

SOURCES, EFFECTS AND RISKS OF IONIZING RADIATION

United Nations Scientific Committee on the
Effects of Atomic Radiation

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with Scientific Annexes



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ANNEX C

BIOLOGICAL EFFECTS OF SELECTED INTERNAL EMITTERS—TRITIUM

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I. INTRODUCTION

1. The Committee has conducted an independent review of the scientific literature on the characteristics of tritium, its biokinetics and dosimetry within the human body for various physical and chemical forms and routes of intake into the body, radiobiological effects of tritium exposure, and epidemiological data relating to its impact on the health of workers and members of the public.

2. Tritium is a radioactive isotope of hydrogen (symbol ^3H , but commonly represented by T). Chemically, it behaves like other isotopes of hydrogen (protium, ^1H , the principal stable isotope, and deuterium, ^2H , the other stable isotope). The word tritium is used here to mean the particular isotope of hydrogen irrespective of the chemical form in which it occurs.

3. Tritium occurs both naturally, mainly as a result of the interaction of cosmic-ray particles with the atomic nuclei of air molecules in the upper atmosphere, and as a consequence of the operation of nuclear reactors and other industries. Tritium in the environment and workplace is encountered predominantly as tritiated water (HTO) in liquid or vapour form.

4. Tritium emits low-energy beta particles with a short range in body tissues and, therefore, poses a risk to health as a result of internal exposure only following ingestion in drinking water or food, or inhalation or absorption through the skin. Unlike external penetrating radiation, such as X-rays and gamma rays, internal exposure to tritium has the potential to result in heterogeneous dose distribution within tissues and cells. Other factors that may affect the potential radiotoxicity of tritium include transmutation and isotopic effects. Transmutation is the term used for the formation of a new element by radioactive decay, which has the potential to adversely affect metabolic processes. Isotopic effects apply to low atomic mass elements such as hydrogen, for which tritium atoms with larger mass may replace the stable protium in cellular processes. Both effects are judged to be minor contributors to radiotoxicity when compared to the predominant effect of the energy deposition from beta particles emitted by tritium decay.

5. Five main chemical forms are of interest when considering the biological and health effects of internal exposure to tritium: HTO, organically bound tritium (OBT), tritiated biochemical substrates (including DNA precursors), insoluble compounds, and tritiated gases. OBT is the general term used to describe tritium that is non-exchangeably bound to carbon atoms within organic constituents of cells and tissues (e.g. proteins, polysaccharides, lipids).

6. Absorbed doses arising from the intake of tritium cannot be measured directly and recourse has to be made to the use of bioassay (such as the determination of tritium in urine) or to assessments based on environmental monitoring. Biokinetic models of the behaviour of tritium in the body are used to determine intake from such measurements and are also used together with dosimetric models to relate retention of tritium in body tissues to the time-course of dose delivery within tissues. For intake of tritium as HTO, distribution between organs and tissues and within cells is quite uniform, depending on their water content, and so the dose is uniformly delivered despite the short range of the low-energy beta particle emissions.

7. However, some organic substrates containing tritium concentrate in specific organs and tissues, and even within specific regions within cells. In such cases, the pattern of dose distribution is very different from that experienced following uniform exposure to external penetrating radiation or

incorporation of HTO, with heterogeneity of dose between organs and tissues, and potentially within organs and even within cells. For intake of tritiated nucleotides and nucleosides, for example, a small proportion has been shown to reach cells intact and may then be incorporated into cellular DNA, resulting in localized energy deposition [D5, N1].

8. There is also some tritium-containing radioactive material with low solubility in aqueous media, such as tritides of metals (e.g. Ti, Zr, Hf), tritiated luminous compounds, micro fragments of glass and carbon and beryllium particles contaminated with tritium. Such inhaled particles exhibit long-term retention in the lungs, leading to prolonged exposure of lung tissue to beta radiation.

9. The International Commission on Radiological Protection (ICRP) has used three main biokinetic models in the estimation of doses from compounds that contain tritium for protection purposes [18, I9, I10, I14, I15, I18]:

(a) A model for tritium absorbed to blood as HTO following either ingestion or inhalation, applied also to other tritiated compounds, including elemental hydrogen and methane, that partially convert to HTO after being taken into the body;

(b) A model for tritium absorbed to blood as OBT, mainly following ingestion in food, but also applied to inhalation of non-specified organic material and to ingestion or inhalation of some specific tritiated organic compounds;

(c) The generic ICRP models for the human respiratory tract, specifying absorption parameter values for inhalation of insoluble forms of tritium used in industry, including metal tritides.

10. The existing ICRP biokinetic and dosimetric models for tritium are currently being upgraded on the basis of recent biokinetic data, especially for recently developed physical and chemical forms of tritium. This work includes models for tritium as gases, HTO, organic substances and OBT, and material with low solubility.

11. Electrons with very low energy, including beta particles from ^3H , have higher linear energy transfer (LET) values than electrons generated by the interaction of higher energy photons (e.g. from external gamma rays). This higher LET may result in greater effectiveness in causing cancer. The assessment of the effectiveness of different radiation in causing health effects relies on data on their relative biological effectiveness (RBE). RBE is an empirical quantity that depends on the biological system, the observed end points, the dose and the experimental conditions. In recent decades, several tens of experiments have been conducted using mammals (mostly mice) and their cells to determine RBE for tritium under various experimental conditions and considering a range of biological end points. However, only a small number of studies were performed to directly measure cancer induction in mammals.

12. Laboratory studies using animals have demonstrated that tritium, like other sources of radiation, can interfere with the development of the embryo or fetus, and can induce carcinogenic, heritable and reproductive effects and cell death. The use of high doses of tritium, for example, in the form of HTO or tritiated thymidine, has also been shown to induce acute radiation syndrome.

13. The dose and risk from some tritiated biochemical substrates and OBT is greater than that from HTO due to their longer residence in the body. However, there are few studies looking specifically at biological effects related to tritiated biochemical substrates and most of them use DNA precursors and amino acids. There is no appropriate ICRP biokinetic and dosimetric model for use in human risk assessment and radiation protection for tritiated nuclear acid precursors and there is a practical need for

the development of such models for intake of tritiated biochemical substrates, including nucleotropic forms even though the number of workers dealing with such forms of tritium is limited.

14. Most experimental studies on tritium were performed 20 to 30 years ago. While this work was competently performed at the time, it did not use modern scientific approaches and procedures that are often more sensitive and can use multiple approaches to test a single question. The application of modern techniques would be helpful in reinvestigating aspects of tritium dosimetry and effects, including fetal and embryo studies, and DNA damage analyses.

15. Workers may be subjected to wide-range occupational exposure to tritium in various chemical and physical forms. Usually, occupational exposure to tritium is low relative to other sources of exposure. However, historically there have been several cases of occupational exposure of workers (Russian Federation, Germany), mostly following accidents but also following chronic exposure to considerable quantities of tritium, resulting in haematological radiation syndrome [M15, O3, S12], including a few cases of radiation-induced death.

16. The principal source of quantitative information on radiation-induced cancer and other health effects in humans remains the epidemiological follow-up studies of the Japanese survivors of the atomic bombings exposed to external radiation [P12, P13, U11]. An important question is the extent to which these risk estimates are applicable to exposure from internal emitters, including tritium with its low dose-rate and low-energy beta radiation with heterogeneity of exposure between and within organs and tissues. Currently, little information on tritium-specific risks can be derived from epidemiological studies of tritium workers or members of the public potentially exposed to tritium, beyond the conclusion that tritium-specific risks have not been substantially underestimated.

17. The Committee has agreed to undertake a comprehensive review of the biokinetics, dosimetry and effects of selected internal emitters. The first radionuclide to be considered is the radioisotope of the element hydrogen, tritium. The main reasons for this selection are as follows:

- The potential for large scale production of tritium in connection with civilian and military fusion activities, as well as its creation as a by-product from operation of nuclear fission reactors, especially heavy water reactors;
- Exposure of workers and the public to various physical and chemical forms of tritium, including organic and substrates with low solubility, with a wide range of radiotoxicity that requires comprehensive scientific analyses;
- Professional and public concerns expressed between 2006 and 2010 regarding the radiotoxicity of tritium, which led to extensive review and data analysis in a number of countries, including Canada, France and the United Kingdom.

II. SOURCES AND LEVELS

A. Natural sources

18. Tritium was discovered in 1934 by Oliphant, Harteck and Rutherford [O4] and isolated in 1939 by Alvarez and Cornog [A2]; the production of tritium by natural processes was reported by Libby [L10]. There are three main sources of natural tritium: production in the atmosphere by galactic cosmic rays, production in the atmosphere by solar flare accelerated particles, and accretion from the sun. This natural production of tritium is estimated to occur at a rate of about 0.12 to 2.0 tritium atoms per square centimetre of earth surface per second, with the most probable values being close to 0.2 to 1.0 tritium atoms per square centimetre per second [J1, N2].

19. Tritium produced by natural processes is rapidly converted into HTO, which then joins the water cycle. Its concentration in continental surface water and throughout the oceans is about 400 Bq/m³ and 100 Bq/m³, respectively. Humans, on average, ingest about 500 Bq of tritium each year, with a resulting average annual effective dose of about 0.01 μ Sv [U11].

B. Artificial sources

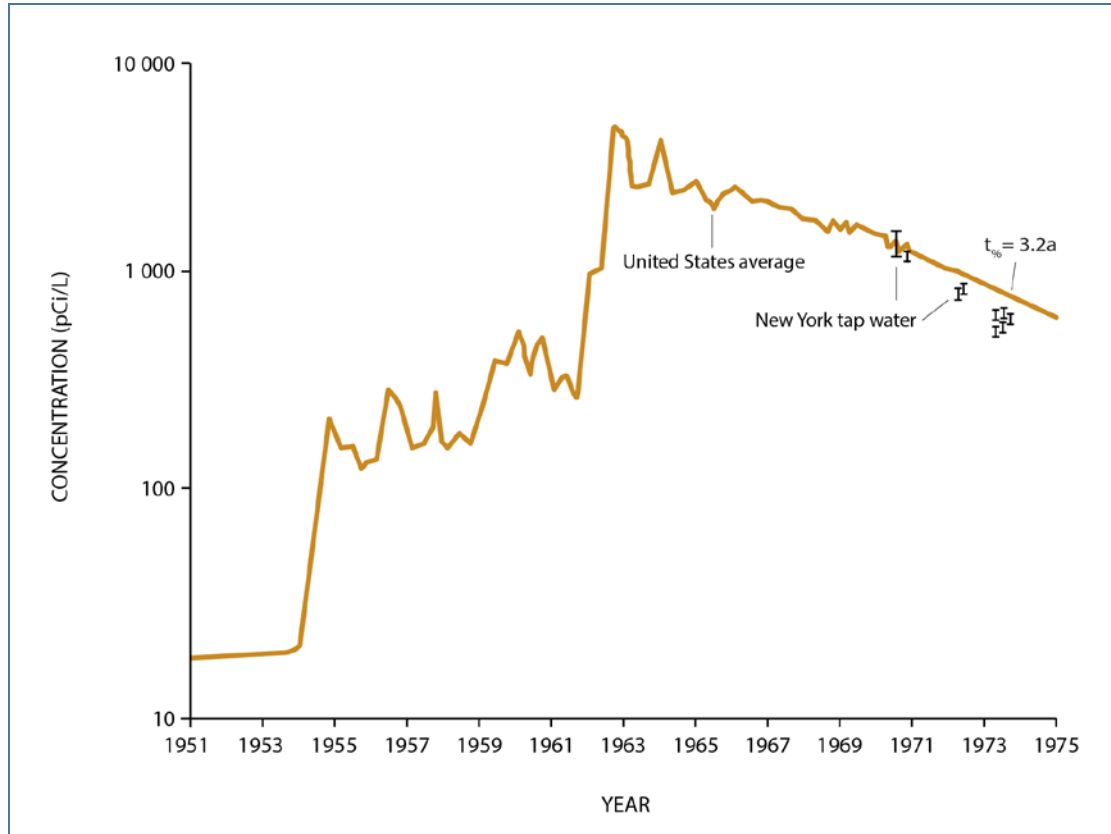
1. Nuclear weapon tests

20. In the mid-1950s and early 1960s, tritium was widely dispersed during the above-ground testing of nuclear weapons. Especially large quantities of tritium in elemental form and as tritium oxide were released in the environment in a series of hydrogen-bomb tests that started in 1952; their total explosive fusion yield was 328 Mt. The total amount of tritium released into the atmosphere from the testing of nuclear weapons from 1945 to 1980 was estimated to be 186,000 PBq [U11]. The quantity of tritium in the atmosphere from weapon testing peaked in 1963 and has since been decreasing.

21. Tritium is readily recycled in the biosphere and becomes homogeneously disseminated in the hemisphere where it has been released. The International Atomic Energy Agency (IAEA) runs a global network of 155 stations to measure tritium in precipitation [I1]. Measurements of tritium in drinking water in the United States in the early 1960s showed concentrations over two orders of magnitude higher than background levels that decreased with a half-time of about three years (figure I).

Figure I. Environmental tritium in surface water (pCi/L) in the United States in 1951–1975 [B15]

1 pCi/L = 0.037 Bq/L

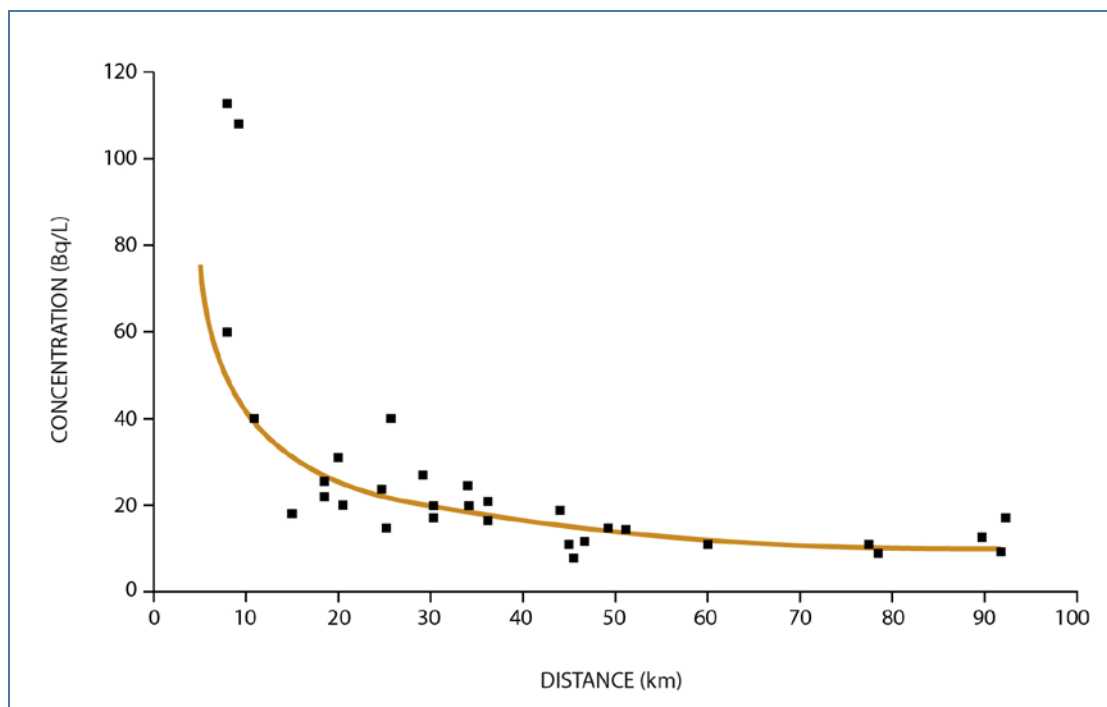


2. Production of tritium

22. In countries with developed nuclear technologies, tritium is produced in large quantities for military and peaceful purposes by means of irradiation with neutrons of lithium enriched with isotope ${}^6\text{Li}$ at industrial nuclear reactors. Tritium can be released into the environment from operational tritium production facilities in the form of elemental hydrogen or tritium oxide with high specific activity.

