up of UKAEA workers for prostate cancer before 1986. Data for a total of 136 cases of prostate cancer and 404 controls (comprised of 372 individuals, some matched to more than one case) were collected. The study assessed possible exposure of each case or control to a number of radionuclides, including tritium, on a four-point scale (none, possible, probable

but low level, probable, and relatively high level). Rooney et al (1993) found a relative risk of 14.26 (95% CI 3.09, 133.16) associated with documented internal contamination by tritium, and an increasing trend (2-sided p<0.05) of prostate cancer risk with degree of potential exposure to tritium. The main problem with this study is a lack of adequate tritium dosimetry, so that interpretation of these figures to derive risk estimates for tritium is problematic. The apparent discrepancy with the later study of Carpenter et al (1998), which examined a group of workers apparently largely included in this cohort (follow-up ends six years earlier for the UKAEA workers in the study of Carpenter et al, and it also includes AWE and Sellafield workers), should also be noted.

In an earlier study, Atkinson et al (2002) analysed the same extended UKAEA cohort considered by the same group in 2004, with particular reference to prostate cancer mortality. An additional 90 prostate cancer deaths occurred in the period 1980–1997. Overall, there were no statistically significant elevations of prostate cancer mortality either in the earlier 1946–1979 cohort, with 27 deaths compared with 23.46 expected (SMR=1.15, 95% CI 0.76, 1.67), or in the later 1980–1997 cohort, with 90 deaths compared with 116.37 expected (SMR=0.77, 95% CI 0.62, 0.95). Among workers monitored for tritium, there was a highly statistically significant elevation of prostate cancer mortality in the earlier 1946–1979 cohort, with 6 deaths compared with 0.77 expected (SMR=7.81, 95% CI 2.85, 17.00), confirming the earlier findings of Beral et al (1985), but not in the later 1980–1997 cohort, with 9 deaths compared with 10.16 expected (SMR=0.89, 95% CI 0.40, 1.68). The study confirmed the previous indications of a statistically significant increasing trend (2-sided p<0.001) of prostate cancer mortality with cumulative radiation dose among the radiation workforce overall, in the period 1946–1979. However, there was no radiation-related excess among the 1980–1997 cohort (2-sided p=0.920), and there were no trends of prostate cancer among those monitored for tritium exposure for either sub-cohort (2-sided p=0.264 for 1946–1979 workers; 2-sided p=0.862 for 1980–1997 workers). There were no data given on tritium doses to this group (nor for doses from any other internally deposited radionuclide), nor was there separate analysis by tritium dose.

In the absence of tritium-specific doses it is difficult to infer very much about risk from tritium in these five studies.

4.1.2 Atomic Weapons Establishment (AWE) workers

The study of Beral et al (1988) involved mortality follow-up of 22,552 AWE workers (of whom about 42% were classified radiation workers) from 1951 to 1982. There are no data given on tritium doses to this group (nor for doses from any other internally deposited radionuclide). Among 1562 workers ever monitored for tritium, and among 20 causes of death considered there was a statistically significant (2-sided p<0.01) elevation in brain and central nervous system mortality relative to other radiation workers, based on a single case; there was no statistically significant trend with dose in the full cohort. There was a non-statistically significant elevation in prostate cancer mortality in the same group. There was no significant trend with dose for prostate cancer in an internal analysis of the full cohort (ie one in which regression of risk relies only upon comparisons of risks between different dose groups), although there was a statistically significant (2-sided p<0.01) increasing trend with dose in SMR, based on

3 prostate cancer deaths. In the absence of tritium-specific doses it is difficult to infer very much about risk from tritium in this study; the apparently significant findings in relation to prostate and brain cancer should be considered against the negative findings for these endpoints in the study of Carpenter et al (1998), which analysed this workforce and various other UK radiation workforces.

Johnson et al (1999) conducted further analyses of this workforce, with mortality follow-up updated to the end of 1996. There were statistically significant increasing trends of mortality from multiple myeloma (p=0.0002, 7 deaths), bladder cancer (p=0.0134, 20 deaths) and all diseases of the circulatory system (p=0.0455, 1157 deaths) with cumulative (film-badge and tritium) dose when a lag of 0 years was used, and 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. Among workers monitored for internal contamination, presumably including those workers exposed to tritium, there was a statistically significant elevated risk of kidney cancer compared with national rates (16 observed deaths, 8.53 expected, SMR=1.88, p=0.0161). Tritium doses were estimated, and combined with film-badge dose, but there was no separate analysis of risk in relation to tritium dose, so that it is difficult to infer very much about risk from tritium in this study.

4.1.3 Three groups of UK classified workers

The study of Carpenter et al (1998) involved follow-up of three groups of UK classified radiation workers, employed at the UKAEA establishments at Harwell (including Culham and London), Dounreay or Winfrith before 1980, the AWE before 1983, and at Sellafield before 1976. A total of 40,751 workers were studied, of whom 4111 were monitored for exposure to tritium. There are no data given on tritium doses to this group (nor for doses from any other internally deposited radionuclide); all analyses are in terms of cumulative external dose. As can be seen from Table 4.1, there is little evidence of a raised risk associated with tritium exposure, but in the absence of tritium-specific doses it is difficult to infer very much about risk from tritium.

TABLE 4.1 Rate ratios[a] (and numbers of deaths) among workers monitored for tritium in three radiation workforces in the UK (taken from Table 6 in Carpenter et al, 1998)

	Cumulative external whole body dose (mSv)		
Cause of death	**<10 mSv**	**>10 mSv**	**Total**
All malignant neoplasms (ICD9 140–209)	1.07 (32)	1.01 (133)	1.02 (165)
Bronchus and lung (ICD9 162)	1.86 (15)[b]	1.05 (42)	1.18 (57)
Prostate (ICD9 185)	0.89 (2)	1.39 (12)	1.33 (14)

Notes
(a) Relative to workers not monitored for any radionuclide, adjusted for age, sex, calendar period, social class and establishment.
(b) 2-sided p<0.05.

4.1.4 Savannah River workers and other US nuclear workers

Cragle et al (1988) assessed mortality in a cohort of 9860 white male workers at the Savannah River Site, South Carolina, USA, from 1952 to 1980. A further analysis of this cohort by Cragle et al (1998) extended follow-up to 1986, but has not been published in the peer-reviewed literature. There are few data given on tritium doses to this group (nor for external doses nor from any other internally deposited radionuclide), although there are indications that the workforce was relatively heavily exposed to tritium. About 800 employees received 0.5 mSv from tritium, and one worker received a dose of over 30 mSv from this source per year (Cragle et al, 1988). There are few indications of excess mortality in this cohort; in particular, there were 18 prostate cancer deaths versus 21.15 expected (SMR=0.85, 95% CI 0.50, 1.35), although there were stronger (but still not statistically significant) indications of an excess for leukaemia and aleukaemia (25 deaths versus 19.63 expected, SMR=1.27, 95% CI 0.82, 1.88) (Cragle et al, 1998). In the absence of tritium-specific doses it is difficult to infer very much about risk from tritium in this study.

Cragle et al (1998) performed an analysis in relation to cumulative external dose in this cohort, and found a marginally statistically significant increasing trend in mortality for leukaemia excluding chronic lymphocytic leukaemia (CLL) (2-sided p=0.049). There was no statistically significant trend for prostate cancer (2-sided p=0.38) or for 13 other endpoints considered by Cragle et al (1998).

Schubauer-Berigan et al (2007) assessed acute leukaemia and chronic myeloid leukaemia mortality at four nuclear sites in the USA, ie Hanford, Oak Ridge National Laboratories, Savannah River Site and Los Alamos National Laboratories, together with the Portsmouth Naval Shipyard. A nested case–control design within the respective cohorts was employed. Various periods of follow-up were used for the various component cohorts, finishing between 1990 and 1996. A total of 206 leukaemia cases and 823 age-matched controls were used. Dose estimation included that from tritium, as well as photons, neutrons and plutonium. Using a two-year lag there was an unadjusted excess odds ratio (EOR) of 5.96 Sv^{-1} (95% CI 0.32, 16.5), although after adjustment for sex and benzene exposure this fell to 2.60 Sv^{-1} (95% CI <–1.03, 10.3). The unadjusted EOR for the Savannah River Site workers, likely to be among the most heavily exposed to tritium among these five workforces, was 30.6 Sv^{-1} (95% CI 4.77, >130). There was no analysis accounting separately for the effects of tritium and other radiation exposures, and in the absence of this it is difficult to infer much about tritium risks from these three studies. However, the Savannah River Site workers are potentially informative about tritium risks.

4.1.5 Capenhurst uranium enrichment workers

At the Capenhurst uranium enrichment facility tritium gas was processed between 1965 and 1987 for defence purposes (Jackson et al, 1997). It is not clear how many of the 12,540 Capenhurst workers assessed in the report of McGeoghegan and Binks (2000) were exposed to tritium; tritium doses were not available. This workforce has been followed-up over the period 1946–1995. Urinalysis data consisting of paper records are currently being computerised; there may be some gaps in tritium urinalysis data for this cohort as it has proved difficult to locate some of the original records, but most appear to be available. Computerisation of records should be complete within two years with currently committed

effort, if no obstacles are encountered (see Appendix B). As with most radiation workforces, mortality was generally below national rates, as also those calculated for regional rates: most SMRs are less than one, several (eg all cause, all cancer, lung cancer, bladder cancer, and leukaemia excluding CLL) statistically significantly so; the only cancer site with elevated SMR was pleural cancer (11 observed versus 4.66 expected, SMR=2.36, 2-sided $p<0.05$). There were no statistically significant positive trends of cancer mortality with cumulative external dose. 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 cases. The trend of prostate cancer with cumulative external dose was negative. In the absence of tritium-specific doses it is difficult to infer very much about risk from tritium in this study. However, as these workers may be quite highly exposed, if tritium dose data were to become available in the future, this cohort could be potentially informative.

4.1.6 Chapelcross nuclear reactor workers

The four Magnox reactors at the Chapelcross plant have been used to produce tritium for defence purposes since 1980. It is not clear how many of the 2628 Chapelcross workers assessed in the report of McGeoghegan and Binks (2001) were exposed to tritium; tritium doses were not available. This workforce has been followed-up over the period 1955–1995. All tritium urinalysis data for Chapelcross have been computerised, so that the construction of tritium doses should be relatively straightforward (see Appendix B). As with most radiation workforces, mortality was generally below that expected from national rates, whether for Scotland or for England and Wales: most SMRs are less than one, several (eg all cause, all cancer, lung cancer, diseases of the respiratory system, and diseases of the circulatory system) statistically significantly so; the only cancer site with elevated SMR was benign and unspecified neoplasms (6 observed versus 1.81 expected, SMR=3.31, 2-sided $p<0.05$). Similarly, most cancer standardised registration ratios are less than one. The only statistically significant positive trend of cancer mortality with cumulative external dose was for prostate cancer (1-sided $p=0.036$ for 10-year lag, adjusted for age, sex, calendar year, industrial status, worker status, and time since first exposure), based on 8 deaths. However, with increasing lag the significance of the trend progressively decreased, so that with a 20-year lag the trend was no longer conventionally statistically significant (1-sided $p=0.062$). None of the 8 deaths had been monitored for tritium, or for ^{51}Cr, ^{59}Fe, ^{60}Co or ^{65}Zn, the radionuclides suggested by the study of Rooney et al (1993) as being associated with elevated risk. There was also a statistically significant increasing trend for bronchitis deaths (1-sided $p=0.018$ for 0-year lag, adjusted for age, sex, calendar year, industrial status, worker status, and time since first exposure), based on 6 deaths. There was a suggestive increasing trend of prostate cancer incidence with cumulative external dose (1-sided $p=0.086$ for 10-year lag, adjusted for age, sex, calendar year, industrial status, worker status, and time since first exposure), based on 12 cases, none of whom was monitored for tritium. All but two of the workers registered with, or dying from, prostate cancer had left Chapelcross prior to the production of tritium there, so that the excess risk of prostate cancer is not due to tritium exposure. In the absence of tritium-specific doses it is difficult to infer very much about risk from tritium in this study, and until tritium doses are calculated it is difficult to assess how informative this cohort might be.

4.1.7 Sellafield workers

There are tritium-exposed workers at the Sellafield site, although they have never been separately assessed, nor are there analyses in relation to tritium dose – for example, in the analyses by Omar et al (1999) or McGeoghegan et al (2003). The workforce in the most recent analysis includes 14,319 workers, followed-up over the period 1947–1992 (Omar et al, 1999); the female workforce, numbering 6376, has been followed-up over the period 1946–1998 (McGeoghegan et al, 2003). Tritium urinalysis records for Sellafield workers have been computerised and tritium doses are now available. The highest tritium exposures at Sellafield occurred in the late 1950s and early 1960s when tritium was produced by irradiation of lithium in reactors and then extracted from these rods in a specifically designed plant (see Appendix B).

In contrast to most radiation workforces, mortality was generally at about national rates; for example, the SMR for all-cause female mortality is 1.02 (671 observed deaths versus 659.5 expected) (McGeoghegan et al, 2003). The only causes of death with statistically significantly elevated SMRs among the total workforce are pleural cancer (14 observed versus 3.99 expected, SMR=3.51, 1-sided $p<0.001$), thyroid cancer (6 observed versus 2.16 expected, SMR=2.78, 1-sided $p<0.05$), diseases of the circulatory system (1989 observed versus 1858.19 expected, SMR=1.07, 1-sided $p<0.01$), ischaemic heart disease (1354 observed versus 1217.67 expected, SMR=1.11, 1-sided $p<0.001$) and symptoms, signs and ill-defined conditions (13 observed versus 6.47 expected, SMR=2.01, 1-sided $p<0.05$) (Omar et al, 1999). The only causes of death with statistically significantly elevated SMRs among the female workforce are bone cancer (3 observed versus 0.5 expected, SMR=5.54, 2-sided $p<0.05$), aplastic anaemia (4 observed versus 0.4 expected, SMR=11.35, 2-sided $p<0.001$), diseases of the circulatory system (291 observed versus 258.1 expected, SMR=1.13, 2-sided $p<0.05$) and ischaemic heart disease (150 observed versus 126.6 expected, SMR=1.18, 2-sided $p<0.05$) (McGeoghegan et al, 2003). Most cancer standardised registration ratios are less than one.

The only statistically significant increasing trend with cumulative external radiation dose in the latest analysis of all workers is for leukaemia excluding CLL (1-sided $p=0.015$ for 2-year lag), based on 13 deaths (Omar et al, 1999); for all leukaemia the trend just attains conventional levels of statistical significance (1-sided $p=0.05$ for 2-year lag), based on 16 deaths (Omar et al, 1999). There is a statistically significant increasing trend for multiple myeloma mortality, but only when a 20-year lag is used (1-sided $p=0.017$ for 20-year lag), based on 8 deaths (Omar et al, 1999). There are no statistically significant trends with cumulative external radiation dose in the analysis of the female workers (McGeoghegan et al, 2003). Tritium-specific doses have been estimated for this workforce, although they have not been taken into account in the analyses discussed here. In the absence of analysis in which these are explicitly taken into account it is difficult to infer very much about the risk from tritium in these studies, although this cohort should be regarded as potentially informative.