23. Elevated levels of HTO were measured in lakes located in the area of the Mayak facility (Ozyorsk, Russian Federation) in 1982, 1986 and 2001–2003 by Chebotina and Nikolin [C12] and in 2009–2012 by Kazachenok et al. [K5, K6]. In the former measurement series, tritium concentration in lake water in 2001–2003 was inversely proportional to the distance from the Mayak facility (figure II). During the observation period 1982–2003, the HTO concentration in lake water decreased by a factor of 2 to 16 while during the same period its mean concentration in major Russian rivers went down by a factor of about 3, from 8 to 3 Bq/L [S20].

Figure II. Dependence of tritium concentration in lake water (Bq/L) in 2001–2003 on the distance (km) from the Mayak facility [C12]



3. Operation of nuclear facilities

24. Tritium is produced in nuclear reactors by ternary fission, one triton per around 1 in 10^4 fissions of ^{235}U induced by thermal energy neutrons and by neutron reaction with light elements such as boron, lithium and hydrogen (deuterium) [N2]. Tritium is produced in much larger quantities in heavy-water-moderated nuclear reactors through neutron capture by deuterium atoms.

25. Tritium is released into the environment from nuclear reactors, especially heavy water reactors, and spent fuel reprocessing plants, including waste storage and waste disposal sites. In the future, there is potential for significant releases during the operation of fusion reactors. Tritium is released predominantly as HTO or elemental hydrogen, partially converted by environmental biota to OBT. From 1998 to 2002, the global annual average releases of tritium to the atmosphere and to the aqueous environment from nuclear facilities were estimated to be 11.7 PBq and 16.0 PBq, respectively. The resultant average annual collective effective doses from these releases were estimated to be 25 and 10.5 person-Sv, respectively [I2, I3, U11].

26. In the vicinity of nuclear installations, especially near heavy water reactors, tritium activity in environmental compartments can be above background values. For example, while tritium (HTO) activity concentrations in air at background locations in Ontario, Canada, range from 0.01 to 0.08 Bq/m³, tritium in the vicinity of CANDU nuclear power plants (NPPs) range from 0.05 to 31 Bq/m³. Fish caught in the vicinity of NPP effluent discharges have HTO activity concentrations up to 50 Bq/L while in fish from background locations, it was less than 9 Bq/L [C23].

4. Incidental releases from nuclear facilities

27. Large incidental releases of tritium from tritium production facilities have been reported to occur from Lawrence Livermore Laboratory, United States in 1970 and from Savannah River Plant, United States in 1974–1984 shown in table 1 [O2]. The released activity decreased with time from 11 to 0.3 PBq in early 1970s to 0.3 PBq in 1984. The chemical forms of the released tritium were predominantly elemental hydrogen (gas) or tritium oxide or their mixture. Monitoring has shown that elemental tritium was gradually converted in the environment to tritium oxide.

Table 1. Large incidental releases of tritium in the United States [O2]

Lawrence Livermore Laboratory (LLL) and Savannah River Plant (SRP)

Site	Year	Tritium release (PBq)	HTO (%)
LLL	1970	11	<1
SRP	1974	18	<1
SRP	1975	6.7	0.6
SRP	1981	1.2	>99
SRP	1983	2.1	1
SRP	1984	0.3	70

28. Elevated levels of tritium in the environment were also observed following major nuclear accidents—the Chernobyl accident in the USSR in 1986 and the Fukushima accident in Japan in 2011. In May 1986, tritium concentrations in precipitation collected in the Ukraine and the European part of the Russian Federation had increased by a factor of two–three compared with 1985, as had tritium concentration in river water [S20].

29. After the Fukushima accident, tritium concentrations in precipitation collected 170–700 km southwest from the Fukushima Daiichi Nuclear Power Station and in plant water collected in its vicinity were substantially elevated (up to a factor of a few tens) compared with pre-accident levels [K2, M4]. According to Povinec et al. [P11], the amount of tritium released and deposited over the north-west Pacific Ocean was in the range of 0.1–0.5 PBq.

5. Other tritium-bearing facilities and commodities

30. Elemental tritium and tritiated luminous compounds are widely used in the luminizing industry, e.g. for illuminating watch and compass dials and as permanent warning lights. Metal plates with incorporated tritium are used in nuclear physics as targets for nuclear reactions, e.g. neutron production. Other metal plates with incorporated tritium are used as sources of air ionization in industry and agriculture. Tritiated biochemical substrates are produced at radiopharmaceutical facilities and then applied for diagnostic health examinations in hospitals, and research activities in medicine and biology.

31. Tritium used in such industrial, health care, research and other applications is partially released into the working environment, human habitat and natural environment and becomes incorporated in the bodies of workers and members of general public in various physical and chemical forms.

III. PHYSICAL, RADIOLOGICAL AND BIOCHEMICAL CHARACTERISTICS

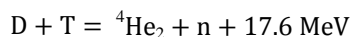
A. Physical characteristics

32. Tritium (^3H or T) is the heaviest radioactive isotope of hydrogen. The tritium atom has one proton and two neutrons in its nucleus and one electron. The binding energy of nucleons is 8.4 MeV, and the diameter of a tritium atom is 1.1 Angstroms. The dissociation energy, T_2 to 2T , is 4.59 eV; ionization energy, T to $\text{T}^+ \text{e}^-$, is 13.55 eV.

33. Tritium's physical properties are similar to those of common hydrogen (^1H), which dominates in nature over tritium and the intermediate by mass, stable deuterium (^2H or D). Under ambient conditions, tritium is a colourless highly flammable diatomic gas with the molecular formula T_2 . It is possible to make liquid tritium at atmospheric pressure by cooling it to below 25 K ($-248\text{ }^\circ\text{C}$). Liquid hydrogen can be stored in insulated containers under pressure.

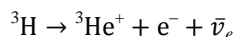
34. Tritium has a high coefficient of diffusion. It readily diffuses through porous substances such as rubber and can also diffuse through metal. Tritium, like common hydrogen, easily undergoes various chemical reactions depending on physical and chemical conditions. The prevailing form of tritium in nature is tritium oxide (T_2O) or HTO.

35. Tritium figures prominently in studies of nuclear fusion because of its favourable reaction cross section and the large amount of energy (17.6 MeV) produced through its reaction with deuterium:



B. Radiological characteristics

36. The nucleus of the tritium atom is unstable and decays with the emission of a beta particle and an antineutrino to stable ^3He . The antineutrino is of no biological significance because it does not interact with matter:



37. Tritium has a physical half-life of 12.3 years and, in the pure elemental state, a specific activity of 3.56×10^{14} Bq/g. Emitted beta particles are very low energy, mean 5.7 keV (90 fJ) and maximum 18.6 keV (300 fJ).

38. In water, the average track length of the beta particle is 0.56 μm and the maximum track length is 6 μm , which compares with a typical cell nucleus diameter of 6–15 μm , while a cell has a diameter of 10–100 μm [V1]. Tritium beta particles are completely absorbed by sheets of plastic, glass or metal. They do not penetrate dead layers of skin. However, following intake of tritium, beta radiation can irradiate internal organs. Within the body it gives a relatively low absorbed dose per disintegration compared with other beta-emitting radionuclides, but the ionization density of the electron is greater.

39. Radioactive decay of tritium atom also results in transfer of some recoil energy to a daughter ${}^3\text{He}^+$ positively charged ion. This energy depends on the random dispersion angle between the emitted electron and antineutrino and comprises 1.0 eV as average and 3.3 eV as maximum [F2, G8]. This energy is insufficient for either daughter atom self-ionization (required energy of the order 10 keV) or tissue ionization (about 30 eV). Besides the recoil energy, the daughter ${}^3\text{He}^+$ ion also carries excitation energy of about 11 eV that can influence the fate of the molecule to which the tritium atom was bound and result in its chemical transmutation and modification of its chemical properties.

C. Biochemical characteristics

1. Tritiated water

40. Tritium is most commonly found in natural and working environments in the form of HTO, which has the same chemical properties as ordinary water. Water with a tritium activity of 1 Bq/L contains less than one tritium atom among 10^{17} molecules of water. HTO can enter the human body by inhalation, skin absorption (liquid and vapour) [D3, P9], or ingestion of water or food [B14, I13]. Once inside the body, HTO diffuses freely and rapidly across cellular membranes, and reaches equilibrium throughout the total body water pool [H12]. HTO is excreted via urine, faeces, sweat, and breath [N1]. Since HTO quickly reaches equilibrium with the water in the body and is distributed uniformly among all soft tissues, the concentrations of HTO in sweat, sputum, urine, blood, perspiration, and exhaled water vapour are considered to be equal [H12].

2. Tritiated gases

41. Tritiated elemental hydrogen (HT or T_2) is relatively inert in biological systems and has a very low uptake into body fluids and tissues [H12]. Humans are mostly exposed to HT by inhalation or skin contact with contaminated surfaces. A small fraction of inhaled HT is converted to HTO in the human body. The primary sources of HT are tritium production and processing facilities (such as those involved in making gaseous tritium light sources), tritium recovery facilities, and nuclear fuel reprocessing facilities. HT is readily converted to HTO in the environment, with soil microorganisms playing an important part in this process [A3].

42. Tritiated methane (CH_3T) is relatively inert in biological systems. Humans can be exposed to CH_3T by inhalation in workplaces or in the public domain following biochemical degradation of OBT in the environment. Because of the low solubility of methane in body fluids, the radiological implications of inhaling CH_3T are mostly determined by its oxidation to HTO and biochemical conversion to OBT in the human body [P5].

3. Organically bound tritium

43. Because tritium atoms are exchangeable with normal hydrogen atoms, a fraction of the tritium absorbed by plants or animals can become incorporated into organic compounds such as carbohydrates, fats, proteins, and collagen: this is referred to as OBT¹. Animals, including humans, ingest OBT and form OBT from HTO within their tissues [D5, K14].

44. A tritium atom in OBT attached to a carbon atom is essentially fixed until the compound is metabolized (i.e. the tritium is non-exchangeable). However, a tritium atom attached to an oxygen, sulphur, nitrogen or phosphorus atom is readily exchangeable with hydrogen in water and is not considered as OBT in this annex [D5, R11, S1] or specifically qualified as exchangeable OBT [K14]. OBT exhibits longer retention times in the body than HTO.

4. Tritiated organic substances

45. A broad spectrum of organic substances labelled with tritium, including biochemical substrates, are produced and used widely in research and for other purposes. Workers may be exposed by inhalation or through skin contamination, and also by inadvertent ingestion. In the human body, labelled biochemical substrates (e.g. amino acids, DNA precursors, glucose, hormones) may be metabolized with partial loss of tritium label converted to HTO, or be incorporated into biological macromolecules as OBT [B11, H12]. Foreign organic compounds (such as organic solvents) are usually rapidly excreted from the body in urine and faeces [B8].

46. Labelled DNA precursors (e.g. ³H-thymidine, ³H-deoxycytidine) belong to a special group that, in the mammalian body, are partially degraded to HTO and partially incorporated into the DNA of dividing cells, and thereafter selectively expose the nuclei of proliferating cells to beta radiation [D5, N1].

5. Metal tritides and other low soluble forms of tritium

47. Tritiated compounds with low solubility, which are widely produced and used in industrial or research facilities, include luminous compounds (as powders), particles of metal tritides that are used as accelerator targets or as ionization sources in industry and agriculture, and carbon, beryllium and tungsten dust, micro-fragments of glass contaminated with tritium used in fusion experiments. Airborne particles with insoluble tritium are inhaled by workers and, depending on their dimensions and respirability, deposited in the respiratory tract. Following inhalation, such substances can remain in the pulmonary region of the lungs and expose tissues to both beta radiation and, to a lesser extent, to bremsstrahlung.

48. Although insoluble particles are largely retained in lung tissues, transported by macrophages to regional lymph nodes, or escalated from the lungs by mucociliary clearance, some dissolution will occur and a proportion of their tritium content will be removed and absorbed to blood as HTO. When luminous powder produced from zinc sulphide granules coated with a thin layer of high activity tritiated polymer is inhaled, some tritium is detached from the polymer and absorbed to blood as low molecular organic foreign compounds that are rapidly excreted from the body in urine and faeces [B8, B11, B14].

¹ OBT in biological tissues is carbon-bound tritium that was originally formed in living systems through natural environmental or biological processes from HTO (or HT via HTO). OBT is not exchangeable with hydrogen in water.

IV. HUMAN EXPOSURE

A. Exposure of the public

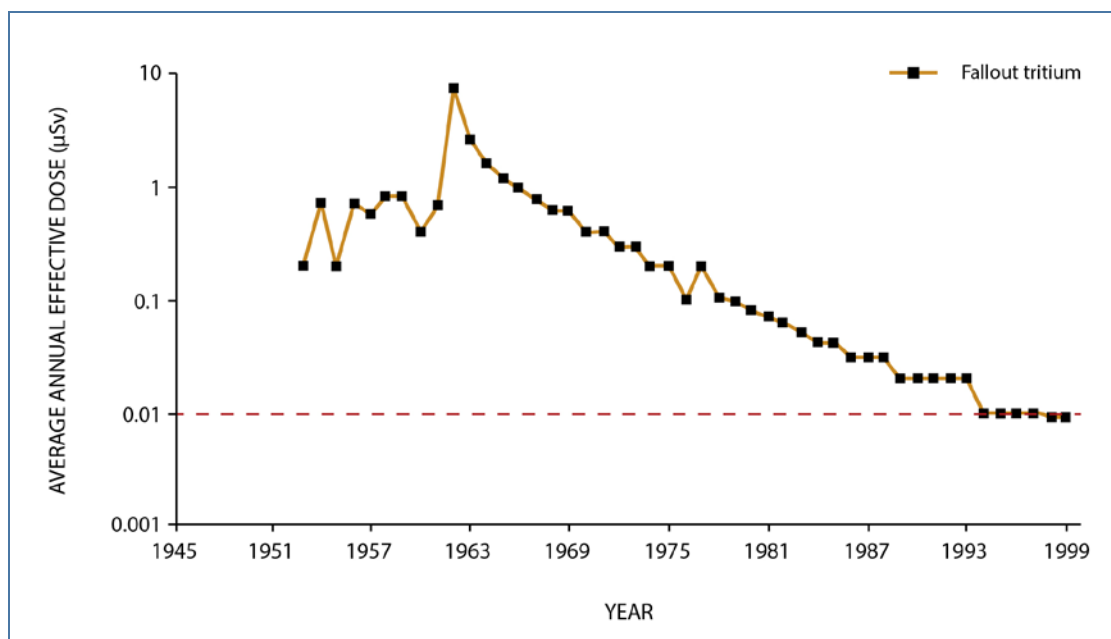
1. Tritiated water in global water cycle

49. The Committee [U9] has estimated worldwide average annual individual effective doses mainly from data on ingestion of the globally dispersed HTO created as a result of fallout from above-ground nuclear weapon testing (figure III) [B25, U9]. The doses received from the inhalation of ^3H are negligible in comparison with those received from ingestion. The derivation of these doses is largely based on environmental measurements and is described by the Committee in its UNSCEAR 2000 Report [U9], Bouville et al. [B25] and Bennett [B16]. The background concentration of tritium in humans is calculated from an average of the concentrations in the sources of water ingested, assumed to be 33% from the atmosphere, 53% from fresh water, 13% from groundwater and 0.7% from ocean surface water (through fish) [B25, N2].

50. The largest annual doses from tritium in fallout were received by the world population during the period of intense nuclear weapon testing during the late 1950s and early 1960s, before the Limited Test Ban Treaty of 1963. The peak global average annual effective dose from tritium in fallout was $7.2 \mu\text{Sv}$ in 1962. Since the majority of atmospheric nuclear weapon tests during that period took place in the Northern Hemisphere, average doses from tritium were greater in the Northern Hemisphere than in the Southern Hemisphere. Generally, tritium follows the global water cycle: a large proportion is transferred to the oceans within a few years of production and a very small fraction is ingested by humans [U9].

Figure III. Worldwide average annual individual effective dose in 1950s–1990s from the ingestion of tritium produced in atmospheric nuclear weapon testing [B25, U9]

Dashed line is for dose from natural tritium



2. Local exposure of the public from nuclear facilities

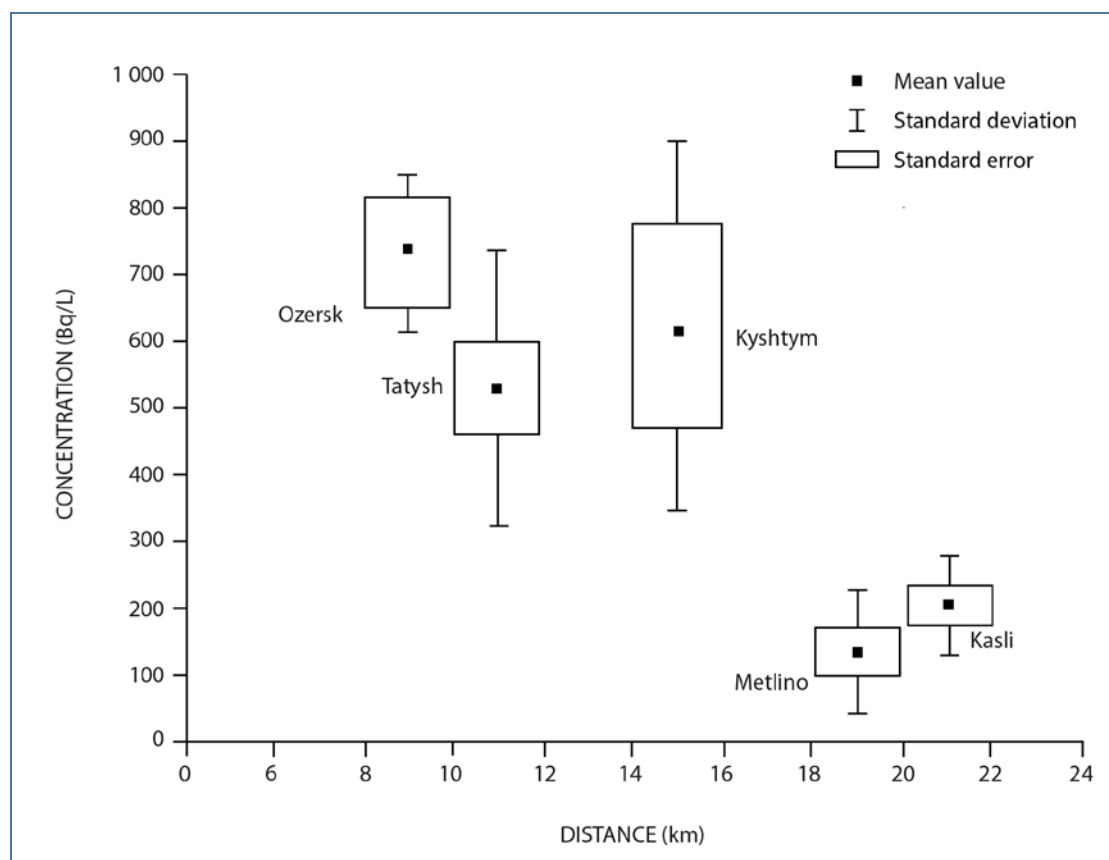
51. Tritium released from nuclear facilities, especially from those operating with large amounts of tritium (i.e. tritium production facilities, heavy water reactors or reprocessing plants) may enter the bodies of people residing in the vicinity in drinking water or via inhalation. In these conditions, human doses caused by local intake of environmental tritium are usually larger than those caused by global tritium levels common in neighbouring areas with no facilities releasing tritium.

52. Measurements of tritium (HTO and OBT) in environmental media are carried out routinely in the vicinity of Canadian nuclear facilities. These measurements allow estimation of doses to members of the public from all exposure pathways (e.g. inhalation, skin absorption, ingestion of food and drinking water). In 2006, annual tritium doses to members of the public living in the vicinity of NPPs were less than 2.5 μSv whereas they were slightly higher in the vicinity of two facilities manufacturing gaseous tritium light sources (GTLS). The annual tritium doses of respective critical groups for the two GTLS facilities were 15 and 67 μSv [C23].

53. Kim and Han [K13] studied environmental radiation conditions in 1992–1993 around the Wolsong NPP, Republic of Korea, for a CANDU-6 heavy water reactor that had been operational since 1983. Activity concentrations of HTO and OBT were analysed in food samples collected within 1–15 km of the reactor site and HTO was collected from the air in some locations. In water samples extracted from rice, Chinese cabbage, radish and pumpkin, HTO concentration was in the range of 3–100 Bq/L and that in combustion water obtained from organic parts of vegetables was 4–130 Bq/L, both inversely proportional to the distance from the site. The ratio of tritium concentration per unit hydrogen mass in OBT to that in free HTO was in the range of 1.0–2.8, with an average of 1.35. On the basis of monitoring data, the authors assessed the annual effective dose for adult members of the public to be in the range of 1.3 μSv in a radius of 0–1.6 km to 0.15 μSv at 8–16 km. Although both values are much lower than the background dose, they are substantially higher than the annual dose from environmental tritium to the Korean public residing away from NPPs, assessed by Yoon et al. [Y7] from urine samples of 50 persons to be about 2 nSv.

54. In 2008, Chebotina and Nikolin [C13] measured elevated tritium concentrations in the urine of 45 residents of five towns located in the vicinity of the Mayak facility (figure IV). The average concentrations, in the range of 100–800 Bq/L, correlated inversely with the distance between the town and the Mayak facility. Those values are much higher than tritium concentrations in potable water measured in the area in the 2000s, indicating inhalation as a possible intake pathway. The measured concentrations of tritium in urine correspond to average annual effective doses incurred by the residents of five towns in 2008 in the range of 3–14 μSv .

Figure IV. Average concentration of tritium in 2008 in urine of residents of towns located in the area of the Mayak facility [C13]



3. Organically bound tritium in human tissue

55. Very few authors have directly measured tritium content in human tissue. Bogen and Welford [B21] for example have summarized results of tritium measurements in the United States' environment carried out in 1960s to early 1970s in non-equilibrium conditions caused by termination of nuclear weapon tests in 1963 and continued radioactive fallout (decreasing with time) from the stratosphere. They sampled water vapour from the air, tap water, soil, vegetation, food, animal and human tissue and they measured HTO in water distilled from the samples and OBT in water from combustion of dried samples. Both sets of data were presented in terms of HTO activity concentration in water. In all links of the ecological chain up until 1973, the tritium specific activity in the OBT fraction was higher than that found in the free water fraction. The ratio of specific activities OBT/HTO decreased by a factor of about 1.5–2 from each trophic level: soil 6–8, vegetation 3–4, animal 2–3 and human 1.5–2. Those patterns can be interpreted by slower clearance of OBT compared to HTO from various organisms of the trophic chain and their residues (soil organic matter) in conditions of decreasing HTO concentration in the environment, as was the case in the 1970s.

56. Ujeno et al. [U3] measured tritium in tissue water distilled from samples of human organs and tissues (brain, lung, liver, kidney and muscle) collected by staff of Kyoto University during forensic autopsy of eight dead bodies. The tritium concentration in water from various organs and tissues was similar and not affected

by sex or age. The average HTO concentration in tissue water was 2.5 ± 0.7 Bq/L, which was similar to that measured in tap water, rain water and water distilled from local food.

57. Hisamatsu et al. [H13, H14] presented the results of tritium measurements in organs and tissues collected from 11 human cadavers (10 males, one female, mean age \pm SD = 46 ± 16 year), who died suddenly in 1986 at Akita Prefecture in northern Japan. They measured tritium concentrations in free water (HTO) distilled from human samples (brain, liver, lung, heart, kidney, blood serum and whole blood) and in combustion water obtained by combustion of dried samples in oxygen atmosphere. The mean tritium concentrations in free water from seven diverse organs and tissues were similar, with a range of 1.5–1.9 Bq/L and average of 1.6 Bq/L. Mean tritium concentration in combustion water of various organs/tissues varied in the same range, average 1.7 Bq/L. The ratio of OBT/HTO tritium concentrations in human tissue varied between 0.95 and 1.3 with an average of 1.1. Tritium concentrations in local food sampled in 1985–1987 were also reported. Free water concentration in six samples of the total human diet varied between 1.4 and 2.2 Bq/L and combustion water varied in the range of 1.7–2.2 Bq/L. Their ratio varied between 0.9 and 1.6 with an average value of 1.2. Thus, in equilibrium conditions of low-level intake of environmental tritium, no differences in tritium concentrations were revealed between various human organs and tissues, between diet and human tissue, and between free water tritium and OBT.

4. Measurements of environmental tritium

58. The measurement of environmental tritium in its various forms as gases or vapours (HT, HTO, organic molecules), liquids (HTO or OBT in solution) and solids (OBT, hydrides) is a key step for dose assessment and evaluation of health and environmental risks. Sampling, storage and treatment are important points in the analytical procedure for tritium. The final form of tritium for analysis is usually water, and low concentrations of tritium in water (few Bq/L) are currently measured either by gas proportional counter or by liquid scintillation counter. They can also be determined indirectly using a sensitive mass spectrometer, measuring the amount of the decay product, helium-3, formed in a water sample in a closed vessel during a given period [W8].

59. Reference water that is virtually tritium-free is used as calibration blanks for the analytical system and a recent comparison of these water sources gave results ranging from 0.004 to 0.17 Bq/L [F9]. Analytical procedures have been developed to measure OBT [B2] and respective standards are under development. Recent studies of the speciation of tritium as OBT are investigating variations in the hydrogen content of different forms and identifying compounds solubilized in the samples during labile exchange [B1].

B. Occupational exposure

60. In working environments, tritium is present in various physical and chemical forms depending on the production processes. Working environments may contain tritium in a variety of different chemical forms, including HTO, elemental hydrogen, organic solvents, airborne particles of metal tritides (e.g. Ti, Zr, Er), tritium contaminated glass and dust particles, luminous compounds, and labelled biochemical substrates (e.g. amino acids, DNA precursors, glucose, hormones) [B11, H16, I2, I3, J1].

61. Occupational exposure to tritium is usually low relative to other sources of exposure. For example, in 2006 average annual tritium doses for NPP workers in Canada ranged between 0.07 and 0.26 mSv, which represented between 14 and 29% of the total effective dose. In the same year, workers employed at two Canadian GTLS manufacturing facilities had annual tritium doses of 0.19 and 0.3 mSv [C23].

V. BIODYNAMICS AND DOSIMETRY

62. Biokinetic models describe the time-dependent deposition and translocation of radionuclides in the body and the rates at which they are removed from the body. Biokinetic models are used to calculate the number of nuclear transformations of radionuclides in each source organ during a specified period following an intake. Dosimetric models are then used to calculate the absorbed doses to specific organs and tissues (referred to as target organs) per nuclear transformation of radionuclides in each source organ (i.e. each site of radionuclide deposition or transit in the body).

63. For protection purposes, ICRP calculates values of committed effective dose as a doubly weighted sum of organ and tissue doses—first, adjustment to take account of the relative effectiveness of different radiation types in causing stochastic effects using radiation weighting factors (w_R), and second, adjustment for differences between organs and tissues in their contribution to total detriment from stochastic effects using tissue weighting factors (w_T) [I23].

64. Because the range of the beta radiation emitted by tritium is short, all the radiation energy is generally assumed to be absorbed in the tissues and organs in which the tritium decays. Therefore, organ or tissue dose from tritium radiation is entirely determined by a relevant biokinetic model and not by radiation transport in the body. The biokinetic model for tritium depends on the type of tritiated compound taken into the body, as this dictates its deposition, translocation, retention and excretion.

65. In animal studies, the absorbed dose in tissue resulting from an acute administration of tritium can be calculated using information on the initial activity concentration of tritium in the tissue and the rate of removal of tritium from that tissue arising from biological processes and radioactive decay. This section presents the basis for the biokinetic models used for the intake of tritiated compounds by inhalation, ingestion or absorption through the skin. Examples of dose coefficients (committed effective dose per unit activity taken into the body) for tritium calculated with the various biokinetic models are provided.

A. Information on biokinetics and dosimetry of tritiated compounds

1. Tritiated water

(a) *Early biokinetics of HTO in mammals*

66. Tritiated water can enter the human body via ingestion of food and drink and—mostly for occupational exposure—by inhalation of HTO vapour or direct absorption through skin exposed to water or water vapour. Following ingestion, absorption from the alimentary tract into the bloodstream is complete within a time range from a few minutes to some tens of minutes. Following inhalation, almost the entire amount of inhaled HTO vapour is absorbed very rapidly from the respiratory tract into the bloodstream [B7, P9]; absorption through skin provides an additional common route of entry into the bloodstream [D3, O6, P9].

67. Following uptake to blood from the alimentary or respiratory tracts or through the skin, HTO is transported by the circulatory system to all the body organs and tissues and diluted uniformly in body

water. This process takes from a few hours to some tens of hours. A small fraction of tritium from HTO (0.5 to 4%) exchanges very rapidly with hydrogen in organic molecules as OH, NH and SH bonds throughout body tissues. Another small fraction (from less than 1 to 3% in humans) is gradually converted to OBT as a result of biochemical processes, i.e. CH bonds in organic molecules [B8, H12, P9].