4.1.8 Canadian nuclear workers

The study of Zablotska et al (2004) involved mortality follow-up of 45,468 Canadian nuclear workers between 1957 and 1994. Tritium doses were calculated from urinalysis data for all workers who had potential exposure, and added to external (film-badge) doses. There is no indication in the published analyses of the magnitude of the tritium doses, but for some workers they are likely to be relatively substantial. Overall, this cohort had a mean dose of 13.5 mSv, and among those workers recorded as having some dose the mean was 19.7 mSv. As with many studies of nuclear workers the expected numbers were below national rates. For example, this was the case for all cancers (531 observed versus 721.0 expected, SMR=0.74, 95% CI 0.68, 0.80) and leukaemia excluding CLL (18 observed versus 22.6 expected, SMR=0.80, 95% CI 0.47, 1.26).

An unusual feature of this cohort is the large and generally borderline statistically significant trend with dose for many diseases, both malignant and non-malignant. For example, for all leukaemias excluding CLL the excess relative risk (ERR) is 52.5 Sv^{-1} (95% CI 0.205, 291, 2-sided p=0.048), for all leukaemias the ERR is 18.9 Sv^{-1} (95% CI <−2.08, 138, 2-sided p=0.25), for all solid cancers the ERR is 2.80 Sv^{-1} (95% CI −0.038, 7.13, 2-sided p=0.054), for rectal cancer the ERR is 34.1 Sv^{-1} (95% CI 1.41, 165, 2-sided p=0.029), and for lung cancer the ERR is 4.34 Sv^{-1} (95% CI −0.193, 12.7, 2-sided p=0.066). In this respect the pattern of risks exhibited in the study of Zablotska et al (2004) is similar to that in the studies of Ashmore et al (1998) of mortality and Sont et al (2001) of cancer incidence in rather larger groups of Canadian radiation workers (206,620 and 191,333 workers, respectively). These earlier studies did not adjust for socio-economic status in their analysis, in contrast to the study of Zablotska et al (2004), and their results should therefore be treated with caution. There was separate analysis of all solid cancers excluding tritium doses, for which the ERR, 2.67 Sv^{-1}, was lower than when tritium doses were included, ERR=2.80 Sv^{-1}. Similarly, for all leukaemias the ERR, 16.3 Sv^{-1}, was lower than when tritium doses were included, ERR=18.9 Sv^{-1}.

4.1.9 Conclusions from studies of radiation workers

a Tritium-specific doses have been estimated for some nuclear industry workforces, in particular those of Sellafield and the AWE in the UK, in the Savannah River Site in the USA, and in Canada.

b Only for the Canadian (Zablotska et al, 2004), American (Cragle et al, 1998; Schubauer-Berigan et al, 2007) and AWE workers (Beral et al, 1988; Johnson et al, 1999) are these doses explicitly taken into account in the analysis, although not in a way that facilitates inferences on risks associated with tritium.

c All of the workforces considered are likely to have some workers relatively highly exposed to tritium.

d Some nuclear industry workforces, in particular those at the Savannah River Site (Cragle et al, 1988, 1998; Schubauer-Berigan et al, 2007) and the Canadian workers (Zablotska et al, 2004), have relatively large numbers of workers with appreciable tritium exposures (relative to the other groups), and would be potentially informative.

4.2 Studies of environmental releases and of *in utero* exposure and offspring of radiation workers

4.2.1 Offspring of Canadian electric power workers

Green et al (1997) assessed cases of congenital abnormalities and matched controls in the offspring of Canadian electric power workers, specifically offspring of Ontario Hydro workers. There were 763 case–control pairs of fathers and 165 case–control pairs of mothers. Tritium doses were assessed for this group, although analyses were only of those cases and controls with fathers or mothers having a recorded tritium dose 60 days before conception versus those with no dose. As can be seen from Table 4.2, there is little evidence of a raised risk associated with tritium exposure.

TABLE 4.2 Adjusted odds ratios (and 95% CI) for aetiological groups of congenital abnormalities according to tritium exposure (recorded dose 60 days before conception versus none) (taken from Table 2 in Green et al, 1997)

Aetiological group	Discordant pairs	Odds ratio (95% CI)
Single gene disorders	0/0	–
Chromosomal disorders	3/2	1.46 (0.24, 8.80)
Multifactorial disorders	28/28	1.13 (0.66, 1.94)
Genetic, unspecified	6/8	0.80 (0.27, 2.32)
Unknown disorders	14/15	0.84 (0.40, 1.76)
TOTAL	51/53	0.99 (0.67, 1.47)

4.2.2 Offspring of Ontario radiation workers

McLaughlin et al (1992, 1993) considered cases of childhood (age 0–14 years) leukaemia in the offspring of Ontario radiation workers and matched controls. Workers were those employed at the AECL laboratories at Chalk River, a uranium processing plant at Port Hope, a uranium mining and milling plant at Elliot Lake and five power reactors (Rolphton, Pickering A and B, and Bruce A and B). There were 112 cases and 890 controls. Preconceptional tritium doses were assessed for this group. As can be seen from Table 4.3, there is little evidence of a raised risk associated with tritium exposure.

TABLE 4.3 Odds ratio (and 95% CI) for leukaemia cases among offspring of workers monitored for tritium in Ontario (taken from Table 8 in McLaughlin et al, 1992, and Table III in McLaughlin et al, 1993)

Statistic	Cumulative tritium dose before conception (mSv)	
	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)	
	0 mSv	**≥0.1 mSv**
Cases	112	0
Controls	880	10
Odds ratio (+95% CI)	1.00	0.00[b]
	Tritium dose 3 months before conception (mSv)	
	0 mSv	**≥0.1 mSv**
Cases	112	0
Controls	880	10
Odds ratio (+95% CI)	1.00	0.00[b]

Notes
(a) 1-sided p=0.25 (Fisher's exact test).
(b) 1-sided p=0.40 (Fisher's exact test).

4.2.3 Leukaemia in children in the vicinity of Kruemmel and Savannah River

Grosche et al (1999) studied cases of childhood leukaemia in the vicinity of the Kruemmel nuclear power plant in Germany, and the Savannah River Site in the USA. They observed 9 cases of childhood leukaemia in the period 1990–1996 within 10 km of the Kruemmel plant versus 2.77 expected (standardised incidence ratio, SIR=3.25, 95% CI 1.58, 5.96); over the period 1991–1995 Grosche et al observed 41 cases of childhood leukaemia in the Savannah River Region Health Information System versus 49.6 expected (SIR=0.86, 95% CI 0.59, 1.21). Although there is no individual dosimetry for either group, Grosche et al pointed out that tritium releases from the Savannah River plant exceed by several orders of magnitude those from the Kruemmel plant, so that the apparent excess leukaemia risk near the Kruemmel plant is probably not associated with tritium exposure.

4.2.4 Leukaemia in children in the vicinity of Canadian nuclear facilities

Clarke et al (1989, 1991) examined mortality and incidence of childhood leukaemia in the vicinity of nuclear facilities in Ontario. The first report (Clarke et al, 1989) considered leukaemia cases and deaths at ages 0–4 years, and the second report (Clarke et al, 1991) considered cases and deaths at ages 0–14 years. These facilities comprised the AECL laboratories at Chalk River (which started operations in 1944), a uranium processing plant at Port Hope (1935), a uranium mining and milling plant at Elliot Lake (1954) and six power reactor sites (Rolphton, Douglas Point, Pickering A and B, and Bruce A and B, which opened in 1962, 1967, 1971, 1982, 1976 and 1984, respectively). It is the heavy water power reactors that are expected to be the main sources of tritium exposure. Overall there is no evidence of excess leukaemia incidence or mortality near the six power reactor sites or the other nuclear installations. For example, in areas 'nearby' (less than 25 km from) the Pickering plants over the period 1971–1987 there were 33 leukaemia deaths in those aged 0–14 years versus 24.6 expected (SMR=1.34, 95% CI 0.92, 1.89), and the corresponding incidence figures (over the period 1971–1986) were 72 cases versus 62.8 expected (SIR=1.15, 95% CI 0.90, 1.44) (Clarke et al, 1991). In the area 'nearby' the Douglas Point plant over the period 1967–1987 there were 3 leukaemia deaths versus 1.1 expected (SMR=2.78, 95% CI 0.56, 8.13), and the corresponding incidence figures (over the period 1967–1986) were 4 cases versus 2.6 expected (SIR=1.57, 95% CI 0.42, 4.01) (Clarke et al, 1991). If all sites except Rolphton are pooled, based on figures in Clarke et al (1991; Tables 6–10) then the evidence becomes, if anything, weaker. In all counties containing the plants there are 164 leukaemia cases versus 148.4 expected, an SIR of 1.11 (95% CI 0.94, 1.29), whereas in the areas 'nearby' there are 95 cases versus 88.4 expected, an SIR of 1.07 (95% CI 0.87, 1.31). The figures with respect to cases and deaths at ages 0–4 years are similar (Clarke et al, 1989). There are no estimates of tritium doses in these studies, so it is difficult to infer risks from tritium.

4.2.5 Birth defects and infant mortality in the vicinity of the Pickering nuclear facility, Ontario

Johnson and Rouleau (1991) studied birth defects, stillbirths, and perinatal, neonatal and infant mortality within 25 km of the Pickering nuclear generating facility in Ontario. There is no overall evidence of excess mortality near Pickering – if anything rates were significantly less than the Ontario average. Johnson and Rouleau (1991) also studied these endpoints in relation to airborne and waterborne discharges of tritium from the Pickering plant, concentrating on the Pickering and Ajax townships, those closest to the plant. The incidence of central nervous system defects was significantly elevated in Pickering for airborne discharges at the highest of five levels (odds ratio, OR, in highest group = 4.01, 95% CI 1.25, 14.04, based on 6 cases), but there was no statistically significant trend with tritium exposure (p=0.197). However, when the analysis was repeated using Health and Welfare ground monitoring data for tritium there was no association for this endpoint (or any other) (OR for central nervous system defects in the highest exposure group = 0.24). There was a statistically significantly raised prevalence of births with Down's syndrome in Pickering (24 observed versus 12.9 expected, relative risk, RR=1.85, 95% CI 1.19, 2.76), the only endpoint out of 23 birth defect endpoints to show such an excess. There was a correlation, although not statistically significant (p=0.468), between Down's syndrome prevalence and

airborne tritium release, but no such correlation with Health and Welfare ground monitoring data. There were no such excess birth defect risks in Ajax, although there was a positive correlation, but again not statistically significant (p=0.282), with Health and Welfare ground monitoring data. As the authors pointed out, the few positive findings in this study are likely to be due to chance. The ecological design of the study is also a potential source of bias, firstly because airborne release levels in an area are poor indicators of individual exposure and secondly because geographical confounding factors may influence the relationship between outcomes such as congenital abnormalities and area-averaged tritium releases. A similar study of other nuclear power stations in Ontario does not appear to have been carried out.

4.2.6 Conclusions from studies of environmental releases and of *in utero* exposure and offspring of radiation workers

Epidemiological studies of environmental tritium exposure and of the offspring of workers exposed to tritium are not sufficiently robust to reach firm conclusions on the risks posed.

4.3 Conclusions from epidemiological studies

a In general, the available epidemiological studies do not contain enough detail to estimate risks from tritium exposure.

b Of the populations identified, the best prospects for more robust analyses exist in the nuclear worker studies in Canada (Zablotska et al, 2004), Savannah River Site (Cragle et al, 1988, 1998) and possibly other sites in the USA, and the five main tritium-exposed UK nuclear workforces, namely those at Sellafield, Chapelcross and Capenhurst and of the AWE and the UKAEA.

c All of these workforces have some groups who are relatively highly exposed to tritium, and with apparently good dosimetry. These could be used as the basis of a further study.

5 Biokinetic Models for Tritiated Water and Organically Bound Tritium

5.1 Overview of current ICRP models for HTO and OBT

Compartmental (biokinetic) models are usually used to describe the uptake, distribution and retention of tritium following intake. The most widely accepted models are those developed by the ICRP (eg ICRP, 1989, 1993). Dose coefficients (dose per unit intake values, Sv Bq^{-1}) published by the ICRP are incorporated into legislation in Europe (EC, 1996) and into international basic safety standards (IAEA et al, 1996). ICRP dose coefficients apply to reference members of population groups and are intended principally for prospective dose assessments and for testing compliance with limits and constraints.

The ICRP has published dose coefficients for the ingestion or inhalation of tritium as HTO or OBT by adults and children (ICRP, 1994, 1996). OBT applies here to tritium incorporated into the main dietary constituents rather than specific forms of OBT. In calculating doses, the ICRP made assumptions regarding absorption to blood, incorporation into organic molecules within the body, retention in body tissues, and distribution of energy from beta-particle emissions within cells. The ICRP also applies a radiation weighting factor (w_R) of one to all beta emitters.

Tritium can be present in organic molecules in exchangeable and non-exchangeable forms depending on the chemical bonds involved. In most organic molecules, the majority of tritium atoms bound to oxygen, nitrogen, phosphorus or sulphur atoms can be readily exchanged with hydrogen in body water and will exhibit similar kinetics to HTO. The term OBT applies only to tritium replacing H in C–H bonds which will not be exchangeable in this way and will normally only be released as a result of enzymically controlled breakdown of the molecules containing these C–tritium bonds. In the context of retention in tissues, OBT refers to the non-exchangeable organically bound component of tritium [see Diabate and Strack (1993) for details]. More generally, and in particular when describing intakes of tritium, OBT applies to tritium incorporated into the major dietary constituents: carbohydrates, proteins and lipids, but the term is also applied to all organic forms including labelled nucleic acids.

The currently recommended ICRP adult model for systemic HTO assumes that 97% of ingested activity is incorporated into tissue as HTO, where it is retained with a half-time of 10 days, and that 3% is converted to OBT, and retained with a half-time of 40 days. The latter half-time is derived from studies on the mean turnover of carbon in the body. The model for ingested OBT assumes that 50% of activity remains as OBT while 50% is converted to HTO by catabolism, the same half-times as HTO applying. Other retention parameters are recommended for children (Table 5.1). Dose coefficients (dose per unit intake values) for the six standard ages adopted by the ICRP calculated using these models are also given in Table 5.1 (ICRP, 1996).