68. The absorption of HTO through the skin from either the vapour or liquid phase has been investigated by several authors. DeLong et al. [D3] exposed mice, rats and human adult volunteers to HTO vapour in air. Animals were sacrificed following exposure. Urine and blood samples were collected from human subjects for 48 hours after the end of exposure. Absorption rates of HTO, calculated from measurements of tritium in blood and total body water, suggested that a delay occurred in the distribution of the absorbed HTO. The absorption rate of HTO through the skin was the same whether the skin was covered with a cloth (cotton) or uncovered. It was also proportional to the water vapour pressure. This suggested a single diffusion mechanism for percutaneous absorption. However, the absorption rate for the vapour phase was larger than could be accounted for by diffusion due to vapour pressure alone, perhaps as a result of capillary action. The absorption rate increased with increasing skin temperature. DeLong et al. [D3] and Pinson and Langham [P9] concluded similarly that the quantity of HTO entering the body through the total skin, when exposed to an atmosphere containing a given activity per unit volume, would be about equal to that entering through the lungs. Osborne [O6] exposed volunteers to HTO in air and measured the tritium activity in urine, showing a correlation between skin absorption rate and skin temperature.

(b) Long term biokinetics of HTO in mammals

69. Several studies have examined the biological half-time of HTO in a total of about 400 adults by measuring tritium activity concentrations in urine. Butler and Leroy [B28] found this parameter to vary with the amount of water ingested (decreasing with increasing water intake rate), with the ambient temperature (decreasing with increasing ambient temperature) and with age (decreasing with increasing age in adults). Their study, based on 310 cases of HTO intake, showed that the biological half-time of HTO varied from about 4 to 18 days, with a mean of 9.5 days. During the warmer months, the average half-time was lower; the difference being attributed to increased water intake. Other studies, based on fewer cases, showed similar results [H12]: from 6 days for 8 cases [R16], to 12 days for 5 cases [B7]. In a few cases of accidental intake of large amounts of HTO, the excretion rate was accelerated with diuretics and increased intake of fluids (e.g. [S2, T14]). The ICRP model uses a biological half-time of 10 days for HTO and 40 days for OBT formed from HTO in the body of adults [I8, I9, I10, I14, I17].

70. A number of studies have reported evidence for the presence of a second exponential component of tritium activity concentration in human urine associated with the formation of OBT from HTO and its subsequent removal. The biological half-time for OBT removal mostly ranged from 23 to 104 days (mean 59 days) and its contribution to total excretion in 17 study subjects varied between 0.01 and 0.7% (mean 0.2%) [B7, H9, L4, S2, S17, T14]. A value of 40 days, based on carbon turnover in the body, was adopted by ICRP [I13]. This was derived from the ratio of reference values for the body content of carbon (16 kg) and daily carbon intake (0.3 kg) for adults [I7].

71. Some studies have reported an even longer component for the removal of tritium from the body (e.g. [M15, M16, S2]). However, the parameters of this component as derived from data obtained on five subjects occupationally exposed to either HTO or tritiated luminous compounds are very uncertain. Such a component would contribute in only a minor way to tissue doses, as it represents less than 1% of total OBT. The biological half-times of tritium following acute intake of HTO by adults reported by various authors are shown in table 2.

Table 2. Biological half-times of tritium in humans following acute HTO intake

Study	Number of cases	Biological half-time (days)		
		Compartment 1 (body water)	Compartment 2 (organically bound)	Compartment 3 (organically bound)
Pinson and Langham [P9]	9	11.3	—	—
Foy and Schnieden [F10]	10	5–11 (mean: 7.5)	—	—
Wylie et al. [W9]	7	6.4–12.1 (mean: 8.5)	—	—
Butler and Leroy [B28]	310	4–18 (mean: 9.5)	—	—
Osborne [O6]	30	6.4–14.4 (mean: 10.5)	—	—
Snyder et al. [S17]	1	8.7	34	—
Sanders and Reinig [S2]	1	6.1 ^a	23	344
Minder [M15]	1	—	10–30	139 to 230
Lambert et al. [L4]	1	9.1 ^b	36	—
Moghissi et al. [M16] ^c	3	—	21 and 26	280, 550±140, 350±190
Henry [H9]	1	7.5	63	—
Balonov et al. [B7]	5	11–13 (mean: 11.9±0.3)	39 to 76 (mean: 51±7)	—
Trivedi et al. [T14]	8	6.2–12.8 ^d (mean: 8.4)	58–104 (mean: 74±18)	—

^a Oral diuretic administered from day 3–35 post-intake.

^b HT/HTO acute intake.

^c Data for three tritium luminous dial painters collected 6–10 months after termination of employment.

^d During the initial period when the exposed individuals increased fluid intake one month post-intake, the biological half-time varied from 5.0 to 8.1 days with a mean of 6.3 days.

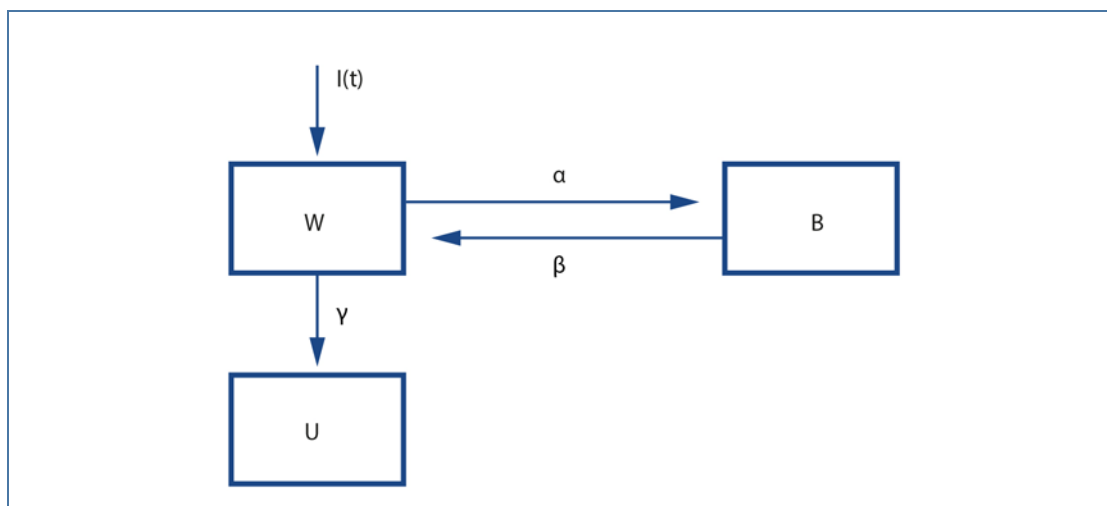
72. The partitioning of HTO and OBT after intake of HTO was examined by Takeda and Kasida [T1] as part of a study of the biokinetics of HTO in rats. These investigators found that “initially, the ratio of tissue-bound tritium to total tritium was about 3% in the kidney and 1–5% in other tissues.” Measurements of tritium in human tissue are generally unavailable, but information can be derived by biophysical modelling using long-term measurements of tritium in urine or, in some cases, blood samples. The published data from the six studies [B7, H9, L4, S2, S17, T14] are available for such analysis (table 2). Additional information can be derived from tritium measurements for organic components of urine (urea) or blood (proteins, dehydrated cells). However, the number of reliable measurements is limited [L4, R16, T16] and their representativeness with regard to tritium content in organs and tissues is questionable.

73. The long-term retention of tritium in the human body as shown in figure V was modelled by several authors as linear recurrent two-compartment models with transfer of tritium from HTO to OBT (synthesis of biomolecules with OBT) and subsequent catabolic loss (degradation of biomolecules with OBT) with all tritium excretion as HTO [B7, S17, T14]. Using this approach, the peak OBT activity

was calculated by Balonov and Chipiga [B6] from the data of the six studies referred to above [B7, H9, L4, S2, S17, T14]. The peak OBT activity was estimated to be reached in 16–38 days (mean 26 ± 5 days) after a single HTO intake and accounted for 0.1–1% (mean $0.4 \pm 0.2\%$) of the initial intake of tritium. Balonov and Chipiga estimated the contribution of OBT to total soft tissue doses after intake of HTO using 17 available data sets and obtained values of 1.8–4.6% (mean $3.0 \pm 0.9\%$) [B6]. It is notable that the contribution of OBT to the total dose was estimated to be similar in nine subjects with relatively low previous occupational tritium intake [H9, L4, S2, S17] or in five volunteers with no previous tritium intake [B7] ($3.0 \pm 0.9\%$) and in eight workers at a Canadian heavy water reactor ($3.0 \pm 0.8\%$), indicating that the contribution of previous chronic HTO intake by the workers was insignificant.

Figure V. Schematic two-compartment recurrent model of tritium biokinetics following HTO intake in the body [B7, S17]

$I(t)$ is HTO intake rate (Bq/day); $W(t)$ is tritium activity in the body as HTO (Bq); $B(t)$ is tritium activity in the body as OBT (Bq); $U(t)$ is tritium activity excreted from the body as HTO (Bq); α , β and γ are transfer rate constants (day^{-1})



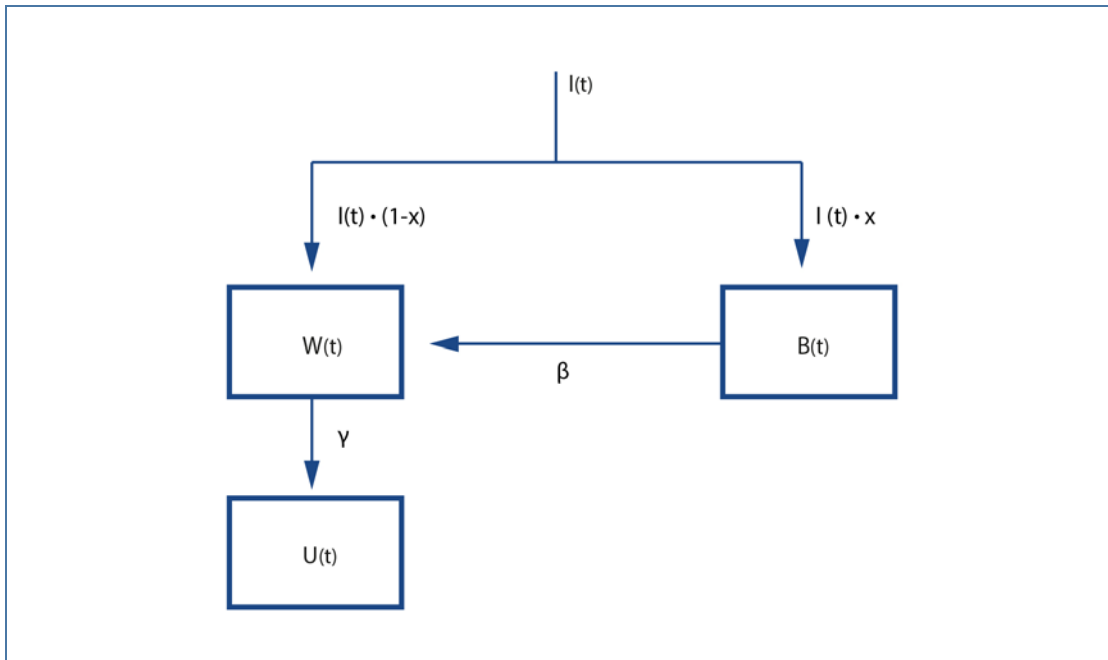
74. Trivedi et al. [T14] assessed the contribution of OBT to effective dose following acute intake of HTO by calculations based implicitly on a simpler linear two-compartment model with no transfer of tritium from HTO to OBT. Instead, it was assumed that some fraction of HTO taken in was instantly converted to OBT that was gradually degraded to and excreted as HTO (figure VI). The contribution of OBT to the effective dose assessed with this model was 3–9% (mean $5.3 \pm 2.1\%$) for 15 subjects [B7, H9, I14, S17, T14] excluding data from Rudran [R16] obtained on workers occupationally exposed to tritiated luminous compounds. In another study by Trivedi et al. [T16] the tritium concentrations in urine and blood samples both as HTO and OBT for six workers chronically exposed to low levels of tritium were measured. The activity concentration of OBT per gram of hydrogen in OBT from urine and blood samples (their ratio was 0.95 ± 0.25) was assumed to be equal to that in body tissues. By means of a simple equilibrium model, they calculated the contribution of OBT to the total dose to be equal to 4.7–9.9% (mean $6.9 \pm 3.1\%$) for the six workers. This is in good agreement with the previous results from 15 subjects with acute intake of HTO.

75. The estimate of Trivedi et al. for the contribution of OBT to dose following acute intake of HTO (figure VI) is 1.8 times greater than that obtained by Balonov and Chipiga using a more physiologically realistic model (figure V); it does not account for the gradual bioaccumulation of OBT and assumes its instant formation from HTO. A similar conservative approach is used by the ICRP model for HTO (see also figure VIII) which is applied for radiation protection purposes [I14]. According to this model, 97% of HTO absorbed to blood is distributed in body water ($T_{1/2}=10$ days in adults) and 3% is instantly

converted to OBT ($T_{1/2}=40$ days in adults); the contribution of OBT to the effective dose in the ICRP model is about 9% under assumption of uniform OBT distribution in organs and tissues.

Figure VI. Schematic two-compartment model of tritium biokinetics following HTO intake in the body [T14]

$I(t)$ is HTO intake rate (Bq/day); x is fraction of tritium instantly converted to OBT (dimensionless); $W(t)$ is tritium activity in the body as HTO (Bq); $B(t)$ is tritium activity in the body as OBT (Bq); $U(t)$ is tritium activity excreted from the body as HTO (Bq); β and γ are transfer rate constants (day^{-1})



76. Other authors [H12, J3, N1, S2, T9] have used the limited available human data to develop a three-compartment model of tritium retention following intake of HTO. The results showed considerable variation, both in the observed biological half-times and in the proportions of tritium entering OBT compartments. The model parameters suggested by Taylor [T9] for adults are shown in table 3. The resulting committed effective dose per unit intake of HTO by adults, on the basis of this model, is 1.7×10^{-11} Sv/Bq. The current ICRP dose coefficient for HTO is 1.8×10^{-11} Sv/Bq [I15].

Table 3. Parameter values for HTO model proposed by Taylor [T9]

<i>Model component</i>	<i>Distribution (%)</i>	<i>Biological half-time (days)</i>
HTO	99	10
OBT ^a	0.98	40
OBT ^b	0.02	350

^a Short-term OBT compartment.

^b Long-term OBT compartment.

2. Inhalation and skin absorption of elemental tritium gas

77. Tritiated elemental hydrogen (HT) is only slightly soluble in body fluids and has a much lower uptake into biological systems than HTO. After inhalation, most of the HT is exhaled, but a small fraction is dissolved in body fluids and is then oxidized to HTO by anaerobic bacteria in the gastrointestinal tract, the only known biological site of HT oxidation [I6].