TABLE 5.1 ICRP retention parameters and dose coefficients

	Retention half-times (days)		ICRP dose coefficients (Sv Bq^{-1})	
Age	**Compartment A (HTO)**	**Compartment B (OBT)**	**HTO**	**OBT**
3 months	3	8	$6.4\ 10^{-11}$	$1.2\ 10^{-10}$
1 year	3.5	15	$4.8\ 10^{-11}$	$1.2\ 10^{-10}$
5 years	4.6	19	$3.1\ 10^{-11}$	$7.2\ 10^{-11}$
10 years	5.7	26	$2.3\ 10^{-11}$	$5.7\ 10^{-11}$
15 years	7.9	32	$1.8\ 10^{-11}$	$4.2\ 10^{-11}$
Adult	10	40	$1.8\ 10^{-11}$	$4.2\ 10^{-11}$

Note
The proportion of activity assigned to compartments A and B is the same for all ages, namely 97% and 3%, respectively, for intakes of HTO, and 50% to each compartment for intakes of OBT.

Before discussing experimental results, it is helpful to explore one aspect of this type of model. In situations of protracted intake, equilibrium amounts of HTO and OBT will be established in the body. Using simple models such as those adopted by the ICRP for tritium, equilibrium values in a compartment (i) are proportional to the product of the fraction, a_i, assigned to that compartment from blood, and the retention half-time in the compartment, T_i. Thus the ratio at equilibrium, R_E, of activity in the OBT compartment of the model to that in the HTO compartment is given by

$$R_E(\text{OBT} : \text{HTO}) = \frac{a_{\text{OBT}}\, T_{\text{OBT}}}{a_{\text{HTO}}\, T_{\text{HTO}}}$$

In the case of the ICRP HTO model described above, this expression gives a ratio of 0.12 (0.03 x 40/0.97 x 10), ie four times higher than the ratio of the fractions, a_i, assigned to the OBT and HTO compartments (0.03/0.97). This result simply reflects the more substantial build-up in the OBT compartment due to its longer-retention half-time. However, the difference between the fraction assigned to a compartment in the model, a_i, and the fraction of total retained activity which would be observed in experiments of protracted administration is often a cause of confusion, and it is important to understand this point when interpreting published information. (The value of R_E for the OBT model is 0.5 x 40/0.5 x 10 = 4.)

It should be noted that the ratio R_E also represents the relative contributions to committed dose of activity assigned to the HTO and OBT compartments.

5.2 Review of key information underlying current models

Studies with HTO in animals suggest that 1–5% of tritium is incorporated into OBT (Takeda and Kasida, 1979). The use by the ICRP (1989) of a value of 3% is consistent with human data on the whole-body retention of tritium after intakes of HTO (see below) and the conclusion that the OBT component will contribute 10% or less to the total dose (Balonov et al, 1974; Lambert et al, 1971; Moghissi et al, 1971; Sanders and Reinig, 1968; Snyder et al, 1968; Trivedi et al, 1995, 2000). The results from the study by Rudran (1988) on eight subjects after chronic and acute intakes of HTO, which apparently indicated doses from the OBT compartment in the range 0.4–2.4 times that from HTO, are totally at variance with all other studies [see Richardson et al (1998) for review].

Comparison of the relative incorporation of tritium into OBT after intakes of HTO and OBT have shown that between about 3 and 20 times more OBT is present after intakes of OBT (ICRP, 1989; Mewissen et al, 1979; Moghissi et al, 1971; Pietzrak-Fils et al, 1978; Rochalska and Szot, 1977; Sanders and Reinig, 1968; Snyder et al, 1968; Takeda and Kasida, 1979).

Takeda (1991) exposed rats to chronic ingestion of HTO or tritiated leucine, lysine, glucose, glucosamine, thymidine or uridine for 22 days. At the end of this time, the greatest concentrations of OBT were found in rats exposed to tritiated amino acids with intermediate concentrations after exposure to tritiated DNA/RNA precursors.

Rochalska and Szot (1977) fed tritiated food or HTO to rats for 5 days and determined the OBT content of tissues on day 6. Incorporation into OBT was greatest after intakes of OBT by factors ranging from 3 for brain tissue to 15–17 for liver and small intestine. From these animal data it has been concluded that the uptake of tritium into OBT following intake of a tritiated diet is up to 20 times that from HTO intake. This provides further support for the ICRP model parameters – 50% for OBT : 3% for HTO, ie a ratio of about 20. This has been confirmed by other authors after intake of water and tritium-labelled wheat (Lu and Takeda, 1992).

However, the implications for dose depend also on the retention times in the HTO and OBT compartments, and this point has been well made by Rodgers (1992). The uptake into OBT is slow, and less well quantified because few studies have ensured that the animals were in a steady state. Published reports of OBT specific activities significantly greater than the tissue water in animals contaminated in the natural environment (Kirchmann et al, 1979; Martin and Koranda, 1972) may indicate that either these animals consumed a diet with high specific activity OBT or they were not in a steady state.

This is important and was exemplified by Rodger's experiments in 1992 in which he fed mice with either HTO or tritiated food (a tritiated amino acid mixture) or both over a period of 56 days (enough time for the animals to reach equilibrium, ie steady state). He then followed the concentration of HTO and OBT in the mice for a further 35 days. The results are shown in Figure 5.1.

During tritium exposure, the steady-state specific activity of OBT in mice exposed to HTO alone was roughly 22% of the steady-state specific activity of what the author refers to as the tissue water tritium, TWT (essentially HTO in tissues) in these mice, or 15% of their drinking water concentration.

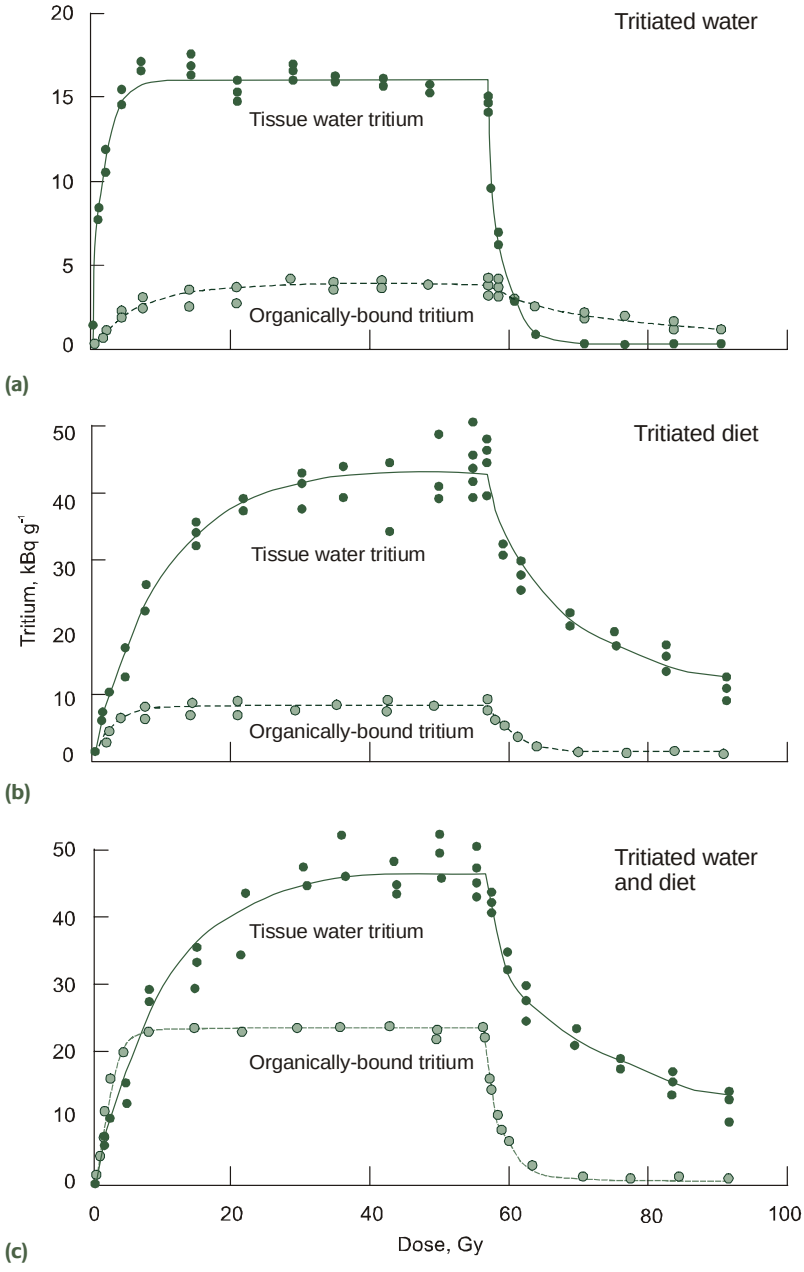

FIGURE 5.1 Specific environment of tissue water tritium and organically bound tritium of mice during and following exposure to: (a) tritiated water, (b) tritiated diet or (c) tritiated water and diet. Tritium exposure was terminated at day 56. Taken from Rodgers (1992), published courtesy of *Health Physics*

The influence of diet was evident due to the elevated steady-state specific activity of OBT attained by mice fed the diet alone or in combination with HTO. These results were in good agreement with earlier studies in which tritium specific activities in the OBT fraction of rats or rabbits exposed to OBT in the diet were significantly greater than the specific activities of tissues in animals exposed to HTO alone (Pietzrak-Fils et al, 1978; Rochalska and Szot, 1977). Thus when fed a diet with an OBT specific activity significantly higher than the specific activity of the ambient water, the specific activity of OBT in mice corresponded to the diet rather than to the water.

On the basis of all the data, the ICRP (1989) suggested, as a rounded value, that approximately nine times more OBT may be present after intakes of OBT than after intakes of HTO, corresponding to a range of 9–45% in uptake of tritium reaching blood, the remainder being converted to HTO (the wide range resulting from the differing metabolic roles of different OBT molecules, eg as an energy source or as a structural component). On this basis, it was also concluded that the use of a value of 50% would be suitable for general radiation protection applications.

While the biokinetic parameters used by the ICRP are supported by a range of data, there have been suggestions that the contribution to dose from OBT may be greater for intakes of either HTO or OBT. The postulated resulting increase in dose from intakes of OBT compared with HTO of about a factor of two is consistent with the conclusions of Takeda (1991), Komatsu et al (1990) and Rodgers (1992). This is reasonably consistent with the ICRP conclusion that the contribution to dose from OBT after intakes of HTO will be small (less than 10%) and that the overall dose from intakes of OBT will be greater than that from HTO by about a factor of two (the data in Table 5.1 show the ratio in ICRP dose coefficients is about 2.5).

Some experimental data suggest that after chronic intakes of HTO, equilibrium tissue concentrations of HTO and OBT are similar (Commerford et al, 1977). Etnier et al (1984) used a four-compartment model of hydrogen metabolism to show theoretically that OBT in foodstuffs can increase the cumulative total body dose by a factor 1.7–4.5 times the free body water dose alone. This model is regarded as providing a reliable representation of tritium biokinetics. The predictions in the model were demonstrated by Takeda et al (1985) using rats and tritiated wheat and HTO. The relative concentration of TWT and OBT at the end of chronic ingestion of tritiated food (70 days) was 1–9 times (of the administered activity) higher than those after intake of HTO.

In his experiments Rodgers (1992) also made assessments of the dose patterns and these are shown in Figures 5.1 and 5.2. For mice exposed to HTO only (Figure 5.2a), TWT was responsible for more than 95% of the cumulative dose during exposure. In contrast, OBT was responsible for a significant proportion of the cumulative dose to mice during exposure to OBT in the diet, either alone (approximately 50% of the dose, Figure 5.2b) or with HTO (approximately 25% of the dose, Figure 5.2c). Further, because of its much slower clearance, OBT was responsible for the majority of the cumulative dose in the 35 days following the tritium exposure. Consequently the cumulative *post-exposure* dose of mice exposed to OBT in the diet alone was about an order of magnitude greater than the cumulative post-exposure dose of mice exposed to HTO alone – even though the cumulative dose during *exposure* was slightly higher in mice exposed to HTO alone. The important point to emphasise is that this higher

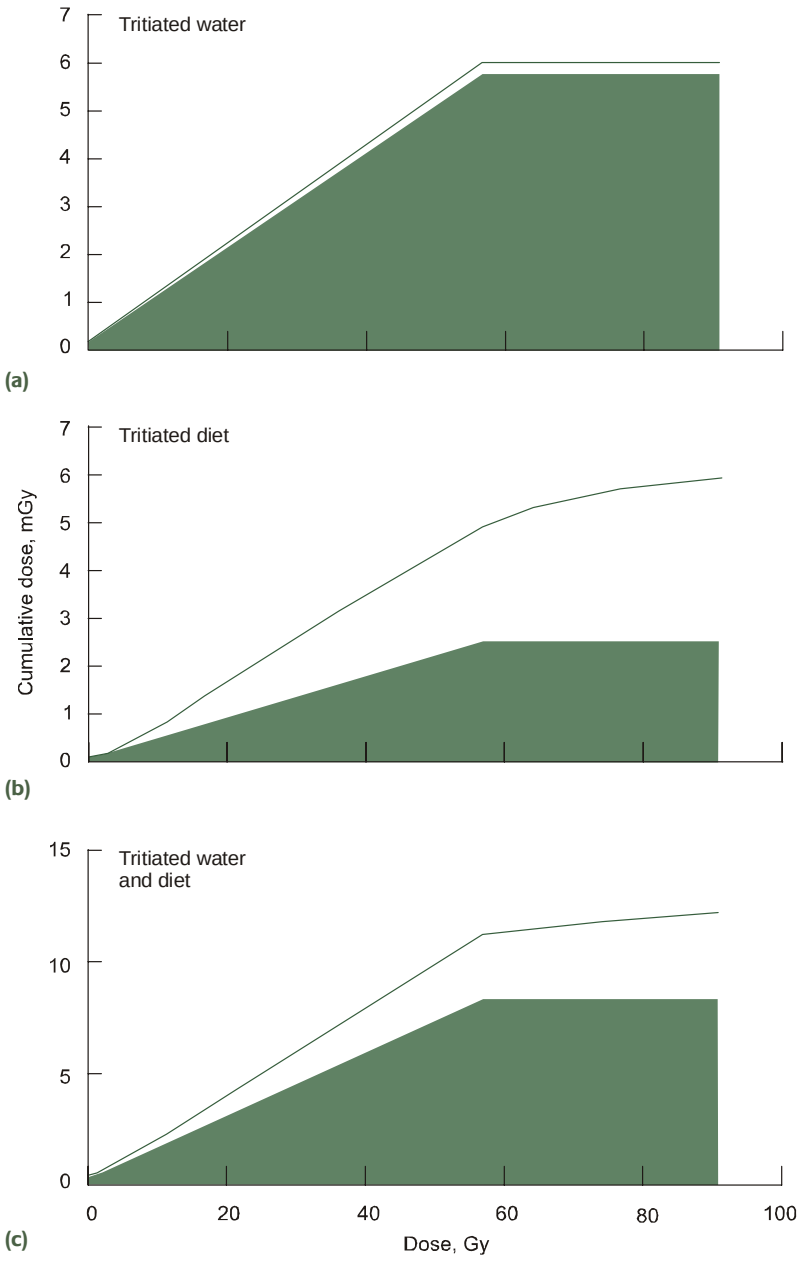

FIGURE 5.2 Calculated cumulative dose to mice exposed to: (a) tritiated water, (b) tritiated diet or (c) tritiated water and diet. Tritium exposure was terminated at day 56. The shaded area represents dose attributable to tissue water tritium; the open area represents dose attributable to OBT. Taken from Rodgers (1992), published courtesy of *Health Physics*

dose ratio is evident only after exposure has finished. Owing to the slow uptake of OBT and more rapid uptake of HTO, a single or short exposure would not result in such increased dose ratios.