78. The ICRP based its assessment of the effective dose resulting from the inhalation of HT primarily on exposure of the lungs, as opposed to exposure of the skin. Oxidation to HTO in vivo was not considered [I9]. The absorption of HT through the skin appears to be negligible and it does not convert to HTO on contact with the skin [H12].

79. The studies of Pinson and Langham [P9] and Peterman et al. [P3, P4] found that exposure to HT resulted in excretion of HTO in urine, and that the HTO, formed from the oxidation of HT, was retained in the body and excreted with the usual biological half-time of about 10 days. About 0.01% of the HT inhaled by human volunteers was converted to HTO in the body [P3, P4, P9].

80. Using their biokinetic models for HT and HTO and data from studies with human volunteers, Peterman et al. [P3] concluded that the effective dose from inhaled HT was dominated by two roughly equal contributions: the effective dose resulting from exposure of the lungs to HT in inhaled air, and the effective dose resulting from exposure to HTO caused by the oxidation of HT. The current dose coefficient for inhalation of HT given by the ICRP Publication 68 [I15] is based on the work of Peterman et al. [P4] and its human respiratory tract model.

81. Most of the energy of the tritium beta particles is not deposited in the target cells of the respiratory tract due to their short range. The average depth of the nuclei of these cells range from about 10 to 50 μm in the extrathoracic, bronchial and bronchiolar regions of the respiratory tract [I16]. In the current ICRP model of the human respiratory tract [I16], the tritium beta particles are assumed to deliver a dose only in the alveolar-interstitial region after inhalation of HT. Trivedi and Gentner [T15] noted that the nuclei of target cells within the alveolar-interstitial region, at depths of less than 10 μm , are assumed to receive some dose.

3. Contact of skin with tritium-gas-contaminated surfaces

82. Eakins et al. [E1] applied tritium-gas-contaminated metal surfaces to the forearms of four volunteers. The estimated average body content of HTO and OBT were about 0.5 and 0.3%, respectively, of the applied activity of tritium gas. The results did not depend on the type of material tested and the initial body content of organic tritium was less than that of HTO for each volunteer. Urinary excretion of tritium, initially primarily OBT, reached a peak about 24 hours after exposure. Up to 50% of the OBT was excreted via urine with a biological half-time of about one–two days; the rest of the OBT was excreted with a biological half-time of 0.1–0.2 days. One–three weeks after exposure, the tritium was excreted predominantly in the form of HTO with a biological half-time of about 14 days. The effective dose resulting from intake of tritium from contact with a contaminated surface was estimated to be about 9×10^{-12} Sv/Bq [J4].

83. Similarly, Trivedi [T13] used hairless rats and showed that when HT-contaminated stainless steel was brought in contact with intact skin, tritium was fixed as OBT and HTO in the skin and demonstrated biphasic excretion of OBT and HTO.

4. Ingestion of organically bound tritium

84. While HTO diffuses freely in body tissues and enters into equilibrium with body fluids in a matter of minutes or hours [H12, P9], several factors determine the distribution in the body of OBТ ingested through the diet. These include the biochemical composition of OBТ as a mixture of tritiated carbohydrates, fats and proteins, the oxidation rates of the dietary constituents, absorption from the alimentary tract, and the synthesis and retention of organic forms and the HTO and OBТ excretion rates [D5].

85. Experiments indicate that about 3–20 times more tritium is bound to organic compounds in more metabolically active tissue after ingestion of food containing OBТ than that after ingestion of the same activity of tritium in the form of HTO [P7, R11, T3, T6]. This ratio depends on the animals studied (rabbits, rats, mice), the kind of tritium-labelled food (e.g. alfalfa, wheat, meat, shrimp) and the duration of tritium intake (single, few weeks, three generations). Takeda and Kasida [T1] found that, following the intake of HTO by animals, 1–5% of the tritium was incorporated into organic constituents of rat tissue. Therefore, several tens of per cent of the tritium ingested as OBТ would be expected to be incorporated into organic molecules in mammal tissues. The assumption made in the ICRP Publication 60 [I13] that 50% of tritium is incorporated into OBТ in tissues after an intake of OBТ stems from this reasoning.

86. On the basis of all available data, several authors [I12, K15, M1, P6, R11, R12] suggested—as a rounded value—that approximately nine times more OBТ may be present after intake of OBТ than after intake of HTO. This corresponds to a range of 9–45% for the proportion of tritium reaching blood that was retained as OBТ, the remainder being converted to HTO (the wide range resulting from the differing metabolic roles of different OBТ molecules, e.g. as an energy source or a structural component). Further, it was also suggested that the use of a value of 50% would be suitable for general radiological protection applications.

87. While the biokinetic parameters used by ICRP are supported by a range of data, there have been suggestions that the contribution to dose from OBТ may be greater for intake of either HTO or OBТ than predicted by ICRP models. However, the conclusions of Takeda [T4], Komatsu et al. [K21] and Rodgers [R12] are reasonably consistent with the ICRP conclusion that the contribution to dose from OBТ after intake of HTO will be small (<10%) and that the overall dose from intake of OBТ will be greater than from HTO by about a factor of two (the data in table 4 show the ratio in ICRP dose coefficients to be about 2.5).

88. Some experimental data suggest that after chronic intake of HTO, equilibrium tissue concentrations of HTO and OBТ are similar [C25]. Etnier et al. [E3] used a four-compartment model of hydrogen metabolism to show theoretically that OBТ in food 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. [T3] using rats fed with tritiated wheat and HTO. After chronic ingestion of tritiated wheat (22 days), the amount of OBТ in the tissue of rats exposed to tritiated wheat was about 6–11 times higher than when exposed to HTO.

89. Hunt et al. [H19] measured the retention time of tritium in volunteers who had eaten fish that contained OBТ or HTO as a consequence of discharges from the General Electric Healthcare Ltd. plant in the United Kingdom. The excreta from five volunteers were screened for a period of up to 150 days after intake. The results suggested biological half-times ranging from four to eleven days for the retention of the total amount of tritium, with no evidence for a statistically significant contribution from a component with a longer half-time.

90. Animal studies have shown a non-uniform distribution of OBT in soft tissue, and also a non-uniform distribution of tritium in the various organic compounds in the body [D5, I13]. However, with the exception of the special case of DNA precursors, discussed later, any non-uniformity of distribution within cells appears to be small.

91. Richardson and Dunford [R9] conducted a literature review of the studies of exposure to OBT. They proposed two biokinetic models governed by the overall metabolic reactions of the principal nutrients: carbohydrates, fats, and proteins. The parameters for two models of differing complexity—called the HCNO-S and HCNO-C models—were evaluated on the basis of biochemical reactions. The simpler model has a single compartment representing the principal nutrients. The more complex model includes compartments representing the longer-term retention of carbohydrates as glycogen, fats as adipose tissue, and proteins in bone and soft tissue. The differences in the water and organic contents of tissues and organs and the different biokinetics for the different organic components were considered [R8, R9].

92. Melintescu et al. [M10] and Galeriu and Melintescu [G1] developed other physiologically based multicompartiment models where OBT exchange rates were associated with energy metabolism of major groups of human organs and tissues. Model predictions for HTO intake were successfully tested against available human data, e.g. from Trivedi et al. [T14]. Final model solutions were presented as dose coefficients for both HTO and OBT for all ICRP age groups separately for males and females and sex-average values.

93. Table 4 shows values of committed effective dose per unit intake for adults obtained from Richardson and Dunford [R8], an earlier paper of Richardson et al. [R6], other physiologically based models of Melintescu et al. [M10] and Galeriu and Melintescu [G1] and the corresponding values calculated using the ICRP models for HTO and OBT. The dose coefficients from the various studies are similar to the ICRP values [I17]. Richardson and Dunford [R8] also provided dose coefficients for tritiated nutrients, with the lowest value for tritiated carbohydrates equal to 3.3×10^{-11} Sv/Bq, which is 21% lower than the ICRP value for OBT, and the highest value for tritiated protein being 8.4×10^{-11} Sv/Bq, which is twice the ICRP value for OBT [I17, R8].

Table 4. Adult effective dose coefficients from physiologically-based biokinetic models and ICRP models for ingestion of HTO and organically bound tritium

<i>Biokinetic model</i>	<i>Dose coefficient (10^{-11} Sv/Bq)</i>
Ingestion of HTO	
ICRP [I14]	1.8
Richardson et al. [R6]	1.8 (males); 2.2 (females)
Melintescu et al. [M10]	1.7 (males); 2.4 (females)
Galeriu and Melintescu [G1]	2.0
Ingestion of OBT	
ICRP [I14]	4.2
Richardson et al. [R6]	4.2 (males); 6.1 (females)
Richardson and Dunford [R8] and ICRP [I7]	5.0–7.4
Melintescu et al. [M10]	3.9 (males); 5.7 (females)
Galeriu and Melintescu [G1]	4.9

94. Physiological models of OBT biokinetics proposed by Richardson et al. [R6] and Melintescu et al. [M10] provide sex- and age-differentiated biokinetics and dose coefficients. This analysis was based on estimates of daily intake rates of carbon in females (228 g carbon) and males (303 g carbon) and calculated biological half-times of carbon of 51 days and 40 days for female and male adults, respectively. Table 4 presents the dose coefficients from physiologically-based OBT biokinetic models by sex. The dose coefficient is higher in females by about 20–40% for HTO and up to 50% for OBT. Further, the authors state that the modelling of age dependence of the dose coefficients both for HTO and OBT is in good agreement with ICRP data [I17, M10].

5. Intake of tritiated biochemical substrates

95. Tritiated biochemical substrates, such as glucose, amino acids, hormones, and DNA and RNA precursors, are produced and widely used in biomedical research, leading to possible exposure by inhalation, skin contamination and possible inadvertent ingestion. A general metabolic feature is that such biochemical substrates may be directly incorporated into organic molecules in body tissue if absorbed to blood and transported intact to sites of active metabolism within cells. The extent of incorporation of tritium into specific forms of OBT is determined by such factors as the chemical compound containing tritium, its isomeric form, the position of the label in the molecule, and the amount of carrier [B11, B12, F2, L1, T2, T4, T8, T10]. Catabolism of labelled compounds will result in tritium being partially oxidized and entering the body water as HTO or catabolized and excreted as low molecular weight organic substances.

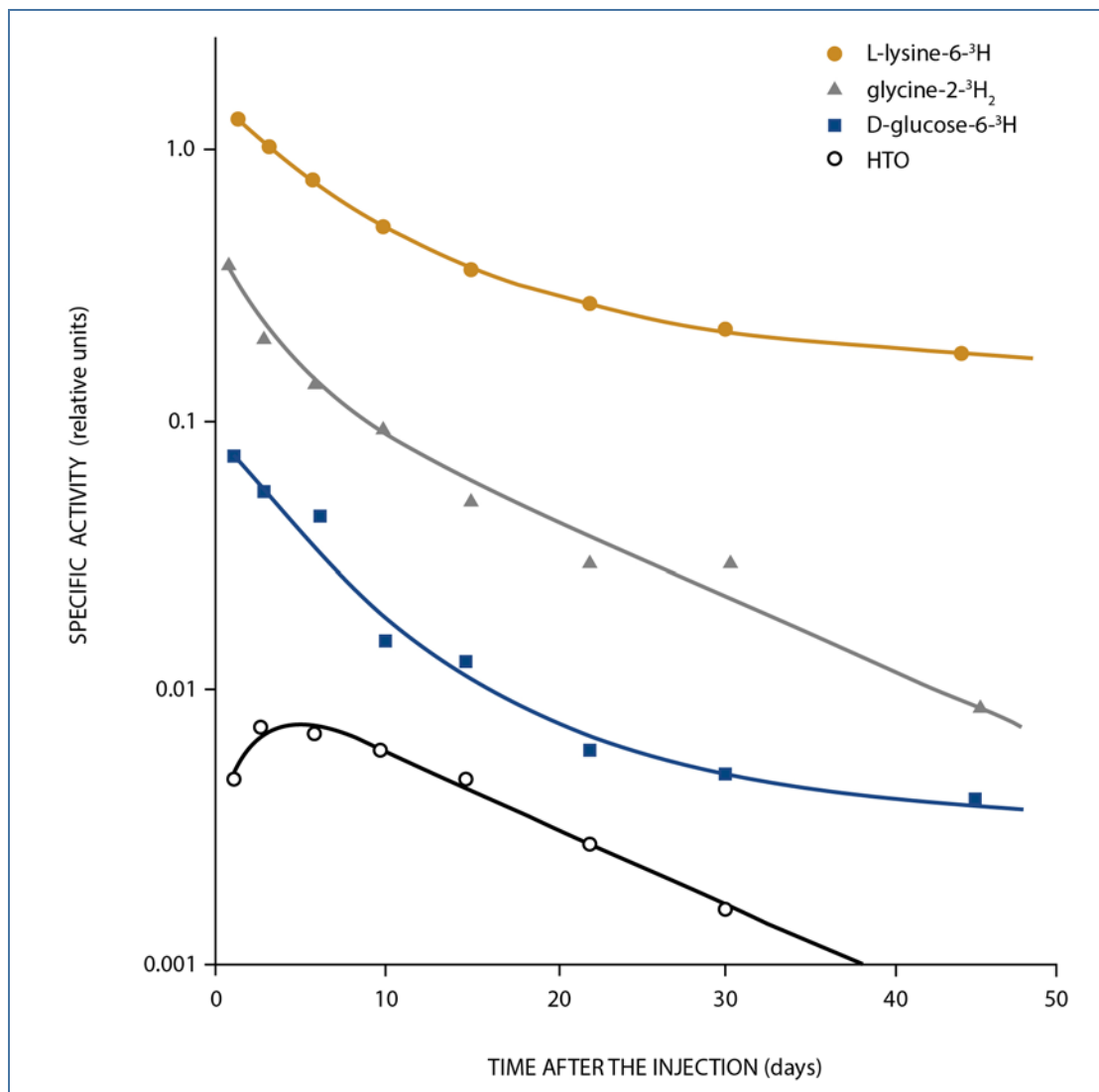
(a) *Tritiated glucose and amino acids*

96. Studies by Takeda [T2, T4] and Balonov et al. [B8, B11, B12], have shown that the bound fraction of tritium administered intraperitoneally to rats as biochemical substrates varied from 3–5% (tritiated D,L-alanine, glucose) to 50–80% (tritiated L-tyrosine, L-lysine). The bound fraction of tritium from tritiated biochemical substrates was substantially larger than that of HTO. The low retention of tritium as OBT after administration of tritiated glucose is consistent with its rapid catabolism while the high retention of tritiated lysine is consistent with its incorporation into protein as an essential amino acid.

97. Retention of tritium administered as the amino acids, glycine, leucine and methionine, was intermediate between that of glucose and lysine. D-isomers of ^3H -amino acids were assimilated considerably less than L-isomers. Thus, the level of binding of $^3\text{H}_2$ -L-leucine-2,3 in different tissues, except kidneys, was 2–2.5 times higher than that of the D-isomer, and 1.5–2 times higher than that of racemic mixture. Similar results were obtained with ^3H -lysine isomers [B8, B12].

98. Figure VII shows the retention curves for OBT in rat spleen after intraperitoneal injection of HTO and some biochemical substrates [B8, B12]. Tritium was rapidly excreted after administration of ^3H -glucose with a half-time of 3–4.5 days. Retention functions for the majority of ^3H -amino acids showed two components: one with a half-time from 0.7 to 2 days and the second with a half-time from 7 to 16 days, presumably reflecting metabolism of two groups of functionally different proteins. Retention times were shown to be tissue specific. In actively proliferating tissues—bone marrow, small intestine, testis—the observed kinetics of OBT is influenced by the processes of cell differentiation and movement of labelled cells out of the organ. Due to high demand for L-lysine in tissues and its reutilization, the kinetics of its excretion from tissues is slowed two–three-fold relative to other amino acids [B8, B12, T2, T4].

Figure VII. Specific activity of bound tritium in rat spleens normalized to intraperitoneally injected activity of tritium (per g of body weight) after injection of HTO, D-glucose-6- ^3H , glycine-2- $^3\text{H}_2$ and L-lysine-6- ^3H [B8, B12]



99. Table 5 presents estimated values of absorbed dose (D) in four organs and tissues and the contribution of OBT to dose for HTO and three biochemical substrates derived from the same studies of intraperitoneal administration to rats [B8, B12]. Injection of ^3H -glucose did not create a dose significantly higher than the dose from an equal amount of HTO, and differed only in the increased contribution to dose from OBT (7–23% against 2.5–4%). The dose following administration of ^3H -glycine was 5–40% greater than for HTO, and contribution of OBT to the dose reached about 20–40%. Notably, for administration of L-lysine- ^3H , the dose was two–eight times that for HTO, and the contribution from OBT was >90%.

Table 5. Absorbed dose, *D*, in rat organs and tissues (mGy) and OBT contribution to dose (%) after intraperitoneal injection of 37 kBq/g of HTO and tritiated biochemical substrates [B8, B12]

Organ, tissue	HTO		<i>D</i> -glucose-6- ³ H		Glycine-2- ³ H ₂		<i>L</i> -lysine-6- ³ H	
	<i>D</i> (mGy)	OBT (%)	<i>D</i> (mGy)	OBT (%)	<i>D</i> (mGy)	OBT (%)	<i>D</i> (mGy)	OBT (%)
Bone marrow	21	4	21	19	26	38	92	97
Small intestine	–	–	22	23	–	–	59	95
Testis	20	3	19	7	21	24	40	92
Muscle	20	2.5	–	–	28	43	150	98

100. Absorption coefficients for ingestion of and skin contamination by tritiated biochemical substrates were obtained in experiments in which preparations were administered to rats. The absorption coefficient was defined as the average ratio of OBT levels in tissue after ingestion or skin application to those after intraperitoneal injection. While ³H-glucose and ³H-amino acids were completely absorbed by the gastrointestinal tract [B12], absorption of ³H-thymidine was considerably lower (10–20%) because of its degradation to ³H-thymine in the gastrointestinal tract. In contrast, ³H-deoxycytidine was absorbed almost completely (60–100%). In rats fed HTO, tritiated amino acids, glucosamine, or tritiated DNA or RNA precursors for 22 days, the greatest concentrations of OBT were found after exposure to amino acids, with intermediate concentrations found after exposure to DNA and RNA precursors [T4]. Studies using rat everted gut sacs showed only about 2% of tritiated thymidine crossed the intestinal epithelium [L2].

101. During six hours after the application of preparations on rat skin, 1–4% of tritiated substrates were absorbed in blood, and 0.01–0.5% of tritium activity was measured in the skin layer at the place of application after its decontamination [B8, B12].

(b) Tritiated nucleic acid precursors

102. The DNA precursors, deoxythymidine and deoxycytidine labelled with tritium, have most commonly been used in studies of cell kinetics. For work involving RNA, tritiated uridine and adenine are the precursors that have been used [H16]. After tritiated thymidine has been orally administered to humans or animals, about 2% is incorporated into DNA during the synthesis stage of the cell cycle [L2], and the remainder appears as HTO. Tritiated thymidine is available for only a short time after intake and primarily for uptake by rapidly cycling cells such as those of the bone marrow or gut. However, prolonged administration of ³HTdR throughout gestation results in labelling of slower cycling cells [K11].

103. According to Feinendegen et al. [F5], nuclei of 5–30% of proliferating cells in mammals are labelled by tritium. As the average range of tritium beta radiation is considerably less than the dimensions of the nuclei of mammal cells, and distribution of DNA-bound tritium is extremely inhomogeneous both on the scale of organs and tissues and also within cells, the concept of the average organ or tissue dose in the case of incorporation of ³H-nucleosides requires care in its interpretation. An alternative is to estimate dose to radiosensitive nuclei in rare cases of tritiated DNA-precursor incorporation by workers.

104. Especially in embryo, ^3H -deoxynucleosides are actively included in intensively proliferating cell systems of bone marrow and small intestine, and considerably less in tissues with small frequency of mitoses (e.g. muscle, liver). A high concentration of ^3H -CdR in bone marrow of rats is noteworthy [B12], contrasting with lower values obtained in mice [F5]. The dose in cell nuclei of bone marrow labelled by ^3H -CdR estimated in studies by Balonov et al. [B8, B12] according to the methodology suggested by Feinendegen and Cronkite [F4, F5] is larger by two orders of magnitude than the average tissue dose from an equal amount of injected HTO.

105. Taylor [T10] reviewed the biokinetics of 11 xenobiotic tritiated organic compounds and estimated that the clearance half-time in humans was less than 40 days in all cases. Some organic compounds may be incorporated directly into structural components and retained for longer periods.

6. Metal tritides and other forms with low solubility

106. Tritiated compounds with low solubility include luminous compounds (powder and paint), tritides of metals (e.g. Ti, Zr, Hf), microfragments of glass and carbon and beryllium particles contaminated with tritium. Such compounds are produced and widely used in industry (painting wrist watches and compasses with luminous paint, ionization sources) and research (e.g. accelerator targets, tritium carrier in fusion physics). Tritiated compounds with low solubility are considered as sources of internal exposure in workplaces.

(a) *Metal tritides*

107. When tritides of metals (e.g. Ti, Zr, Hf) are used for industrial or research purposes, the tritium chemically bound in the crystal matrix is gradually desorbed from the metal surface in the form of HTO or HT. Due to external exposure of the device surface to radiation fluxes and heat, metal tritides can also be released into the work environment in particulate form. The main pathway of radiation exposure of workers dealing with devices containing metal tritides is the inhalation of HTO vapour and airborne particles of metal tritides.

108. Balonov et al. [B8, B11] reported that, following short-term inhalation by rats, titanium tritide (TiT) showed slow lung clearance during one month after exposure. Similar experiments of Cheng et al. confirmed slow clearance of a fraction of TiT (1 μm count median diameter (CMD)) after intratracheal instillation of TiT suspension into rats [C18, Z8]. Similar results were obtained in experiments on rats with hafnium tritide (1 μm CMD) [Z7] and zirconium tritide (0.3 μm CMD) [Z9]. The size of the slow cleared fractions and uptake rates of tritium dissolved from articles depend on the methods of TiT particle production and particle size.

109. In a series of in vitro experiments with powders of titanium, hafnium and zirconium tritides aimed at simulating time-dependent absorption functions of tritium in the respiratory tract of rats and humans, the dissolution of tritium in synthetic serum ultrafiltrate was studied during 30–200 days by Cheng et al. [C17, C19, Z9]. The dynamics of tritium release from particles was well described with two exponentials, one with a half-time in the range from one day (TiT) to about 50 days (HfT and ZrT) and the second with a half-time in the range from one month (TiT) to one year (ZrT) and several hundred years (HfT). The long-term dissolution half-time from coarse powder ($\sim 100 \mu\text{m}$) was larger than from fine powder ($\sim 1 \mu\text{m}$) [C17].

110. In vitro and in vivo experiments were complemented with dosimetric considerations of beta radiation self-absorption in particulate material [C19], which became important for particle sizes of 0.1 μm and more. From the available data, it was concluded that airborne ZrT and HfT should be considered in human internal dosimetry as material of slow solubility (ICRP Type S), and TiT as material of medium solubility (ICRP Type M).

(b) *Components of nuclear fusion reactors*

111. Tritium is present in nuclear fusion facilities in various physical and chemical forms, some of which have radiological properties different from HTO and HT. In the 1980s, features of tritiated microballoon glass fragments that could be potentially inhaled by workers were studied both in vitro and in vivo [C27, C28]. The median diameter of glass fragments was initially estimated to be about 4 μm but, accounting for fragment shape, the mass median diameter was specified as 20 μm . Experiments in vitro have shown that 98% of tritium is released from glass with a half-time of 3–9 days and 2% with longer half-time of 23–280 days. After intratracheal instillation of tritiated glass fragments in rats, 93% of the tritium activity was removed from glass with half-time of 6 ± 0.5 days and 7% with a longer half-time of 43 ± 3 days, consistent with the results of the in vitro study. The resultant dose to the lung was three orders of magnitude greater than the dose to other tissues, and approximately 40 times greater than the dose incurred in the lung from the inhalation of a similar quantity of HTO. However, because of the low inhalability of tritiated glass fragments of such sizes, this ratio would be much lower in a direct comparison of inhalation doses.

112. Since 1999, when the Joint European Torus (JET) fusion tokamak started its operation with tritium, tritiated dust and flakes were observed predominantly during maintenance operations. Those carbon, beryllium and tungsten particles were formed due to the interaction of plasma with the carbon-based first internal wall of the fusion reactor. The activity median aerodynamic diameter (AMAD) of the dust particles was assessed to be ~ 4 μm with high specific activities of up to 3 GBq/g and AMAD of flakes as about 100 μm [D4]. After inhalation, the former can deposit in different parts of the respiratory tract and expose its tissue to beta radiation. The in vitro dissolution tests with tritiated dust have shown that 1–5% of tritium activity was dissolved in lung serum simulant within one minute and a further 1–20% of tritium were dissolved over the next 100 days [H15]. Slow excretion of tritium deposited in lungs may complicate its individual monitoring [R13]. From the available data, it can be concluded that carbon and beryllium dust particles from fusion reactors can be classified as material of medium or slow solubility (ICRP Type M or S).

(c) *Luminous compounds*

113. The basis for self-luminous tritium paint is fine zinc sulphide powder (~ 10 μm) coated with a thin layer (0.01–0.1 μm) of tritiated polymer with high specific activities. In order to reach higher light intensities, tritiated polymers (polystyrene, silicon rubber) with specific activities up to 20 TBq/g have been used [B8, I3]. During the paint luminizing process, workers may be exposed to T₂, HTO, and vapours of tritiated organic solvents via inhalation and skin contact. Particles deposited in the lungs will irradiate tissues by emission of beta particles and bremsstrahlung. HTO and unknown organic compounds have been detected in urine [B8, R15], formed by degradation of polymers by radiolysis, oxidation and isotopic exchange.

114. In the past, some workers were exposed to high internal doses that were fatal in a few cases [M15, S12]. Lambert and Vennart have shown that radiological control in the workplace usually necessitates continuous biological monitoring of workers for tritium in urine at relatively short intervals [L5].

115. In vitro experiments have shown that 0.5–5% of tritium from tritiated polystyrene-based “Soviet luminous powder (PS-A)” was gradually released in buffer mixture as HTO and low molecular organic foreign compounds [B8, B11]. In vitro studies of the dissolution of commercial luminous powder made from tritium-labelled polystyrene in bovine serum over five days [R15] showed that an average of 12% dissolved on the first day, and about 2% of the remaining activity on subsequent days.

116. Similar uptake (0.5–5% depending on compound age) of both HTO and low molecular organic compounds was observed in experiments with PS-A luminous powder orally administered to rats and in a similar study with three volunteers [B8, B11]. Substantial fractions of the tritium compounds were rapidly excreted in urine and faeces of rats, a proportion was retained for some days in the liver/kidney, and the remainder was catabolized to HTO. The half-time of organic tritium in human urine was about one day and the remaining tritium was excreted as HTO with a mean half-time of about 16 days.

117. Experiments on cats showed that absorption of tritium from luminous paints depended on the plastic substrate involved, with values of 0.007 for polystyrene, about 0.03 for silicone rubber and 0.8 for polyester [H12, W6]. Balonov et al. [B8, B11] also reported that following intratracheal instillation of PS-A luminous powder into rats, the lung specific activity showed essentially no decrease within five months, demonstrating its very low solubility.

118. In summary, from the available experimental and human data, it can be concluded that the specific characteristics of tritiated luminous compounds differ substantially from those of HTO. Special attention should be paid to individual bioassay monitoring.

B. Overview of current biokinetic models for tritium

119. Tritium may enter the body by inhalation, absorption through skin, and ingestion. The first two are the more frequent routes of intake in the workplace, while the latter mostly contributes to exposure of members of the public. Furthermore, skin contact with tritium-contaminated surfaces, such as metal and glass, has been shown to result in the formation of OBT in the body [E1]. This has been shown to be a route of tritium intake in the workplace [H12].

120. The fate of tritium once taken into the body is determined mostly by its chemical form. One can expect to find HTO in most workplaces and environmental media where tritium is present. In general, consideration of the biokinetics of OBT refers to the non-exchangeable component resulting from tritium atoms bonding directly to carbon in organic molecules and exhibiting retention times relating to carbon turnover; the exchangeable component of tritium in organic molecules, in the form of hydroxyl and sulphhydryl groups, for example, has the same metabolism and distribution in the body as HTO.

121. Tritiated compounds may also exist as airborne particles, e.g. metal tritides or luminous powder. The retention and clearance of these particles from the respiratory tract depend on several factors, such as particle size and chemical composition. For dose assessment purposes, tritium absorbed into blood after tritiated particles have been inhaled is usually treated as being in the form of HTO [C18, C19, C20, I17].

122. Tritiated compounds are categorized by ICRP for radiation protection purposes according to the metabolic model that best describes their dynamics after intake and subsequent uptake. Three primary metabolic models are currently used by ICRP either separately or in combination to calculate committed effective dose for an intake of tritiated compounds [I8, I9, I10, I12, I14, I17]:

- (a) A model for tritium absorbed to blood as HTO following either ingestion or inhalation, applied also to other tritiated compounds that partially convert to HTO after being taken into the body;
- (b) A model for tritium absorbed to blood following intake of OBT, mainly by ingestion in food, but also applied to inhalation of non-specific organic molecules, and to ingestion or inhalation of some specific tritiated organic compounds;
- (c) The generic ICRP model for the human respiratory tract, specifying absorption parameter values for inhalation of poorly soluble forms of tritium.

123. All three models and respective sets of dose coefficients are widely used by the Committee in its main reports, by the IAEA in its international standards (e.g. [I4]) and also in documents of WHO [W7], FAO and the CODEX Alimentarius Commission [C24]. The ICRP models—and especially dose coefficients—are included in numerous national regulations on worker and public protection against internal exposure with different forms of tritium.