In fact the results of Rodgers (1992) show general support for the current ICRP models. In the steady-state period (about 40 to 60 days in Figure 5.1), the ratio of the specific activity of OBT to HTO is about 0.25 for intakes of HTO (Figure 5.1a) and about 6 for intakes of OBT (Figure 5.1b). These values compare reasonably well with the equilibrium values of 0.12 and 4 predicted by the ICRP models (Section 5.1).

5.3 More recent models

5.3.1 Model for tritium in Cardiff Bay flounders

The ICRP has recognised that, when justified, site- or material-specific models can be used for dose calculations (ICRP, 1979, 1994, 1995). Routine investigations of fish caught in the Cardiff Bay area revealed unexpectedly high concentrations of tritium in flounders. Thus the NRPB was commissioned to study the retention of tritium in rats following ingestion of contaminated flounder flesh, and to explore the implications for doses to the local population.

Hodgson et al (2005) administered activity as either HTO or dried flounder flesh containing OBT. Two components of retention were obtained in each case. The first component, attributable to tritium equilibrating with body water, had a half-time of retention of 3 days in each case, and accounted for 97% of the intake as HTO and 70% after intake of OBT in flounder. Results were consistent with rapid catabolism of a large proportion of flounder OBT to HTO. The second component of retention, attributable to OBT in rat tissues, accounted for 3% of tritium intake as HTO and 30% after intake as flounder OBT; the half-times of retention were 10 and 25 days, respectively.

The results obtained after administration as HTO are consistent with published animal data and agree well with the ICRP assumptions for adult man of half-times of 10 days for 97% behaving as HTO in body tissues and 40 days for 3% incorporated into OBT in body tissues. The results obtained after administration of flounder OBT suggest that appropriate assumptions for retention in adult man are 70% with a 10-day half-time and 30% with a 100-day half-time. These assumptions result in an ingestion dose coefficient (committed effective dose per unit intake) of $6\ 10^{-11}$ Sv Bq^{-1}. This compares with the ICRP value for OBT ingestion by adults of $4.2\ 10^{-11}$ Sv Bq^{-1}, based on half-times of 10 and 40 days applied to equal proportions of retained tritium (Section 5.1).

Hodgson et al (2005) proposed that the dose coefficient of $6\ 10^{-11}$ Sv Bq^{-1} should be applied to tritium intakes resulting from the consumption of flounders taken from the Cardiff Bay area; the implications of this are explored in Appendix 5 of the RIFE 11 Report (EA et al, 2006).

While this experiment is of interest to the population, regulators and plant operators in the Cardiff Bay area, and has certainly answered many questions about potential doses to people who consume flounders, it should be noted that calculations of dose based on the Hodgson et al dose coefficient result in doses that are about 50% higher than calculations based on the ICRP default dose coefficient for OBT.

5.3.2 Proposed new ICRP models for HTO and OBT

5.3.2.1 HTO

Many human and animal studies suggest that the loss of tritium from the body could be described by a three-component exponential function (Bennett, 1973; Hill and Johnson, 1993; Sanders and Reinig, 1968; Thompson, 1953). The first compartment represents body water, the second tritium incorporated into organic compounds within the tissues, and the third tritium incorporated into structural, or other, very slowly turning-over tissue components. It should be noted that the second and third components mentioned here constitute the non-exchangeable OBT discussed in Section 5.1.

Although current ICRP models do not take into account the third component, its likely existence was acknowledged in ICRP Publication 56 (1989), and the ICRP has recently published, for discussion, a new model for HTO which takes into account the third component (ICRP, 2007b). The proposed model is based on the work of Taylor (2003), who reviewed the available data published by Balonov et al (1974), Moghissi et al (1971, 1972), Rudran (1988), Sanders and Reinig (1968), Snyder et al (1968) and Trivedi et al (1997). Taylor proposed a three-component exponential model, with half-times of 10 days (99.00%), 40 days (0.98%) and 350 days (0.02%) to describe the retention of tritium following intakes of HTO.

Dose coefficients based on the proposed HTO model are only slightly lower than those currently published by the ICRP. The main difference in the implications of the model is in the interpretation of measurements of tritium in urine made more than about 100 days after intake. The third component leads to higher model predictions of body content at these times which could lead to much lower estimates of intake, and hence a lower assessed dose. However, in practice this is unlikely to be of importance at well-regulated sites since urine samples are usually collected at least monthly.

5.3.2.2 OBT

Soluble organic compounds of tritium entering the blood will be incorporated into body tissues to an extent that depends on the chemical compound and the metabolic activity of the individual tissues.

Biokinetic and dosimetric studies have been carried out in experimental animals, mainly rats, for more than 20 tritium-labelled biochemical compounds (Balonov et al, 1984, 1993; Lambert and Clifton, 1967, 1968; Standeven and Clarke, 1967; Vennart, 1969) including tritium-labelled folic acid, thymidine, corticosteroids, cholesterol, lysine and tyrosine among others. This information indicates that tritium retention in the human or animal body may vary between compounds from a few hours to many days. In view of this wide variation in retention times, the range of tritium-labelled substances that could be encountered, and the general lack of data on their biokinetics, the ICRP proposes that it is not practicable to provide a single model for OBT (ICRP, 2007b). However, the ICRP is likely to provide a dose coefficient for OBT for use in planning purposes.

5.4 Special aspects of DNA precursors

A number of tritiated compounds are produced commercially for the purposes of labelling DNA and RNA. Owing to the specific incorporation of tritium into, for instance, DNA, these compounds are particularly useful in experiments designed to study cell kinetics. However, this highly specialised work limits the risk from tritium in these materials to a small group of researchers, a few workers involved in their production, and (theoretically) people who live near industrial biotechnology sites which discharge such compounds.

The most commonly used tritiated precursor for DNA is the deoxyribonucleoside, thymidine – although tritiated deoxycytidine is also used for DNA labelling and tritiated uridine and adenine are used for RNA.

Tritiated thymidine, usually labelled in the 5-position, can be obtained at very high specific activity. When administered to animals or people, and available from the blood, the tritium label will be incorporated into DNA during the synthesis stage of the cell cycle. This label will then be lost – although there is some evidence that 30–40% may be re-used (Feinendegen et al, 1973) – as it is diluted by further cell divisions. Even after injection into animals or in cell culture the period of availability of the label can be quite short (around an hour) and so the compound is most useful in the study of rapidly dividing cells. Continuous administration, particularly *in utero*, will label slowly cycling cells and this has proved a useful experimental tool (Fliedner et al, 1968; Lambert and Phipps, 1977; Kember and Lambert, 1981), especially as the label may be retained for a significant proportion of life.

From the point of view of risk to workers, tritiated thymidine poses a quite small, but unique, risk simply because, after intake, some of the tritium label will be incorporated specifically into DNA. However, after injection about 15–30% (Steel and Lamerton, 1965) is incorporated, whilst after ingestion only about 2% (Lambert and Clifton, 1968) is incorporated into DNA. The remainder, and major fraction of the label, appears, after catabolism, as HTO in the body water. Owing to the relatively short time available, labelling of cells (in the adult) will be restricted to organs and tissues such as the gut, bone marrow, basal layer of the skin and testes. The speed of elimination of tritium will then be controlled by the fairly rapid turnover of these cells and therefore the dose will be less significant. Nevertheless there are data from cell culture systems (see, for example, McQuade and Friedkin, 1960, and Ockey, 1967) and animal experiments of increased damage to cells because of the tritium incorporated into DNA in terms of cell death (Fliedner et al, 1968; Lambert, 1969) and carcinogenesis (Baserga et al, 1966; Johnson and Cronkite, 1967; Lambert and Phipps, 1984; Mewissen and Rust, 1973). However, such damage does not appear to be unique (Dobson et al ,1982; Lambert, 1969).

Tritiated thymidine itself is notoriously unstable unless stored in optimum conditions (−4°C or less) (McCubbin et al, 2001; Sheppard et al, 1974) and therefore when released to the environment it can be expected to be substantially degraded. Thus the risk of intake of tritiated thymidine as a specific DNA label from the environment is not great. For instance, uptake into fish and shellfish has also been studied (McCubbin et al, 2001) and shown to be considerably (ten times) less than that for other compounds, such as tritium-labelled amino acids and hydrocarbons, which produce more diverse labelling of tissues (Takeda, 1982).

In summary, tritiated nucleic acid precursors could present a unique hazard because of the possibility of DNA incorporation, but because of the likely exposure routes and the amounts available for intake, this risk can be estimated to be small (NCRP, 1979). Nevertheless the risk associated with tritium incorporation indirectly into DNA from OBT in food cannot be discounted – for example, the dose from tritium in DNA in mouse liver after intake of tritiated food was estimated to be twice that from HTO (Komatsu, 1990). Although there are theoretical estimates (NCRP, 1979) of significant doses which could result from intake of nucleic acid precursors, in practice safety procedures in modern laboratories mean the risks to workers and the general population are low.

5.5 Conclusions for biokinetic models

a A wide range of animal and human data provide general support for the current ICRP models.

b Studies involving chronic exposure need careful interpretation and consideration of whether the system studied is at a steady state of retention. This is difficult when exposure has occurred in the natural environment, but results of controlled laboratory experiments are generally in agreement with the predictions of the ICRP models.

c A special model has been developed for OBT in flounders taken from the Cardiff Bay area, and has been applied to critical group calculations.

d A new ICRP model for HTO is being developed. This will have little impact on dose coefficients (dose per unit intake values, Sv Bq^{-1}) but could significantly affect some calculations of intake and dose for workers, based on urine measurements.

e The ICRP is unlikely to recommend a single model for OBT due to the wide range of tritiated organic compounds to which people could be exposed.

f Tritiated nucleic acid precursors can present a unique hazard because of the possibility of their incorporation in DNA. However, in practice safety procedures in modern laboratories mean the risks to workers and the general population are low.

6 Reproductive Effects in the Female

Tritium taken into the body will be incorporated into most tissues and during pregnancy it will be taken up also by fetal oocyte DNA and other organic fractions during the five-month period from two months after fertilisation until seven months of gestation. This tritium will effectively irradiate the oocytes throughout the time before ovulation and fertilisation or before they are lost by atresia; this could in principle be over a time of 30+ years for tritium incorporated into DNA.

These cells do not divide during this period and therefore, assuming no turnover of tritium, the half-time of elimination will be the physical half-life (12.3 years). Thus the dose to the nucleus will be greater than that estimated using the ICRP half-time of 40 days. The extent of the increase will be the ratio of the integrals of the decay function. Over a period of 15 years the ratio is 65, for 20 years it is 77, for 30 years it is 93, and for 40 years it is 101. Of course any instability in DNA would result in these figures being overestimates.

6.1 Stability of DNA between oocyte formation and fertilisation

The argument that tritium incorporated into oocyte DNA during gestation remains there until fertilisation depends on there being no DNA turnover. If any DNA is replaced then the tritium incorporated therein will be lost. Damage to DNA occurs as a result of several spontaneous processes and the oocyte must either repair the damage or die. Early experiments showing DNA turnover in resting cells had their limitations but collectively they suggested that the phenomenon is widespread (see review by Pelc, 1968). In resting lymphocytes Forell et al (1982) estimated around 2000 bases per hour were turned over. Incorporation of labelled thymidine was temperature dependent and attributed to repair of thermal damage (probably hydrolysis of DNA). Given that there are $3.2\ 10^9$ bases in the genome of each human cell, such a rate *in vivo* would lead, if constant for 50 years, to around 5% of the genome being replaced.

There is little quantitative evidence from oocytes but experiments with brief periods of incubation indicate that labelled thymidine is incorporated into the nuclei of resting, growing, and fully grown germinal-vesicle-stage mouse oocytes (Masui and Pedersen, 1975; Pedersen and Mangia, 1978). There is no reason to believe that the DNA of oocytes is immune to depurination, hydrolysis, and endogenous oxidative and methylating agents, all of which produce damage, and the repair of which involves DNA turnover. Repairable spontaneous depurination has been estimated to occur at a rate of 20,000 bases per day per mammalian cell, and over 50 years implies $7.3\ 10^6$ purines are turned over in a human oocyte, about 2% of the genome.

In addition to turnover due to DNA damage and repair there is likely to be a degree of turnover associated with postnatal synthesis of RNA in oocytes (NCRP, 1979). Of course, we have no idea as to the

frequencies of these events in oocytes or how they are handled by the cell; their consequences might vary depending on their location within the oocyte genome.

There is also inferential evidence that DNA turnover occurs during the lifetime of oocytes in the female. In humans the factor IX haemophilia mutation is X-linked. An analysis of 43 independent origins of factor X mutations suggested that replication-arrested oocytes accumulate mutations at nearly the same rate as replicating sperm line cells (Ketterling et al, 1993). This work was subsequently extended to show that the rate of mutation increased with maternal, but not paternal, age (Ketterling et al, 1999). The age-dependent occurrence of mutations indicates the activity of error-prone DNA mechanisms in the absence of replicative DNA synthesis, and presumably reflects the continual occurrence of DNA damage and repair.

While the work described above does not allow a quantitative estimate of DNA turnover, it serves to show that DNA in human oocytes should not be regarded as physically stable. Any calculations that assume complete persistence of tritium in oocyte DNA are thus likely to give an overestimate (possibly quite small) of the possible risk.

6.2 Doses from tritium in oocytes

In the ATSDR report (LLNL, 2002) on the implications of the tritium discharges from the Lawrence Livermore National Laboratory and the Savannah River Site in the USA, the effects on oocytes were assessed using an approach which involved the reasonable assumption that the oocytes are labelled with tritium to the same concentration as the rest of the body. We have used a similar approach (calculating from first principles) in the context of the Cardiff Bay area where there is an accumulation of OBT in flounder. Concentrations of OBT in a variety of fish species have been reported as ranging from 20–120 kBq kg^{-1}, but with most values between 20 and 50 kBq kg^{-1} (Williams et al, 2001). The critical group consumption rate is taken to be 24 kg per year (EA et al, 2006), and assuming a concentration of 50 kBq kg^{-1} implies an intake of 1200 kBq of OBT per year.