1. Dosimetry of tritium using model for HTO

(a) *Biokinetic model for HTO*

124. The ICRP biokinetic model for systemic HTO [I12, I14, I17], illustrated in figure VIII, is used to calculate the committed effective dose from:

- (a) Intakes of (HTO);
- (b) HTO formed following inhalation of elemental hydrogen (HT, T₂);
- (c) HTO formed following inhalation of tritiated hydrocarbon vapours and gases (e.g. CH₃T).

Use of this model involves assumptions about the conversion of the other forms of tritium to HTO.

125. For modelling HTO intake, an instantaneous translocation to blood is assumed for both inhalation and ingestion. The ICRP model further assumes that HTO is transferred from blood with a biological half-time of six hours and distributed uniformly throughout the body. It is also assumed that 97% remains as HTO, while 3% is instantly converted to OBT. In adults, HTO is assumed to be retained with a biological half-time of 10 days, and OBT with the biological half-time of carbon, calculated as 40 days (figure VIII). ICRP values for the partitioning between HTO and OBT after acute intake of HTO in various age groups, and the corresponding biological half-times, are given in table 6 [I12, I14, I17]. Age dependence of biological half-time for HTO was derived by ICRP from available human observations and physiological data [I7].

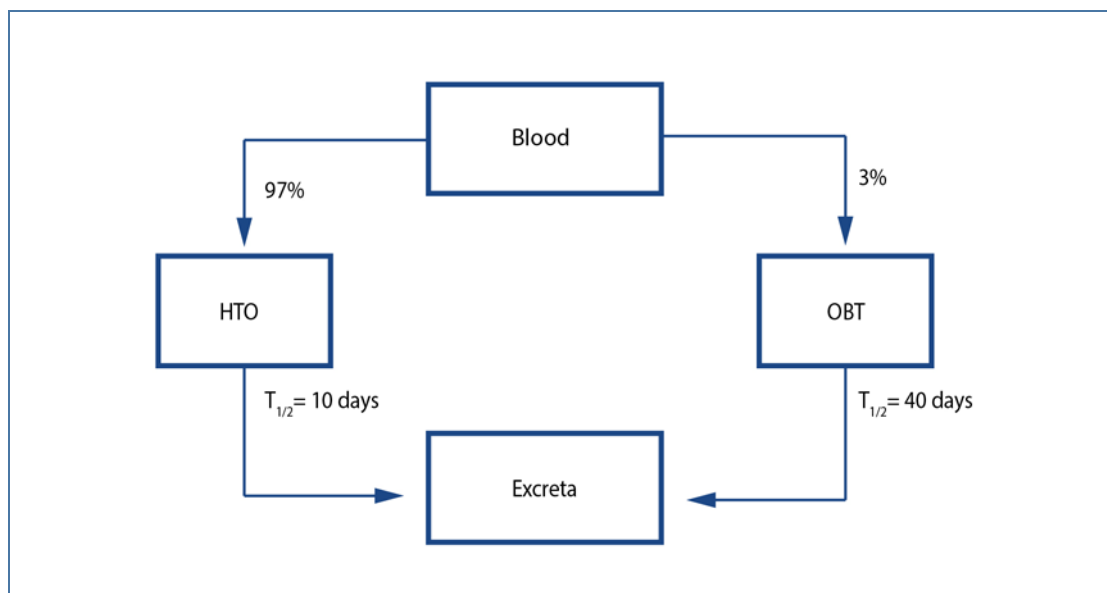
126. The calculation of committed effective dose per unit intake (dose coefficient) for adults resulting from the intake of HTO, as given by ICRP [I14, I17], is based on the model presented in figure VI. The current value for intake of HTO by adults both by inhalation and ingestion computed by ICRP is 1.8×10^{-11} Sv/Bq [I14, I15, I17].

127. The contribution of the OBT fraction to the committed effective dose in the HTO model has been shown to be about 10% [I8, I9, I10, J3]. This is adequate for estimates of dose from both acute and prolonged intake [T16].

Table 6. ICRP parameter values for distribution and retention of tritium after acute HTO intake [112, 114, 117]

Age	Initial distribution (%)		Biological half-time (days)	
	HTO component	OBT component	HTO component	OBT component
3 months	97	3	3.0	8
1 year	97	3	3.5	15
5 years	97	3	4.6	19
10 years	97	3	5.7	26
15 years	97	3	7.9	32
Adult	97	3	10.0	40

Figure VIII. ICRP model for biokinetics of HTO [112, 114, 117]



(b) Absorption of HTO through skin

128. Immersion in a vapour or liquid containing HTO also results in its absorption through the skin [D3, O6, P9]. In the context of occupational exposure to HTO vapour, ICRP [18, 19, 110] referred to the work of Osborne [O6], Hill and Johnson [H12], and the review of Myers and Johnson [M26] and concluded that about 1% of the HTO activity per cubic metre of air may be assumed to be absorbed through the skin in a minute. On this basis, the amount absorbed through skin contributes about one third of the total HTO intake for a given HTO concentration in air when the exposed individual is active during exposure (i.e. breathing in more air than when at rest). The work of Osborne [O6] was based on direct measurements of the absorption rate of HTO vapour through the skin of the whole body.

(c) Inhalation of tritium gas

129. Following inhalation of HT, a small fraction (about 0.01%) is dissolved in body fluids and oxidized to HTO [P4]. The latter is the predominant contributor to the committed effective dose. HT is not significantly absorbed through the skin and does not readily convert to HTO on the skin. Irradiation of the lungs by inhaled HT does not significantly increase the committed effective dose [I16] because of the short range of the tritium beta particles in lung tissue. The dose coefficient for inhalation of HT is therefore about 0.01% of the dose coefficient used for inhalation of HTO.

(d) Inhalation of tritiated hydrocarbons

130. Tritiated methane is the only tritiated hydrocarbon for which ICRP recommends a dose coefficient for inhalation based on the HTO model. Tritiated methane is known to be formed as a result of microbial degradation within tritiated waste. About 1% of the inhaled tritiated methane is assumed to be converted to HTO [P5]. The current ICRP dose coefficient for tritiated methane is therefore 1% of that for HTO [I17]. The ICRP approach is considered to give a conservative dose coefficient [P5].

131. Carlisle et al. reported in a more recent study on rats that the fraction of tritiated methane retained in the body as HTO and OBT after acute inhalation to be about 0.06 to 0.13%, which is lower than that assumed by the current ICRP model [C6]. However, the observed conversion of tritiated methane to OBT in rats was greater than that estimated by the ICRP model in all human tissue examined [I17], in particular in the liver, where the conversion was observed to be 22 times greater than that of HTO estimated by ICRP. The authors further suggested that some of tritium taken in as tritiated methane is converted directly to OBT. They concluded that the committed dose to some organs is one third to one tenth of that estimated by ICRP and that the ICRP value of effective dose may be conservative.

(e) Summary of dose coefficients based on HTO model

132. Table 7 presents the current ICRP committed effective dose coefficients for tritiated compounds based on the biokinetic model for HTO and table 8 illustrates the effect of age on the computed committed effective dose per unit intake for the inhalation of HTO [I17].

Table 7. ICRP effective dose coefficients based on HTO model for various tritiated compounds, modes of intake and age groups [I14, I17]

Tritiated compound	Mode of intake	Dose coefficient (Sv/Bq)	
		Infants (1 year old)	Adults
HTO	Inhalation	4.8×10^{-11}	1.8×10^{-11}
HTO	Ingestion	4.8×10^{-11}	1.8×10^{-11}
HT	Inhalation	4.8×10^{-15}	1.8×10^{-15}
CTH ₃	Inhalation	4.8×10^{-13}	1.8×10^{-13}

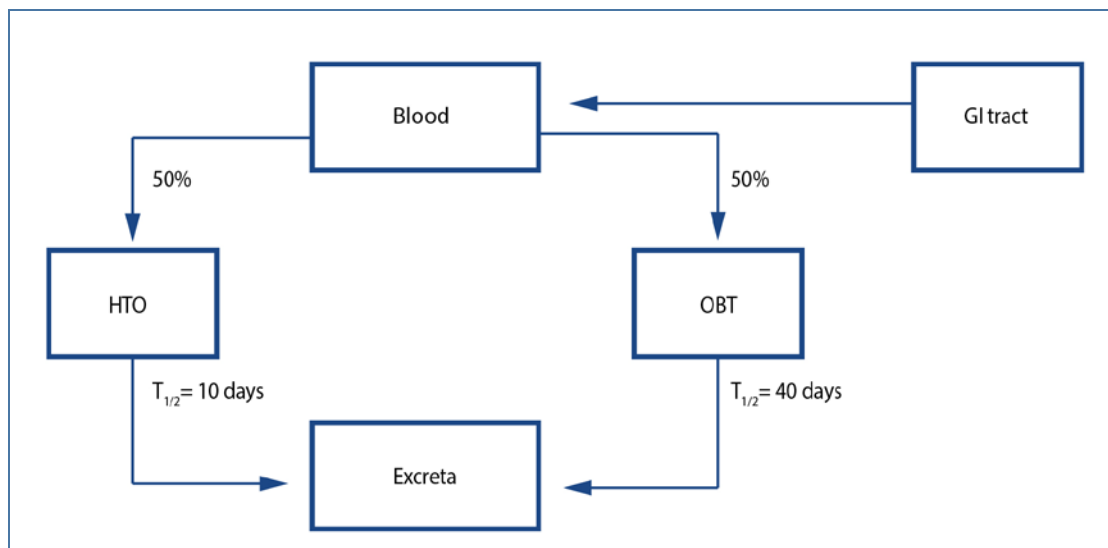
Table 8. ICRP effective dose coefficients for HTO inhalation by various age groups [I17]

Age	Dose coefficient (Sv/Bq)	Ratio of dose coefficient to that of an adult
3 months	6.4×10^{-11}	3.6
1 year	4.8×10^{-11}	2.7
5 years	3.1×10^{-11}	1.7
10 years	2.3×10^{-11}	1.3
15 years	1.8×10^{-11}	1.0
Adult	1.8×10^{-11}	1.0

2. Dosimetry of OBT and tritiated biochemical substrates using model for OBT

133. Figure IX illustrates the ICRP model [I14] used to calculate committed effective dose for the ingestion of OBT. It is assumed that OBT, once taken into the body, is translocated to blood completely and instantaneously, and is transferred from blood to tissue with a biological half-time of six hours, with 50% retained in tissue as OBT and 50% transformed into HTO. The uptake and retention of tritium in various tissues depends on the metabolic activity of the individual tissues and the constituent chemical forms of OBT. However, the ICRP model assumes uniform distribution of doses from OBT to all soft tissue in the body while a greater metabolic activity leads to greater uptake and more rapid loss.

Figure IX. ICRP model for biokinetics of OBT [I14]



134. The ICRP model for the ingestion of OBT [I12, I14] is intended to represent the biokinetics of the average dietary content of the different chemical forms of OBT. The model was developed in the absence of information about the exact proportions of the various chemical components of OBT in the human diet and the turnover of these components [I12, I14]. On the basis of the turnover of hydrogen in Reference Man, less than 10% of tritium taken in daily as OBT in diet is assumed to be excreted daily in the form of OBT (mostly in the form of urea, with about 3% in faeces) while the rest is assumed to be excreted as HTO [R8].

135. Table 9 gives the assumed partitioning between HTO and OBT and the corresponding biological half-times after dietary intake of OBT in various age groups [I14]. The ICRP committed effective dose coefficients for OBT are shown in table 10 [I17]. Table 11 shows the effect of age on the committed effective dose per unit intake for the ingestion of OBT.

136. The ICRP model for OBT and relevant dose coefficients can also be used for prospective dose assessment in cases of intake of tritiated biochemical substrates if more specific biokinetic information is not available. For most biochemical compounds, this approach will lead to some overestimation of effective dose [T10]. Considering a range of biochemical compounds for which biokinetic data are available from animal experiments, only the essential amino acid, L-lysine-³H, resulted in estimated tissue doses greater than those for HTO (by a factor of 2–8) [B11, B12, T2].

137. The ICRP model for OBT and the corresponding dose coefficients are not applicable for dose assessments in cases of occupational intake of tritiated nucleic acid precursors. After tritiated DNA-precursors are taken in by humans or administered to animals, some fraction of tritium is incorporated into DNA during the synthesis stage of the cell cycle [L3], and the remainder appears as HTO or metabolized biochemical substrates. As distribution of DNA-bound tritium and its radiation energy is extremely inhomogeneous in organs, tissues and inside cells, the concept of average organ or tissue dose in this case requires careful consideration. An alternative approach is to calculate dose taking the localization of tritium in cell nuclei into account [F2, F3, F4, F5, N1].

138. The National Council on Radiation Protection and Measurements (NCRP) [N1] examined the absorbed dose resulting from the ingestion of ³HTdR based mainly on theoretical considerations. For acute intake, it concluded that the absorbed dose to stem cells and bone marrow (per unit intake) resulting from the ingestion of tritiated thymidine is greater by an order of magnitude than that resulting from the ingestion of HTO. This conclusion may need to be revised when additional data on stem cells and ³HTdR distribution and incorporation rates become available. It was noted that biokinetics of tritiated nucleic acid precursors is strongly dependant on mammal species [B11, B12]. Without appropriate human biokinetic data, the modelling uncertainty remains unspecified.

Table 9. Partitioning between HTO and OBT after dietary intake of OBT [I14]

Age	Initial distribution (%)		Biological half-time (days)	
	HTO component	OBT component	HTO component	OBT component
3 months	50	50	3.0	8
1 year	50	50	3.5	15
5 years	50	50	4.6	19
10 years	50	50	5.7	26
15 years	50	50	7.9	32
Adult	50	50	10.0	40

Table 10. ICRP effective dose coefficients based on OBT model for various modes of intake and age groups [I17]

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

Table 11. ICRP effective dose coefficients for OBT ingestion for various age groups [I17]

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

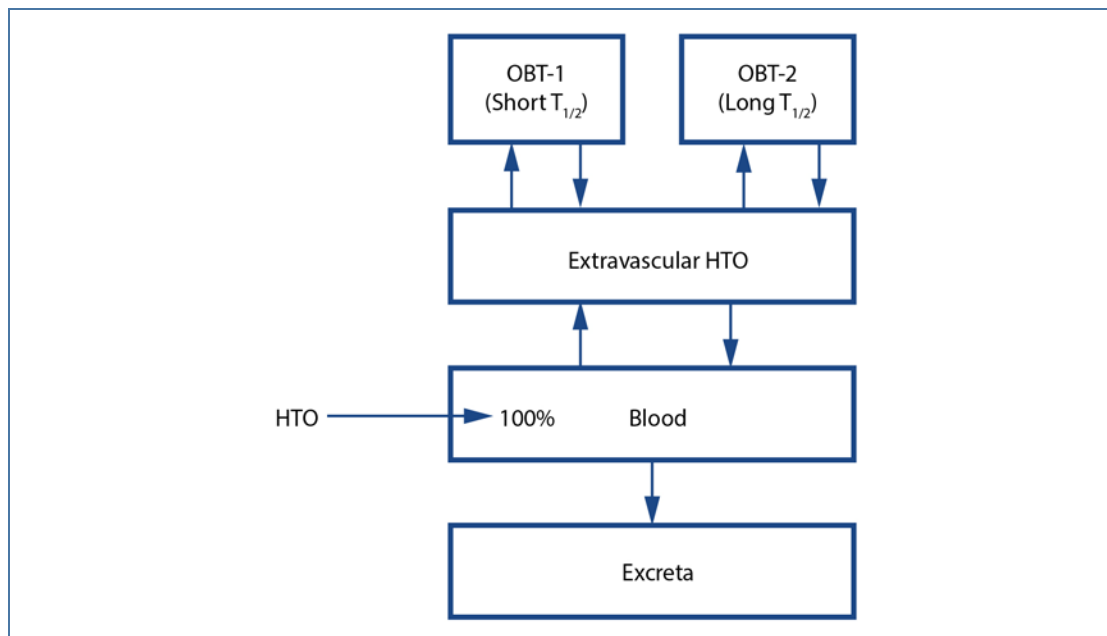
3. Revised ICRP dosimetry models for HTO and OBT

139. ICRP has developed revised models with improved physiological realism focussing on occupational intakes of radionuclides. Intakes by members of the public will be considered by ICRP at a later stage.