Hodgson et al (2005) have developed a model for OBT ingested in Cardiff Bay flounders (see Section 5.3.1). Making the conservative assumption that the intake rate above has persisted for sufficiently long so that an equilibrium level has been reached in the critical group, then we can calculate a whole-body retention of 175 kBq using the Hodgson et al model.

We further assume that this intake is distributed throughout all the maternal and fetal cells (ie about 10^{14} cells). The cell content is thus 1.75 nBq of tritium distributed throughout the cell constituents. Around 5% (87.5 pBq) would be expected to have labelled the DNA. Assuming this DNA is not turned over before the time of possible fertilisation we can calculate the number of disintegrations (N) in an oocyte in, say, 30 years as follows:

$$N = 87.5\ 10^{-12} \int_0^T \exp(-\lambda t)\, \mathrm{d}t$$

$$N = 87.5\ 10^{-12} \times \lambda^{-1} [1 - \exp(-\lambda T)]$$

where λ is $0.693/T_{1/2}$ ($T_{1/2}$ = 12.26 years) and T is 30 years. Therefore

N = 0.04 disintegrations per cell

ie about 4% of the cells will experience a tritium disintegration in 30 years, 96% will not.

The ATSDR has calculated that each disintegration generates a dose of 2.7 mGy on average in an assumed cell nucleus of 8 μm diameter and 270 pg mass. If we adjust for an RBE weighting factor of 2 for tritium, then those oocytes in which a disintegration has occurred will experience an adjusted dose of 2 x 2.7 = 5.4 mGy equivalent.

The ICRP value for the probability of severe hereditary effects is $5\ 10^{-6}$ per mGy based on extrapolation from male mouse data. For those oocytes that experience a tritium disintegration (equivalent to an adjusted dose of 5.4 mGy) accumulated between the formation of the oocyte and the laying down of an oocyte during a pregnancy 30 years later, the probability of a severe hereditary effect is thus likely to be around $2.5\ 10^{-5}$. However, since only 4% of oocytes will experience a tritium disintegration, the overall frequency will be around 10^{-6}.

For the critical group consuming Cardiff Bay flounder during pregnancy, with an assumed body content at equilibrium of 175 kBq based on cautious estimates of intake, we therefore estimate that approximately 4% of oocytes could experience a tritium disintegration within the next 30 years. The frequency of severe hereditary effects resulting from this would be expected to be around 10^{-6}. This may be compared with a spontaneous incidence of around 3 to 4%. Clearly, there are significant uncertainties in the calculation of the value of 10^{-6}, nevertheless this is of little concern when the result is very small compared to the spontaneous incidence rate.

6.3 Response to DNA damage in the oocyte

We have considered whether some sort of amplification of radiation damage may occur during embryonic development, operating through, for example, persisting genomic instability, bystander effects, or clonal expansion. Alternatively, DNA damage responses such as cell cycle checkpoints and entry into apoptosis may be different in the rapidly expanding and differentiating cell populations of the embryo. An important property of genomic instability and the bystander effect is that their consequences are not limited to the cells experiencing the radiation dose but can (via signal transduction processes) occur in neighbouring cells or in the descendants of the irradiated cell.

Effects of this nature have been reported to occur in irradiated male germ cells and may extend into the early cell divisions following fertilisation (for reviews of this area see Bridges, 2001, and Bouffler et al, 2006). Whether genomic instability and bystander effects occur in oocytes and throughout development is unknown, although there would appear to be considerable scope for the bystander effect. Only a very small proportion of oocytes experience a tritium decay and there will be long intervals between decays. It is unclear whether amplification effects such as those mentioned above could have a significant effect on pregnancy outcome other than the severe effects normally considered.

6.4 Conclusions

a Tritium incorporated during pregnancy into the DNA of fetal oocytes could in principle remain there until fertilisation decades later.

b DNA, however, is not stable since it is subject to turnover during DNA repair processes. Such evidence as is available suggests that even over decades, only a small proportion of the DNA will be turned over. A conservative assumption would be to neglect turnover for radiation protection and risk assessment purposes.

c For the critical group consuming Cardiff Bay flounder during pregnancy, we have estimated that approximately 4% of oocytes could experience a tritium disintegration within 30 years. The frequency of severe hereditary effects resulting from this would be expected to be around 10^{-6}. This may be compared with a spontaneous incidence of around 3 to 4%.

d Existing evidence does not enable account to be taken of any consequences there might be resulting from bystander effects or genomic instability phenomena in the developing embryo.

7 Conclusions

This report has reviewed the available published work on the relative biological effectiveness (RBE) of tritium. A variety of theoretical and experimental studies with radiation of LET similar to that of tritium beta particles have led to the general expectation of an RBE of about two for tritium compared with gamma radiation. Moreover, in a wide variety of cellular and genetic studies RBEs for tritiated water (HTO) have generally been observed in the range from one to two when compared with orthovoltage X-rays and in the range from two to three when compared with gamma rays.

For developmental endpoints the RBEs for HTO are similar to those obtained for cellular and genetic studies. Whole animal carcinogenesis studies have yielded RBEs close to one. However, we have several reservations about 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; the crucial low dose sections of the dose–response curves cannot therefore be compared.

Transmutation effects and isotopic discrimination associated with tritium have been suggested as means by which the RBE for tritium could be increased. However, the evidence available indicates that these effects are not likely to be important, and in any case would be already taken into account in the observed RBE values.

There are grounds for thinking that published RBEs could somewhat underestimate the actual RBEs 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.

Having taken into account both theoretical considerations and the best available experimental data it is our opinion that an RBE of two compared with high energy gamma radiation would be a sensible value to assume (pending a published international consensus) in epidemiological and certain other specific studies.

Although a substantial number of epidemiological studies involving radiation workers, their offspring, and members of the public have been carried out, in general the available information does not contain enough detail to estimate risks from tritium. Consequently there is a need for further individual and pooled analyses of groups which include people who have had relatively high levels of exposure to tritium and where good quality dosimetric information has been collected. The workforces investigated in the nuclear worker studies in Canada, the Savannah River Site (and possibly other sites in the USA), and the five main tritium-exposed UK nuclear workforces, namely those at Sellafield, Chapelcross and Capenhurst and of the AWE and the UKAEA, have some groups who are relatively highly exposed to tritium, and with apparently good dosimetry. Therefore, these could be used as the basis of further study and, possibly, a pooled analysis.

The report has reviewed a wide range of biokinetic data from both animal and human studies and concludes that the information available generally provides support for the current ICRP models. It is

noted that studies involving chronic exposure need careful interpretation and consideration of whether the system studied is at a steady state of retention. This is difficult when exposure has occurred in the natural environment, but results of controlled laboratory experiments are generally in agreement with the predictions of the ICRP models.

Past models have considered organically bound tritium (OBT) to have a half-life of 40 days but it is now clear that there is a component which persists for very much longer, perhaps with a half-life of up to one year.

New biokinetic models have been developed which take account of this. A special model has been derived for OBT in flounders taken from the Cardiff Bay area, and has been applied to critical group calculations by regulatory bodies. A new ICRP model for HTO is under development. This will have little impact on dose coefficients (dose per unit intake values, Sv Bq^{-1}) but could significantly affect some calculations of intake and dose based on urine measurements. The ICRP is unlikely to recommend a single new model for OBT due to the wide range of tritiated organic compounds to which people could be exposed.

Tritiated nucleic acid precursors can present a unique hazard because of the possibility of their incorporation in DNA. However, in practice the relatively few people using such compounds and the safety procedures in modern laboratories mean the risks to workers and the general population are low.

Tritium incorporated during pregnancy into the DNA of fetal oocytes could in principle remain there until fertilisation decades later. DNA, however, is not stable since it is subject to turnover during DNA repair processes. Nevertheless, the available evidence suggests that even over decades, only a small proportion of the DNA in oocytes will be turned over. Thus, a conservative assumption is to neglect turnover for radiation protection and risk assessment purposes.

Adopting this approach we have estimated that approximately 4% of oocytes formed in female members of the critical group consuming Cardiff Bay flounder during pregnancy will experience a tritium disintegration within the next 30 years. The frequency of severe hereditary effects resulting from this is expected to be around 10^{-6}, which is small compared with the spontaneous incidence of around 3 to 4%.

We conclude that existing evidence does not enable account to be taken of any consequences there might be resulting from bystander effects or genomic instability phenomena in the developing embryo.

8 Recommendations

Experimentally determined relative biological effectiveness (RBE) values for tritium can vary significantly depending on the choice of reference radiation. Furthermore, it should be noted that the interpretation of RBE experiments is complicated by the fact that dose rates are rarely comparable and the reference radiation may itself be more effective than high energy gamma rays. We recommend that a high energy gamma-ray source, such as ^{60}Co, should be the preferred reference radiation when interpreting RBE values. Where lower energy X-rays and gamma rays have been used as the reference radiation the results should be discussed with respect to any potential increase in RBE when compared to high energy gamma rays. In addition, the reference radiation used should be adequately stated including a description of anything that may modify the energy spectrum, such as filtration. The ICRP has stated that 'the continued use of a w_R of one 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 one 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 one is a surrogate for RBE. Until such time as an internationally agreed RBE is available we propose that a provisional value of two 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 two for w_R for tritium even in routine prospective radiation protection assessments.

We are impressed by the effort that has already been expended in calculating tritium-specific doses from urinalysis monitoring results for tritium workers in the UK. We recommend that this work is completed to produce a comprehensive database of tritium doses for use in epidemiological studies of radiation workers. It is recognised that the limited numbers of tritium workers in the UK, and the generally small tritium doses they have received, will produce a study with relatively low statistical power to detect any effects of exposure to tritium. Consequently, it would be desirable to appropriately combine the UK tritium worker data with the data for tritium workers from other countries to increase study power, and we recommend that the possibility of international collaboration to achieve this is explored.

We recommend that default ICRP models continue to be used in general radiation protection applications. In situations where doses approach relevant limits or constraints, or if there is sufficient concern about doses from tritium, it is appropriate to develop special models for calculating doses to critical groups, as had been done for the Cardiff Bay area. While the consequences of taking account of the much longer-lived component of OBT do not appear to be large, we welcome the new tritium models under development by the ICRP and recommend that they should be considered for adoption in dose assessments when they become available.

While tritiated nucleic acid precursors do not appear to present a major hazard, we recommend that hazard assessments in workplaces which deal with nucleic acid precursors should take account of the special nature of their risk and that care should continue to be exercised.

Tritium doses to oocytes from current exposures, and from any reasonably foreseeable future exposure, pose a very small risk of severe hereditary effects when compared to natural rates. We therefore see no need for special protection of females.

9 References

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Glossary

Absorbed dose The physical dose quantity given by

$$D = \mathrm{d}\varepsilon/\mathrm{d}m$$

where $\mathrm{d}\varepsilon$ is the mean energy imparted by ionising radiation to the matter in a volume element and $\mathrm{d}m$ is the mass of the matter in the volume element. The SI unit for absorbed dose is joule per kilogram ($J\ kg^{-1}$) and its name is gray (Gy).

AML Acute myeloid leukaemia.

Atresia Absence of a normal opening or failure of a structure to be tubular.

Base pairs Pairs of complementary nitrogenous bases that bind to form each rung of the DNA double helix.

becquerel (Bq) The SI unit of radioactivity. 1 Bq corresponds to an average rate of one nuclear transformation per second. Radioactivity is often given in kBq, MBq, GBq or TBq.

Chromosome aberration An abnormality of chromosome number or structure.

CLL Chronic lymphocytic leukaemia.

Committed effective dose, $E(\tau)$ The sum of the products of the committed equivalent doses in organs or tissues and the corresponding organ or tissue weighting factors (w_T), where τ is the integration time in years following the intake. The integration time is 50 years for adults and from the age at intake to age 70 years for children.

Committed equivalent dose, $H_T(\tau)$ The time integral of the equivalent dose rate in a particular tissue or organ T that will be received by an individual following intake of radioactive material into the body, where τ is the integration time in years following the intake. The integration time is 50 years for adults and from the age at intake to age 70 years for children.

Confidence interval, CI An interval calculated from data when making inferences about an unknown parameter. In hypothetical repetitions of the study, the interval will include the parameter in question on a specified percentage of occasions (eg 95% for a 95% confidence interval).

curie The curie (Ci) is an old unit of radioactivity equivalent to $3.7\ 10^{10}$ Bq. A convenient sub-multiple was the millicurie (mCi), ie $3.7\ 10^{7}$ Bq. These units are sometimes used in this report when citing results from publications that gave information in terms of curies.

DDREF Dose and dose rate effectiveness factor. A factor used in radiation protection to allow for the lower biological effects often observed at low doses and low dose rates compared to those at high dose and high dose rate exposures such as those received by the Japanese atomic-bomb survivors.

DNA Deoxyribonucleic acid. The compound that controls the structure and function of cells and is the material of inheritance.

Dose coefficient Committed equivalent dose in organ or tissue T per unit intake $h_T(\tau)$ or committed effective dose per unit intake $e(\tau)$, where τ is the time period in years over which dose is integrated (ie 50 years for adults and from the age at intake to age 70 years for children). It should be noted that the term 'dose per unit intake (Sv Bq^{-1})' is sometimes used to mean dose coefficient.

DSB A double strand break in the DNA molecule, ie both of the pair of molecules comprising the DNA double helix suffer breaks. DSBs are generally less successfully repaired than SSBs.

Effective dose, *E* The sum of the weighted equivalent doses in specified tissues and organs of the body, given by

$$E = \Sigma\, w_T\ H_T$$

where H_T is the equivalent dose in organ or tissue, T, and w_T is the tissue weighting factor for organ or tissue T.

Equivalent dose, H_T The equivalent dose, H_T, in tissue or organ T, is given by

$$H_T = \Sigma\, w_R\, D_{T,R}$$

where $D_{T,R}$ is the mean absorbed dose in tissue T due to radiation of type R, and w_R is the corresponding radiation weighting. Since w_R is dimensionless, the unit is the same as for absorbed dose, J kg^{-1}, and its name is sievert (Sv).

Excess odds ratio, EOR The odds ratio (OR) minus one.

Excess relative risk, ERR The relative risk (RR) minus one.

Excitation A process by which radiation imparts energy to an atom or molecule without causing ionisation.

Gamma rays Gamma rays are an energetic form of electromagnetic radiation produced by radioactive decay or other nuclear or subatomic processes.

Genome The genome of an organism is a complete DNA sequence of one set of chromosomes.

gray, Gy The special name for the SI unit of absorbed dose: 1 Gy = 1 J kg^{-1}.

Ionisation The process by which a neutral atom or molecule acquires or loses an electric charge. For ionising radiation the dominant process is loss of electrons from atoms or molecules.

Linear energy transfer, LET The LET of a material for a charged particle is the quotient of dE by dl, where dE is the mean energy lost by the particle owing to collisions with electrons, in traversing a distance dl, thus

$$L = \mathrm{d}E/\mathrm{d}l$$

Electrons and photons are referred to as low LET particles, while alpha particles are an example of high LET particles.

Lymphocyte A white blood cell present in the blood, lymph, and lymphoid tissue; the two major types are T cells and B cells.

Nanometre 10^{-9} of a metre.

Neoplasm Literally a new growth. A tumour which may be benign or malignant.

Odds ratio, OR The ratio of the odds of disease occurrence in a group with exposure to a factor to that in an unexposed group: within each group, the odds are the ratio of the numbers of diseased and non-diseased individuals.

Oocyte A cell from which an egg or ovum develops by meiosis; a female gametocyte.

Organ or tissue dose The mean absorbed dose D_T, in tissue or organ T, given by

$$D_T = \varepsilon / m_T$$

where ε is the total energy imparted in a tissue or organ T and m_T is the mass of the tissue or organ.

Organically bound tritium, OBT Tritium that is incorporated into organic molecules.

Radiation weighting factor, w_R The radiation weighting factor is a factor to derive the equivalent dose from the mean absorbed dose averaged over a tissue or organ and is based on the quality of radiation and its relative biological effectiveness.

Relative biological effectiveness, RBE The ratio of the absorbed dose of a reference radiation to the absorbed dose of a given test radiation required to produce the same level of response, all other conditions being kept constant.

Relative risk, RR The ratio of the disease rate in a group under study to that in a comparison group, with adjustment for confounding factors such as age, if necessary.

RNA Ribonucleic acid.

sievert, Sv The special name for the SI unit of equivalent dose and effective dose: 1 Sv = 1 J kg^{-1}.

SSB A single strand break in the DNA molecule, ie only one of the pair of molecules comprising the DNA double helix suffers a break.

Standardised incidence ratio, SIR The ratio of the number of cases observed in a specified population to the number that would be expected if that population had the same incidence rate as a standard population.

Standardised mortality ratio, SMR The ratio of the number of deaths observed in a specified population to the number that would be expected if that population had the same mortality rate as a standard population.

Thymidine One of the four basic nucleotides that comprise DNA.

Tissue weighting factor, w_T The factor by which the equivalent dose in a tissue or organ, T, is weighted to represent the relative contributions of that tissue or organ to the total detriment resulting from uniform irradiation of the body.

Tokamak A machine producing a toroidal (doughnut-shaped) magnetic field for containing plasma.

Tritiated water, HTO A water molecule containing one or two tritium atoms (^{3}H).

X-rays X-rays are a form of electromagnetic radiation with very short wavelengths (10^{-9} to 10^{-13} m), corresponding to frequencies in excess of around 10^{18} hertz (Hz). In contrast to other parts of the electromagnetic spectrum, X-rays are usually treated as particles (photons) and are characterised in terms of their energy, which is measured in electron volts (eV).

Most radiobiology experiments, such as those cited in this report, use so-called 'orthovoltage' X-rays, which are produced in X-ray sets by accelerating electrons through a potential of 150 to 300 kilovolts. A spectrum of photon energies is emitted ranging from 0 keV up to the applied (peak) potential on the X-ray tube (kVp). The mean or effective energy of an X-ray beam usually lies at about half the kVp, but depends on the amount of filtration in the X-ray beam, which will preferentially remove low energy photons.

Appendix A

Consultation Seminar

To facilitate the gathering of a wide range of views on the dosimetry of tritium following uptake into the human body a consultation seminar was held in conjunction with the first meeting of the Subgroup on Tuesday 12 July 2005 at the Medical Research Council, Harwell, Oxfordshire.

Invitations were sent to individuals who had published material on dosimetric aspects of the risk from tritium exposure. A wide range of views was canvassed and those who attended are listed here. In addition, written views were available from one individual on the tritium risk to oocytes. These comments were taken into account by the Subgroup.

Seminar presentations and papers were provided by

Dr John Harrison and Dr Ian Fairlie, acting as individuals rather than representatives of organisations.

Dr Fairlie has subsequently published his views in the open literature [Fairlie I (2007): RBE and w_R values of Auger emitters and low range beta emitters with particular reference to tritium. *J Radiol Prot,* **27**, 157–68.]

Subgroup members present

Professor Bryn Bridges (Subgroup chair)

Professor Alex Elliott (Subgroup member)

Dr Mark Hill (Subgroup member)

Dr Barrie Lambert (Subgroup member)

Dr Mark Little (Subgroup member)

Professor Ray Waters (Subgroup member)

Alan Phipps (Subgroup secretary)

Dr John Stather (Health Protection Agency observer)

Other attendees

Professor Dudley Goodhead (the chair of CERRIE)

Dr Philip Day (University of Manchester)

Dr Roy Hamlet (Department of Health)

Dr Hilary Walker (Department of Health)

Dr Simon Bouffler (AGIR secretary, Health Protection Agency)

Dr Richard Wakeford (BNFL)

Appendix B

Occupational Exposure to Tritium and the Potential for an Epidemiological Study of Tritium Workers in the UK

R Wakeford

DALTON NUCLEAR INSTITUTE, UNIVERSITY OF MANCHESTER
(FORMERLY OF BRITISH NUCLEAR FUELS PLC)

B1 Introduction

Occupational exposure to tritium in the nuclear energy and weapons industries mainly occurs in three ways, as follows.

a Since approximately one in ten-thousand fissions of a ^{235}U nucleus induced by a thermal neutron results in the release of a triton (a ^{3}H nucleus), exposure to tritium is ubiquitous in the operation of nuclear reactors and nuclear fuel reprocessing plants. Such exposure to tritium as a fission product, however, does not usually lead to high exposures in the workplace.

b A neutron may be captured by a deuteron (a ^{2}H nucleus) producing a triton. Consequently, in heavy water (D_2O) moderated reactors, tritium is produced through the irradiation of the moderating deuterium by neutrons. This mechanism of tritium production can lead to reasonable doses of tritium being received by workers operating heavy water reactors.

c Tritium is used in some designs of nuclear weapons. This requires the production of tritium, which (since tritium has a half-life of 12.3 years) is more or less a continuous process. Tritium is manufactured by the capture of neutrons by ^{6}Li nuclei in rods positioned within a nuclear reactor. The tritium is then extracted in a separation plant. The tritium so obtained will undergo further processing before it becomes a completed component of a nuclear warhead.

Outside the nuclear energy and weapons industries tritium also features in the manufacture of radionuclide-labelled materials for use in medicine, research and industry, principally to examine the behaviour of biologically important chemicals; tritium-labelled compounds are chemically identical to unlabelled compounds, allowing the investigation of the properties of organic molecules under a variety of circumstances. Radiochemical production plants in the UK that produce, or have produced, tritiated chemicals are located at Amersham and Cardiff and are now operated by GE Healthcare (formerly Amersham plc). Tritium-labelled compounds were produced initially at Amersham from the early 1960s and then at Cardiff since 1980.

Apart from the above, occupational exposure to tritium will also occur to some extent where tritium-labelled compounds are used and where items containing tritium, such as emergency exit signs, are manufactured. Exposures may also occur in plants where tritium is recovered from disused items.

It will be appreciated from the brief background above that occupational exposure to tritium will have occurred, to greater or lesser extent, in those countries that have developed sophisticated nuclear weapons designs. Thus, in the tritium production facility at the Savannah River Site in the USA, a few thousand workers were monitored for exposure to tritium. In the former USSR, tritium was first produced in the 1950s at the Mayak complex near Chelyabinsk (Kruglov, 2002), although details of the consequent (possibly high) occupational exposures are lacking. In the UK, weapons tritium was initially produced at Windscale and Calder Works (by the UK Atomic Energy Authority) and then at Chapelcross (by British Nuclear Fuels plc), and further processing took place at Capenhurst (by the UKAEA and then BNFL). Final operations with tritium then occurred at the Atomic Weapons Establishment at Aldermaston and Burghfield.

Heavy water reactors have been developed in a number of countries, and the CANDU heavy water reactor forms the basis of electricity generation by nuclear power in Canada, with CANDU reactors being 'exported' to countries such as South Korea. In the UK, heavy water reactors were operated at three UKAEA sites: a materials testing reactor (MTR) at Dounreay (DMTR), two MTRs at Harwell (DIDO and PLUTO), and the largest, the prototype power generating heavy water reactor – the Steam Generating Heavy Water Reactor (SGHWR) – at Winfrith.

With the sizeable numbers of workers exposed to tritium in a number of countries, it is, perhaps, surprising that epidemiological studies of tritium workers in terms of the tritium doses that they received have not been conducted. Studies of workers exposed to tritium have been carried out, but these have not specifically and separately used the doses received from tritium: the studies have tended to concentrate upon whether workers had been 'flagged' for exposure to tritium (ie a dichotomous classification), or upon the external doses of radiation received by these workers, or upon external doses of radiation combined with the tritium doses. In the study of Canadian nuclear power industry workers (Zablotska et al, 2004), for example, tritium doses were available for workers, but they were combined with the doses from external sources rather than being used separately. Presumably, it would be relatively straightforward to conduct a study of Canadian workers in terms of tritium-specific doses. Similarly, in the study of workers employed at the Savannah River Site in the USA (Cragle et al, 1988, 1998), about 5000 workers were monitored for exposure to tritium, with around 800 of these workers assessed to have received a dose of at least 0.5 mSv from tritium, but these tritium doses do not appear to have been used separately in any analysis. Again, it would seem that tritium-specific doses might be readily available for this group of workers.

B2 Organisations within the UK

BNFL

At Sellafield, Chapelcross and Capenhurst, 1758 workers (only 27 of whom are female) were monitored for exposure to tritium. Of this total, just over one-half (911) were Sellafield tritium workers, 801 of whom were first monitored for tritium by the end of 1983.

These tritium workers have been followed-up for vital status, cause of death and cancer registration as part of the broader epidemiological study of the cohort of BNFL workers. At the end of 2002, only 4 of these workers remained untraced and 511 had died.

The highest tritium exposures at Sellafield occurred in the late 1950s and early 1960s when tritium was produced by irradiation of lithium in reactors and then extracted from these rods in a specifically designed plant.

Tritium urinalysis records for Sellafield workers have been computerised and tritium-specific doses have been calculated, although data interpretation and dosimetry methodology need to be reassessed.

Sellafield tritium doses were calculated in the early 1990s for the period from 1956 to 1983 shortly after the computerisation of the Sellafield source urinalysis data. The distribution of cumulative tritium dose of the available Sellafield dose data is given in Table B1. The maximum cumulative tritium dose was 127.4 mSv. When the doses were initially calculated, only those of at least 0.1 mSv were reported. So for those 391 tritium workers in the 0–0.099 mSv category, exact cumulative doses are currently unreported. Consequently when calculating the mean and median cumulative doses these workers were assigned a cumulative dose of 0.05 mSv. Based on this assumption the mean cumulative tritium dose at Sellafield was 2.08 mSv and the median cumulative dose was 0.11 mSv. Excluding those in the 0–0.099 mSv group the mean cumulative dose at Sellafield was 4.07 mSv and the median dose was 0.69 mSv.

TABLE B1 Distribution of cumulative tritium doses up to 1983 for Sellafield workers first monitored for tritium between 1956 and 1983

Dose category (mSv)	Number of individuals	Percentage of individuals
0–0.099	391	48.81
0.1–4.99	349	43.57
5–9.99	19	2.37
10–19.99	28	3.50
20–49.99	7	0.87
50–99.99	5	0.62
100+	2	0.25
TOTAL	801	100

All tritium urinalysis data for Chapelcross, where a tritium production plant was operated from 1980 onwards, have been computerised, so that assessment of tritium doses should be relatively straightforward. At Capenhurst a gaseous tritium processing plant operated between 1965 and 1987. Urinalysis data consisting of paper records are currently being computerised. There may be some gaps in tritium urinalysis data for Capenhurst as it has proved difficult to locate some of the original records, but most appear to be available. Computerisation of records should be complete within two years with currently committed effort, if no obstacles are encountered. Once the computerisation of Capenhurst source data is complete, the Chapelcross and Capenhurst tritium doses will be assessed. Additionally the

Sellafield doses will be re-calculated and extended beyond 1983 to include the remaining 110 Sellafield tritium workers.

UKAEA

At Harwell, Winfrith and Dounreay, 2373 workers were monitored for exposure to tritium, as a result of the operation of heavy water reactors at these establishments. Urinalysis records are computerised for workers at these three sites from 1988, 1988 and around 1984, respectively. There are about 6000 person-years of urinalysis data from 1753 individuals that have yet to be computerised, and around 200 person-days of skilled clerical effort is likely to be required to complete the computerisation of the urinalysis data. Further effort may be required to interpret these data in terms of tritium doses. The UKAEA tritium workers are a subgroup of the cohort of UKAEA workers that is the subject of epidemiological investigation, so the necessary health data are available for an epidemiological investigation of these tritium-exposed workers.

Table B2 gives the distribution of tritium doses for UKAEA workers monitored since 1985 (when records were computerised). Results are given for two categories: those whose start date was on or after 1985; all workers.

TABLE B2 Distribution of lifetime tritium doses for workers at UKAEA sites over the period 1985–2006

Dose category (mSv)	All individuals	Those whose start date was on or after 1985
0–0.99	536	251
1–1.99	77	13
2–4.99	49	4
5–9.99	12	3
10–19.99	1	0
TOTAL	675	271
Mean	0.657	0.313
Median	0.058	0.021
Maximum	11.37	7.28

AWE

At the Atomic Weapons Establishment, approximately 3800 workers have been monitored for exposure to tritium from 1956 to the present. This number includes workers who were monitored for short periods or for reassurance purposes and who did not routinely work with tritium. Most of the workers are an identifiable subgroup of the AWE cohort of workers that is continuing to be studied epidemiologically, although more recent workers will not have been entered into this cohort. Urinalysis data are available in

electronic form, although before 1995 results below the limit of detection (BLD) are recorded as zero. Original urinalysis data are available on paper records for these BLD results, which should permit the appropriate re-calculation of doses for any epidemiological study. Approximately 100 person-days of skilled clerical effort is likely to be required to obtain a final set of tritium-specific doses, although the effort will be dependent on the details of the dose assessment protocol.

Tritium doses have been calculated from the monitoring data. However, it should be borne in mind that the pessimistic assumptions used in the calculation of tritium doses at AWE mean that doses are likely to have been overestimated to some extent. Over the period 1956–mid-2005, the exposure of most monitored workers to tritium has been very low (Table B3), with a median lifetime dose of 0.54 mSv (mean lifetime dose of 2.40 mSv and maximum lifetime dose of 124.8 mSv). There are about 200 workers with lifetime tritium doses greater than 10 mSv.

TABLE B3 Distribution of lifetime tritium doses for workers at AWE over the period 1956–2005

Dose category (mSv)	Number of individuals
0–4.99	3266
5–9.99	347
10–19.99	159
20–49.99	44
50–99.99	4
>100	2
TOTAL	3822

GE Healthcare

Work involving tritium started at the Amersham site in the 1960s. Workers at GE Healthcare (and its predecessors) form part of the National Registry for Radiation Workers (NRRW) and these workers are not followed-up in any other epidemiological study, so that vital status, cause of death, and cancer registration data would have to be obtained through the NRRW. As a consequence, relevant workers who left employment before the NRRW was established (or those who declined to permit their data to be registered on the NRRW) will not be available for epidemiological study. The details of almost 750 tritium workers from the two GE Healthcare sites are available on the NRRW. Computerised records of monitoring results are available from 1987 onwards. Before 1987, some dosimetry data are available on paper records, but the availability of urinalysis records for this period is currently unknown. Some effort would be required to investigate the existence of early monitoring results and to convert these data into electronic form. Possible further effort may be necessary for the interpretation of monitoring data and their conversion to tritium doses.

Other workers

Other workers in the UK, such as those working with naval reactors or in particular research establishments, will have been exposed to tritium to some extent. Dose distributions for these workers are not available.

B3 Dosimetry

It will be important in any study of UK tritium workers to ensure that a consistent treatment of urinalysis data (including results that are below the limit of detection – recognising that the limit of detection will have changed during the period studied) occurs across organisations and over time. This will undoubtedly require the input of expert health physicists with experience in this area of data interpretation, from the relevant organisations. Further, the urinalysis data for an individual will need to be converted to time-dependent received dose using the appropriate dosimetry model. A new dosimetry model for tritium is currently being considered by ICRP Committee 2, and this would have to be taken into account in any reconstruction of tritium-specific doses.

B4 Discussion

The status of dosimetry and epidemiological data for tritium workers held by relevant organisations in the UK are such that it would appear that a cohort study of tritium workers in terms of the tritium-specific doses they have received would be possible (presumably taking into account external dose in an analysis of the effect of tritium dose). BNFL has been working towards generating an appropriate set of tritium doses (and other internal doses) for some time, and tritium doses are available for AWE workers, but other organisations in the UK would need to devote effort to reconstructing tritium-specific doses, which would require funding. Further, a consistent approach to the interpretation of urinalysis data across organisations and time would be required, as would a coherent interpretation of monitoring data in terms of tritium dose, utilising the latest tritium dosimetric models. Obtaining the necessary epidemiological data for a cohort of tritium workers should not be a major problem, since these workers form a sub-set of industry workers who are being followed-up anyway. However, the production of tritium-specific doses would take effort and time to achieve.

The implication from published papers is that tritium-specific doses are available for certain groups of tritium workers outside the UK, specifically, the Canadian nuclear workers and workers at the Savannah River Site in the USA. However, inquiries would be necessary before any firm conclusions could be drawn about the availability of reliable tritium doses for these two sets of workers. Tritium exposures in the course of nuclear weapons production in France will also have occurred, as would exposures due to the operation of heavy water reactors, although details are lacking. A long-term study of European tritium workers (including the French workers) co-ordinated by the European Commission may be a possibility, but the results of such a study would be some way off. It seems likely that workers involved in the early production of tritium at the Mayak site in the former USSR were highly exposed. However, just what information might be available concerning tritium doses received by these workers is not known. The level of exposures in the other major nuclear weapons state, China, remains unknown.

A point of interest concerning the matter of future occupational (and environmental) exposure to tritium is the levels resulting from the possible operation of fusion reactors. These reactors will require an initial charge of tritium, but will also 'breed' tritium through the irradiation by the neutrons produced in fusion reactions of lithium in a blanket surrounding the reactor. Tritium will then be extracted from the irradiated lithium for use in the reactor. As a consequence, exposure to tritium will occur, to some degree, as the result of the operation of fusion reactors, so that tritium-related health risks are likely to remain a subject of discussion into the future.

B5 Conclusions

A cohort study of UK tritium workers in terms of tritium-specific doses is a possibility, but effort (and, therefore, funding) would be required for the uniform production of individual tritium doses. Tritium workers outside the UK are possible subjects of epidemiological study, in particular the workers in the Canadian nuclear power industry and workers at the Savannah River Site in the USA, but inquiries are necessary before this could be confirmed. Tritium exposures, to some level or other, will remain a fact in industrialised societies for the foreseeable future.

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B6 References

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Appendix C

Experimental *In Vivo* Studies of Carcinogenesis

C1 Breast cancer in Sprague-Dawley rats

The study of Gragtmans et al (1984) involved treatment of female Sprague-Dawley rats with 200 kVp X-irradiation given either at low/moderate dose rate (total doses of 0.29, 0.57, 1.1 or at 2 Gy over ten days) or at high dose rate (total doses of 0.57 or 1.78 Gy over one hour). Other animals were injected (four times at two-day intervals) with tritiated water (HTO) in saline solution (total doses of 0.46, 0.92, 1.63 and 3.85 Gy). There were about 120–130 animals in each of these dose groups. There was also a control (unirradiated) group of about 200 animals. Animals were followed for breast cancer. As generally with this strain of rat, the underlying incidence of breast cancer was very high, so that by the end of the study 63% of controls had developed cancer. Thus the experiments essentially looked at earlier occurrence rather than lifetime incidence, but they effectively demonstrated this. Interestingly, HTO contributed 10–30 times the dose of organically bound tritium (OBT) in these experiments.

It is not clear from the original paper just how this dataset was analysed, but it is possible that simple linear regression may have been employed, which would not correctly account for the binomial or binary form of the errors. In view of this we have fitted a logistic model to the data given in Table IIb of the paper (relating to percentage of animals at risk with tumours). This entailed estimating the numbers of animals in each group (these were only approximately specified in the original paper). A problem with this re-analysis is that the numbers of surviving animals are not given at each time point. We are therefore necessarily overestimating the numbers of surviving animals at each time point; this is likely to be progressively more serious as the animals get older. In addition, because of the very high percentage of animals that develop breast tumours, the logistic model becomes severely non-linear in dose a long time after treatment. For these reasons we do not analyse animals more than 450 days after treatment [as Gragtmans et al (1984) also did not]; we also analyse the animals up to 300 days after treatment.

It is assumed that the probability, p_i, of being a breast cancer case in group i, with average dose, D_i, average time since treatment, e_i, is given by the standard logistic model:

$$\frac{p_i}{1-p_i} = \exp(\kappa_0 + \kappa_1 \ln e_i + \kappa_2 \ln e_i^2 + \kappa_3 \ln e_i^3 + \kappa_4 \ln e_i^4) \times \{1 + [\alpha D_i \exp(\rho_1 1_{\text{tritium}}) + \beta D_i^2 \exp(\rho_1 1_{\text{tritium}})^2] \exp(\rho_2 1_{\text{low dr}} + \gamma D_i)\} \quad \text{(C1)}$$

where ρ_1 adjusts the dose–response for tritium and ρ_2 adjusts for low dose rate exposure (which is taken to be either tritium or low dose rate X-ray exposure). The form of adjustment for tritium, with a multiplier to the dose, which is squared for the quadratic term, was suggested by other radiobiological data (UNSCEAR, 1993). In fits to the data up to 300 days after treatment an adequate fit was provided by a cubic model in ln e_i, so that in all fits to this subset we set $\kappa_4 = 0$. The model was fitted by binomial

maximum likelihood using Epicure (Preston et al, 1998). Unless otherwise stated, all confidence intervals are derived from the profile likelihood. Examination of the data using spline dose–response models (see Figure C1) suggested that the linear-quadratic-exponential dose–response assumed in expression C1 is reasonable. Table C1 illustrates the results of fitting this model to the data. As can be seen, the estimates of tritium relative biological effectiveness (RBE) that we derive are consistent with those estimated by Gragtmans et al (1984), and are all statistically consistent with an RBE of one, ie all 95% confidence intervals include one. Values of RBE much greater than 1.5 are inconsistent with the data.

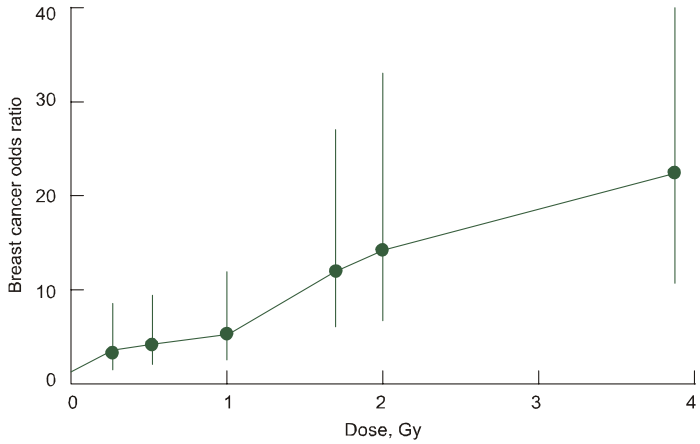

FIGURE C1 Odds ratio (± 95% CI) versus dose (whether from tritium or X-rays) of breast cancer in the study of Gragtmans et al (1984) (animals up to 300 days after treatment, derived from logistic (binomial) model fitted to collapsed version of data derived from Table IIb of Gragtmans et al)

TABLE C1 Estimates of tritium relative biological effectiveness (with 95% CI) derived from the data of Gragtmans et al (1984)

Data	Scaled deviance (df)	Tritium RBE = exp ρ_1
Animals ≤ 450 days, linear model	109.27 (69)	1.19 (0.94, 1.52)
Animals ≤ 450 days, linear-quadratic model	101.46 (68)	1.04 (0.85, 1.28)*
Animals ≤ 450 days, linear-quadratic-exponential model	100.47 (67)	1.08 (0.91, 1.28)*
Animals ≤ 300 days, linear model	52.32 (37)	0.91 (0.65, 1.30)
Animals ≤ 300 days, linear-quadratic model	52.18 (36)	0.89 (0.63, 1.25)*
Animals ≤ 300 days, linear-quadratic-exponential model	52.17 (35)	0.90 (0.57, 1.40)*
Gragtmans et al fit ≤ 450 days, excluding high dose (3.85 Gy) tritium data	–	1.02 (0.77, 1.27)
Gragtmans et al fit ≤ 450 days, all data	–	0.85 (0.56, 1.14)

* Wald-based confidence intervals.

There must, however, be reservations about the relevance of these values, coming as they do from data which measure the earlier occurrence of a cancer which has developed in the majority of the controls by the end of the experiment.

C2 Myeloid leukaemia and other cancers in CBA/H mice

The study of Johnson et al (1995) involved treatment of male CBA/H mice with low/moderate dose rates (total doses of 1.06, 1.98 and 2.64 Gy over ten days) of 200/150 kVp X-irradiation. The first X-ray tube (operating at 200 kVp) failed part way through the experiment and subsequent irradiations were carried out with a 150 kVp tube equipped with an ISO filter designed to produce an X-ray spectrum with an average energy of 104 keV approximately equal to the average energy of the spectrum from the 200 kVp set and therefore a similar average LET (Myers and Johnson, 1990). However, the heavily filtered 150 kVp X-ray spectrum will be significantly narrower in energy range than the distribution from the 200 kVp set. The X-ray dose rate was reduced by 45% every two days to parallel the anticipated reduction in dose rate from injected HTO. Another group of mice were given a single intraperitoneal injection of HTO (total doses of 0.85, 1.86 and 3.04 Gy). There were generally between 730 and 750 animals in each of these groups. There was also a control (unirradiated) group of 747 animals. Animals were principally followed for myeloid leukaemia, although the paper gives brief details of various other cancers that developed (3768 in all, compared with 279 myeloid leukaemias). There are insufficient details given on these other cancers to allow much analysis of them. Acute myeloid leukaemia (AML), the principal endpoint used, has a spontaneous incidence in CBA/H mice that is essentially zero. Johnson et al (1995) used doses which saturated the effect at the lowest dose (1–2 Gy) of both radiations – the authors commented on the fact that the effect had a plateau from 1 Gy (this can also be observed in Figure C2).

It is not clear from the original paper just how this dataset was analysed, but it seems that Johnson et al derived age-adjusted incidence rates for each dose point (taking account of follow-up of each animal), and then fitted curves to the resulting four points, an unorthodox procedure, since this would not correctly account for the (binary/binomial) errors at each age and dose point. In view of this we have fitted a logistic model to the data given in Table III of the paper. As with the re-analysis of the data of Gragtmans et al (1984), a problem with this re-analysis is that the numbers of surviving animals are not given at each time point. We are therefore necessarily overestimating the numbers of surviving animals at each time point; this is likely to be progressively more serious as the animals get older. For this reason we do not analyse animals more than 650 days old at death; we also analyse the animals no more than 450 days old at death.

It is assumed that the probability, p_i, of being a myeloid leukaemia case in group i, with average dose, D_i, average days at death, e_i, is given by the standard logistic model:

$$\frac{p_i}{1-p_i} = \exp(\kappa_0 + \kappa_1 \ln e_i + \kappa_2 \ln e_i^2) \times \{1 + [\alpha D_i \exp(\rho_1 1_{\text{tritium}}) + \beta D_i^2 \exp(\rho_1 1_{\text{tritium}})^2] \exp(\gamma D_i)\} \qquad \text{(C2)}$$

where ρ_1 adjusts the dose–response for tritium exposure and γ adjusts the dose–response for cell sterilisation. As above, the form of adjustment for tritium, with a multiplier to the dose, which is squared

for the quadratic term, was suggested by other radiobiological data (UNSCEAR, 1993). In fits to the data of animals up to 450 days old at death an adequate fit was provided by a linear model in ln e_i, so that in all fits to this subset we set $\kappa_2 = 0$. The model was fitted by binomial maximum likelihood using Epicure (Preston et al 1998). Unless otherwise stated, all confidence intervals are derived from the profile likelihood. Examination of the data using spline dose–response models (see Figure C2) suggested that

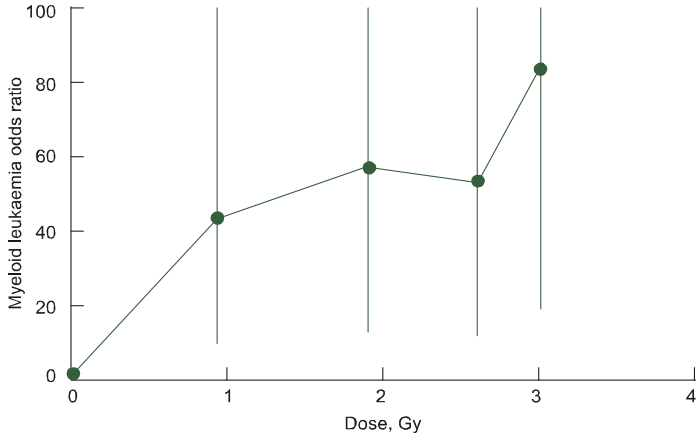

FIGURE C2 Odds ratio (± 95% CI) versus dose (whether from tritium or from X-rays) of myeloid leukaemia in the study of Johnson et al (1995) (derived from logistic (binomial) model fitted to collapsed version of data derived from Tables I and III of Johnson et al)

TABLE C2 Estimates of tritium relative biological effectiveness (with 95% CI) derived from the data of Johnson et al (1995)

Data	Scaled deviance (df)	Tritium RBE = exp ρ_1
Animals ≤ 650 days, linear model	44.49 (30)	1.13 (0.84, 1.52)
Animals ≤ 650 days, linear-exponential model	36.89 (29)	1.18 (0.89, 1.58)
Animals ≤ 650 days, linear-quadratic model	35.63 (29)	1.56 (0.93, 2.60)*
Animals ≤ 650 days, linear-quadratic-exponential model	35.58 (28)	1.61 (0.88, 2.95)*
Animals ≤ 450 days, linear model	17.77 (17)	0.84 (0.42, 1.64)
Animals ≤ 450 days, linear-exponential model	16.78 (16)	0.87 (0.45, 1.62)
Animals ≤ 450 days, linear-quadratic model	13.66 (16)	0.35 (0.12, 1.03)*
Animals ≤ 450 days, linear-quadratic-exponential model	12.32 (15)	0.25 (0.07, 0.83)*
Johnson et al linear model fit	–	1.01 (0.11, 1.91)
Johnson et al linear-exponential model fit	–	1.18 (0.14, 2.22)

* Wald-based confidence intervals.

the linear-quadratic-exponential dose–response assumed in expression C2 is reasonable. Table C2 illustrates the results of fitting this model to the data. As can be seen, the estimates of tritium RBE that we derive are generally consistent with those estimated by Johnson et al (1995), and are generally all statistically consistent with an RBE of one, ie most 95% confidence intervals include one. Values of RBE much greater than three are inconsistent with the data. The fact that there is no useful measure of the slopes of the induction curves below the saturation level means that the RBE does not reflect the incidence of myeloid leukaemia as a function of dose.

C3 All tumours in female rodents

The study of Seyama et al (1991) involved treatment of female mice from three related strains, C57BL/6N x C3H/He, BCF_1 and C57BL/6N, with gamma doses at high dose rate (0.27 or 2.7 Gy from a ^{60}Co source at a dose rate of 0.47 Gy min^{-1}), or to moderate dose rates from a 'tritium simulator' (0.27 or 2.7 Gy from a ^{137}Cs source at progressively reducing dose rates, which were initially 5.9 10^{-5} Gy min^{-1} for the 0.27 Gy dose, and 5.3 10^{-4} Gy min^{-1} for the 2.7 Gy dose). The dose rate reduction regime is not specified in the paper, but presumably matches the reduction in dose rate from tritium. A group of C57BL/6N x C3H/He mice were also exposed to fission neutrons (0.27 or 2.7 Gy from a ^{252}Cf source at a dose rate of 2.7 Gy min^{-1}). Another four groups of BCF_1 mice were injected with single intraperitoneal injections of varying concentrations of HTO (3.75, 7.5, 15 and 20 mCi, resulting in total doses of 1.97, 3.95, 7.90 and 10.53 Gy, respectively). A further four groups of C57BL/6N x C3H/He mice received four weekly injections of 5 mCi (total 20 mCi) or 3.75 mCi (total 15 mCi). For purposes of comparison with the fission-neutron-irradiated and gamma-irradiated animals, two further groups of C57BL/6N x C3H/He mice were given single intraperitoneal injections of HTO (1.9 10^8 and 1.9 10^7 Bq, equivalent to doses of 2.7 and 0.27 Gy, respectively). The numbers of animals in these groups, and in the control group, are not explicitly specified, but from information given in Tables 1 and 2 of the paper numbers in the ^{60}Co, ^{137}Cs, HTO, fission neutron (2.7 Gy + 0.27 Gy) and control groups are 118, 183, 120, 124 and 60, respectively. Animals were followed for a variety of tumours, and a total of 905 tumours developed. The most numerous tumours were ovary (263), pituitary (141), reticulum cell neoplasm (73), lipoma (65), leukaemia (63), liver (62) and lung (58).

The quantitative information that can be derived from this study is limited. The effect (incidence of cancer) seems to have nearly saturated at the lowest dose point, so that this study effectively measures acceleration of onset rather than excess incidence. In the long-term experiments of mice receiving a single intraperitoneal injection of HTO the total incidence of tumours was similar at 500 days in all exposed groups. The cumulative incidence of tumours over a lifetime among mice receiving the single intraperitoneal injections of HTO was 80–90% compared with less than 5% in controls. At 400 days after HTO was administered the cumulative incidence of tumours was 4%, 8%, 18% and 24% in mice given 3.75 mCi (1.97 Gy), 7.5 mCi (3.95 Gy), 15 mCi (7.90 Gy) and 20 mCi (10.53 Gy) HTO, respectively. After a regime of 4 x 5 mCi weekly injections of HTO, T-cell lymphomas dominated, with a cumulative incidence of 80% before 220 days – the authors stated that solid cancers appeared after 270 days. At the lower injection dose, 4 x 3.75 mCi, the incidence of lymphomas was much lower, about 25%, but the cumulative incidence of all tumours was still 76%, not much different from the 4 x 5 mCi group. There is

an extraordinary effect of protraction of dose, so that in the 4 x 5 mCi HTO group the cumulative incidence of lymphoma is 80%, at about 230 days after HTO, compared with around 10% incidence at that time from a single 20 mCi injection – equivalent to a dose and dose rate effectiveness factor (DDREF) of about 0.13, for this endpoint. The difference between the 4 x 3.75 mCi and 1 x 15 mCi groups was less marked, so that by 390 days after HTO was administered there was a cumulative incidence of about 28% for 4 x 3.75 mCi, compared with about 15% for the 1 x 15 mCi animals, implying a DDREF of about 0.54. Interestingly a single injection of 20 mCi HTO to C57BL/6N mice in another experiment killed all mice within 20 days but not in the other experiments described above, in which a different mouse strain (C57BL/6N x C3H/He) was used.

Seyama et al (1991) reported (page 136) a cumulative tumour incidence at 500 days after irradiation of 2.7 Gy of 70% in the neutron group, 35% in the acute ^{60}Co group, 30% in the sub-acute ^{137}Cs gamma ray (constant dose rate) group, 25% in the single dose HTO group, and 10% in the group given ^{137}Cs gamma rays at decreasing dose rate (tritium simulator). Comparing the HTO and ^{137}Cs tritium-simulator groups implies an RBE for tritium of about 2.5. At least up until 500 days after irradiation, the cumulative incidence in the group given 0.27 Gy HTO was at least twice that of the group given ^{137}Cs gamma rays at decreasing dose rate (tritium simulator), although by 600 days the HTO cumulative incidence was less than that for ^{137}Cs. These are very crude calculations, taking no account of the different time course of tumour accumulation in the various groups, but on the available information this is the most that can be derived from the study. Seyama et al (1991) derived an RBE of 2.5 by comparing cumulative incidence at 500 days after exposure in the HTO and low dose rate (tritium simulator) gamma-irradiated groups given 2.7 Gy, but this time point is arbitrary: as indicated above, use of a different time would give very different values of this parameter.

C4 All cancer and leukaemia in Wistar rats

Revina et al (1984) described experiments conducted in Wistar rats, in which 45 rats were administered 3.7 10^5 Bq per gram HTO of animal weight intragastrically, five times a week during six months (group II), 39 rats were chronically exposed to gamma radiation of ^{137}Cs in daily doses comparable with the tritium-exposed animals (group III), and 140 were controls (group I). (It should be noted that in the translation available to the Subgroup, the authors referred to administration of 'tritium oxide' throughout, but the chemical formula given, ^{3}HOH, is (we assume) that of tritiated water.) No details were given on the ^{137}Cs gamma radiation; Revina et al referred to an earlier paper for these. For comparative evaluation of the tumorigenic effect of HTO and gamma radiation, the authors described a procedure for calculation of 'mean probability value', using the formula:

$$\bar{P} = \frac{0.5 \sum_{1}^{m-1} (L_{i+1} - L_i)(Q_{i+1} + Q_i)}{L_m - L_1} \qquad \text{(C3)}$$

where L_i is the survival time of the ith animal (so $L_1 < L_2 < \ldots < L_m$), L_1 and L_m are the survival times of the first and last animals to die of malignant tumour, and Q_i is the cumulative probability of death of the

animal *i* due to malignant tumour estimated by the Kaplan-Meier method. However, this is a curious measure, and it is certainly not a probability. It approximates:

$$\bar{P} = \frac{\int_{L_1}^{L_m}\left[1-\exp\left(-\int_{L_1}^{t} h(s)\,\mathrm{d}s\right)\right]\mathrm{d}t}{\int_{L_1}^{L_m}\mathrm{d}t} = \frac{L_m\left[1-\exp\left(-\int_{L_1}^{t} h(s)\,\mathrm{d}s\right)\right] + \int_{L_1}^{L_m} t\exp\left(-\int_{L_1}^{t} h(s)\,\mathrm{d}s\right)\mathrm{d}t}{\int_{L_1}^{L_m}\mathrm{d}t} \qquad \text{(C4)}$$

where $h(s)$ is the instantaneous cancer hazard function (cancer rate per unit time). The second term in the rightmost numerator is the expected years of life lost, but unfortunately the first term in the numerator does not vanish in general (although it might get small enough in some circumstances). The normalising quantity in the denominator is also curious. This measure has the property that $0 \le \bar{P} \le 1$, but is a lot like a measure of expected days of life, normalised by the duration of tumour occurrence. This measure is not a good one, since it depends in a highly non-linear way on the hazard function $h(s)$. Once they estimated this measure, the authors then estimated the ratio of effects in the HTO- and gamma-irradiated groups by means of the formula:

$$K = \frac{\bar{P}_{3\mathrm{HOH}} - \bar{P}_{\mathrm{c}}}{\bar{P}_{\gamma} - \bar{P}_{\mathrm{c}}} \qquad \text{(C5)}$$

where $\bar{P}_{3\mathrm{HOH}}$, $\bar{P}_{\gamma}$, and $\bar{P}_{\mathrm{c}}$ are the mean 'probabilities of animal death due to malignant tumour' in HTO-exposed, gamma-exposed and control groups. This measure is somewhat analogous to RBE. However, this is not really an RBE using the standard definition (ICRU, 1986; NCRP, 1990), because it is an effect ratio at (approximately) equal dose, rather than a dose ratio for equal effect. To estimate true RBEs would require information on the two dose–responses (HTO-exposed and gamma-exposed), which is not available from the paper.

The total dose accumulated in the rats exposed to HTO amounted to 25.3 Gy, and in the gamma-exposed animals 24.8 Gy. The rat strain used does not seem to be particularly radiosensitive – the number of rats with tumours following chronic administration of tritium and gamma irradiation is also much the same: 78% in the tritium-exposed animals, 87% in the gamma-exposed animals, and 78% in the controls. The shortening of survival time of animals in the exposed groups per unit dose was 9.3 days Gy^{-1} in the tritium-exposed animals and 10.6 days Gy^{-1} in the gamma-exposed animals. Even the mean survival times of animals with malignant tumours were not significantly different (538 days, 95% CI 495, 581, for tritium-exposed and 513 days, 95% CI 466, 560, for gamma exposed). Tritium exposure appeared to produce lung tumours at a much higher rate, 11.1%, than in gamma-exposed animals, 2.5%, and than in controls, 1.4%. For leukaemia the elevation in the tritium-exposed animals was less striking, 15.6%, compared with 10.2% in gamma-exposed animals, and 2.8% in controls. Thyroid tumours occurred in 4.4% of tritium-exposed animals, in 30.7% of gamma-exposed animals, and in 8.6% of controls. Breast tumours occurred in 13.3% of tritium-exposed animals and in 5.1% of gamma-exposed animals, but did not occur in controls. Many other tumours were produced at comparable rates in tritium- and gamma-exposed animals. Adrenal tumours, which accounted for the

vast majority of tumour cases, occurred in 51.1% of tritium-exposed animals, in 53.8% of gamma-exposed animals, and in 61% of controls. These variations are not really commented upon by the authors. How the judgement of malignancy was made from histology is not described, but is quite important. The authors estimated the 'probability' of death from malignant tumour using measure C3 as 0.2032 in the controls, 0.2928 in the tritium-exposed animals, and 0.2247 in the gamma-exposed animals, leading to a measure (using formula C5) of RBE of $K = 4.17$. For leukaemia the analogous 'probability' of death was 0.0202 in the controls, 0.1601 in the tritium-exposed animals, and 0.0753 in the gamma-exposed animals, leading to a measure of RBE of $K = 2.54$. If we adjust these for the ratio of doses in the tritium-exposed and the gamma-exposed these become $K = 4.09$ and $K = 2.49$, respectively. The authors stated that the standard deviation of these measures was about 10% of their value; this is used to derive the 95% CI in Table 3.2a.

A significant problem with this study is the large doses (about 25 Gy), although this is mitigated by the long period over which they are administered. The methodology for estimating 'probabilities' of tumour mortality and with it RBE is also problematic, as is the very high rate (78%) of malignant tumour development in controls (although the leukaemia rate is substantially lower). It is noteworthy that the RBEs derivable from these data are higher than those in other animal studies (eg Gragtmans et al, 1984, and Johnson et al, 1995) and towards the upper end of the biological data that we review (see Table 3.2). Common radiobiological thinking would lead to the expectation that radiation quality effects would be less obvious at high doses than at low (UNSCEAR, 1993), so the result is unlikely to be exaggerated on this score. For this reason it is likely that the 'true' RBE values would be expected to be somewhat greater than those derived by Revina et al (1984). Notwithstanding these considerations, this study is of little use for estimating the limiting low dose RBE, since there is only one dose point in both tritium- and gamma-exposed animals.

C5 Summary

In summary, taken at face value these experimental animal carcinogenesis studies imply fairly modest tritium RBEs, with central estimates generally in the range 0.8–2.5, and an upper 97.5 percentile value of no more than about three. However, the experimental design and statistical analysis of many of these studies leaves a lot to be desired, so that despite their obvious relevance to cancer, their findings should be treated with caution.

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Health Protection Agency
Centre for Radiation, Chemical and Environmental Hazards
Chilton
Didcot
Oxfordshire OX11 0RQ
United Kingdom

Tel: +44(0)1235 831600
Fax: +44(0)1235 833891
Email: ChiltonInformationOffice@hpa.org.uk
www.hpa.org.uk

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