140. The HTO systemic model includes compartments representing blood, extravascular body water that exchanges rapidly with blood, and two components of retention of tritium converted in vivo to OBT. The revised ICRP model structure is shown in figure X. The transfer coefficient from blood to excreta is set to yield an initial removal half-time from the body of 10 days. The transfer coefficients from compartments OBT-1 and OBT-2 back to extravascular HTO correspond to half-times of 40 days and one year, respectively; the net retention half-times in these compartments are slightly longer than 40 days and one year due to recycling of activity. Excretion pathways from blood are not shown in figure X but the following division is assumed on the basis of reference data for water balance ICRP Publication 89 [I19]: urine, 55%; faeces, 4%; exhalation, 12%; and loss through skin (sweat plus insensible loss), 29%.

Figure X. Revised ICRP systemic model for HTO

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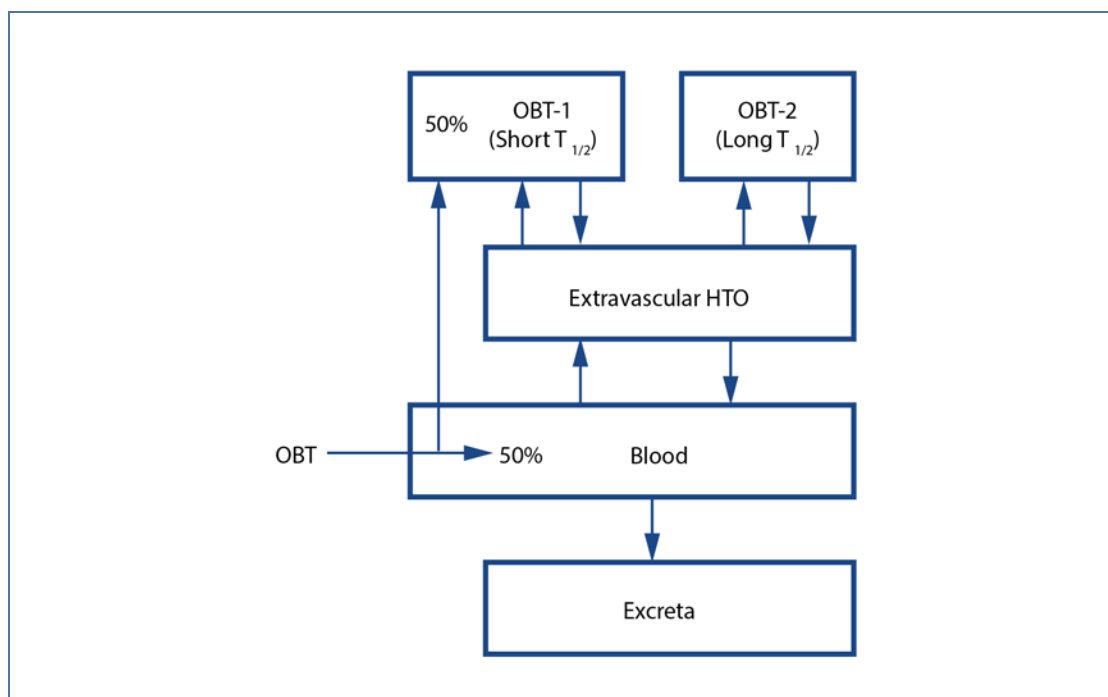
141. The revised model for systemic tritium applied to intake of OBT is a modification of the model for OBT applied in ICRP Publication 56 and is shown in figure XI. In relation to occupational exposures, this model is assumed to apply to “biogenic organic compounds” of tritium for which specific information is not available. It is assumed that 50% of tritium initially entering blood transfers immediately to compartment OBT-1 and 50% is converted immediately to HTO within the blood compartment. Tritium entering OBT-1 or blood subsequently follows the HTO model defined in figure X.

142. The revised model for HTO predicts that OBT would represent about 5–6% of total body tritium following chronic exposure to HTO. The OBT model with the default initial division of activity between OBT-1 (50%) and blood (50%) predicts that OBT would represent about 65–70% of total-body tritium in a worker who is chronically exposed to a biogenic form of tritium. The adult dose coefficient calculated using the revised model for HTO is 1.9×10^{-11} Sv/Bq compared with the current value of 1.8×10^{-11} Sv/Bq. Values for intakes of biogenic organic compounds are given as 3.5×10^{-11} Sv/Bq for inhalation (Type F) and 5.1×10^{-11} Sv/Bq for ingestion (complete intestinal absorption, $f_A=1$). The value for ingestion compares with the current value for OBT of 4.2×10^{-11} Sv/Bq.

143. The ICRP will also publish revised dose coefficients for inhaled tritiated methane and particulate forms for which the HTO systemic model is applied. The revised value for inhalation of tritiated methane by adults is 5.8×10^{-14} Sv/Bq compared with the current value of 1.8×10^{-13} Sv/Bq, reflecting the assumption of 0.3% deposition and absorption to blood as HTO compared with 1% in the current model. Revised values for inhaled particulate forms are 1.3×10^{-11} Sv/Bq for Type F and 2.4×10^{-11} Sv/Bq for Type M, compared with current values of 6.2×10^{-12} Sv/Bq and 4.5×10^{-11} Sv/Bq, respectively. The value for Type S materials is unchanged at 2.6×10^{-10} Sv/Bq.

Figure XI. Revised ICRP systemic model for OBT

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4. Dosimetry of tritiated compounds using model for low solubility particulate tritium

144. Dose coefficients for inhaled particulate tritium were introduced by the ICRP Publication 71 [I17] in 1995 following publication of a number of scientific papers in which those forms of tritium were identified and partially characterized [B8, B11, H12, I3, R15, T8, W6]. The papers described conditions of occupational exposure in research and industry during contact of workers with neutron generators and particle accelerators and with luminous powder.

145. Calculation of dose coefficients for particulate tritium was based on the generic ICRP model of the respiratory tract [I16], categorizing tritium aerosols according to the absorption types specified in the model, i.e. fast (F), medium (M) and slow (S). It was assumed that: (a) beta radiation of tritium located in the alveolar part of the respiratory tract was fully absorbed in lung tissue, and (b) tritium separated from the particles deposited in the respiratory tract, due to both fast and slow processes, behaved as HTO. Therefore, the ICRP generic lung model was combined with the specific ICRP model for HTO (see figure VIII). The clearance of tritium from the respiratory tract following deposition of tritium particles included the escalation of particles through the bronchial tree to the alimentary tract and dissolution and absorption to blood as HTO.

146. Data on the metabolism of inhaled particles of metal tritides are scarce [B8, B11, C17, C18, C19, C20]. In the absence of specific information, ICRP has considered these particles as Type M [I17], meaning that their rate of absorption from the respiratory tract to blood is moderate. Richardson and Hong [R7] conducted dosimetric modelling of inhaled tritiated particles and reported that, while the

dose to the alveole can be up to two orders of magnitude higher than that from the same activity of inhaled HTO, taking account of self-absorption of beta radiation in particulate material can reduce dose by up to an order of magnitude, depending on particle size, in the range of 0.1–10 µm.

147. Following inhalation of tritiated organic compounds such as luminous ones, uptake of HTO is accompanied by uptake of low molecular compounds of tritium originating from degradation of tritiated polymer. The contribution of the tritiated low molecular compounds to the effective dose is generally low because of their rapid excretion in urine and faeces. However, these elevated concentrations of organic compounds of tritium in excreta should be recognized when interpreting the results of individual monitoring.

148. The available dose coefficients for particulate tritium are applicable mostly for occupational radiation protection of workers in research and industry dealing with neutron generators, particle accelerators, and air ionizers and the manufacture of luminous products. However, for the substantially lower probability of exposure of members of the public, ICRP has provided committed effective dose coefficients for different age groups (table 12).

Table 12. ICRP effective dose coefficients (Sv/Bq) for inhalation of particulate tritium of various types [17]

Age	Type F	Type M	Type S
3 months	2.6×10^{-11}	3.4×10^{-10}	1.2×10^{-9}
1 year	2.0×10^{-11}	2.7×10^{-10}	1.0×10^{-9}
5 years	1.1×10^{-11}	1.4×10^{-10}	6.3×10^{-10}
10 years	8.2×10^{-12}	8.2×10^{-11}	3.8×10^{-10}
15 years	5.9×10^{-12}	5.3×10^{-11}	2.8×10^{-10}
Adult	6.2×10^{-12}	4.5×10^{-11}	2.6×10^{-10}

149. Dose coefficients for Type F aerosols are lower than those for HTO despite the assumption of rapid dissolution and absorption of deposited particles. This is because a proportion of inhaled particles is subsequently exhaled while deposition of inhaled HTO vapour is assumed to be complete. The main contribution to effective dose from inhalation of Type M and S aerosols is from lung dose. The dose coefficients presented in table 12 can be applied for internal dose assessment in cases of inhalation of various airborne tritium particles, e.g. metal and graphite tritides and iron hydroxide used in tritium facilities, luminous powder and other particulate forms.

C. Intakes of tritium in relation to pregnancy and breast-feeding

1. Pregnancy and tritium intake

150. A few studies have investigated the transfer of tritiated compounds to the embryo and fetus and their distribution and retention in fetal tissues. In prenatal dosimetry, the term embryo refers to the developing human offspring up to the end of the eighth week of pregnancy, from the initial stages of growth up to the end of organogenesis. At this time, the embryo weighs less than about 10 g.

151. Harrison et al. [H6] measured the transfer, distribution and retention of tritium in rats and guinea pigs following the administration of HTO, tritiated glucose and tritiated food (i.e. liver and cress). Transfer and retention of tritium in fetal tissue were similar for HTO and tritiated food. However, the retention of tritium in both maternal and fetal tissue for tritiated glucose was lower. The ratio of the concentrations of tritium in the fetus (C_F) to that in the mother (C_M) at the end of organogenesis in rats ranged from 0.4 to 1.0. At the end of pregnancy, the ratio ranged from 1.3 to 1.5 in the case of rats and from 1.1 to 1.3 in the case of guinea pigs.

152. Takeda et al. [T5] exposed female rats to single oral administrations of HTO, tritiated thymidine or tritiated lysine. No significant differences were observed between the tritium concentrations in the fetus and in maternal tissue. Tritium concentrations in the fetus were greater following the ingestion of tritiated lysine than following the ingestion of HTO or tritiated thymidine. Tritiated lysine also resulted in greater prenatal and neonatal absorbed doses than tritiated thymidine and HTO by factors of 1.5 (when tritium was administered on the thirteenth day of gestation) and 6 (when tritium was administered on the first day of nursing).

153. Pietrzak-Flis et al. [P7] studied tritium incorporation in rats chronically exposed to tritiated food (activity concentration, 48.1 kBq/g) or HTO (activity concentration, 37.0 kBq/mL) for three successive generations (from three weeks before mating of the parents to the delivery of the F3 generation). The analysis of tissue at various ages showed that the absorbed dose rates were higher in rats exposed to HTO. However, the amount of tritium incorporated into the organic fraction of tissue was several times higher after exposure to tritiated food.

154. Kowalska [K22, K23] reported further results from the same study showing that the amount of tritium incorporated into the amino acids of rat-brain proteins and the main rat-brain phospholipids and gangliosides was higher after the ingestion of tritiated food than after the ingestion of HTO. The highest tritium concentrations in rat-brain proteins followed in utero exposure while the highest tritium concentrations in phospholipids and gangliosides were found in 21-day-old rats exposed during pregnancy and lactation.

155. The ICRP Publication 88 [I18] has provided biokinetic and dosimetric models and dose coefficients for the embryo, fetus and newborn as a result of intake of radionuclides by the mother. The term fetus refers to the developing human offspring after the eighth week of pregnancy [I18]. The equivalent dose to the embryo is assumed to be the same as that to the uterus wall and proportional to the concentration of HTO in maternal body water. For the calculation of the equivalent dose to the fetus, the HTO concentration in fetal body water was assumed to be equal to that in the mother. The ICRP uses a simple approach to the calculation of fetal doses for the majority of elements and their radioisotopes, including tritium, considering data collected from studies of animals and humans [I18, I21]. These fetal doses from tritium are calculated on the basis of relative concentrations of tritium averaged over the whole body of the fetus (C_F) and that of the mother (C_M). The $C_F:C_M$ ratios are taken mainly from studies presenting data obtained at short times post-intake.

156. HTO rapidly crosses the placenta after it is inhaled or ingested by the mother. The resulting equivalent dose to the fetus depends on the water content of the fetus over the course of its development. As gestation progresses, the water content decreases relative to the amounts of protein, fat and minerals—from about 95% of the total body mass at the sixth week of pregnancy to about 70% at birth. For comparison, the percentage of total body water in a non-pregnant woman is about 50%. The total water content of the mother's body is known to increase during pregnancy. This is mainly due to the increase of about 50% in the blood volume in order to carry additional nutrients and other substances needed for the fetus. Calculations have shown that the biological half-time of HTO in the

mother varies from about 10 days at the start of pregnancy to about 12 days at term. This variation does not significantly affect the ICRP fetal dose coefficients for HTO [I18].

157. On the basis of an average body water content of 80% for the fetus and 50% for the mother, ICRP used a $C_F:C_M$ ratio of 1.6 in the derivation of the dose coefficients for HTO. This ratio is applied to both the HTO and OBT components for intake of OBT and is assumed to remain constant throughout pregnancy. Tritium is assumed to be uniformly distributed throughout all tissues of the fetus. Harrison et al. [H7] showed that the $C_F:C_M$ ratio ranged from about 1.4 to 1.8, on the basis of data for the relative water content of the mother to that of the fetus.

158. Following birth, the ICRP biokinetic model for the three-month-old infant [I18] is used to calculate the committed effective dose per unit intake by the newborn child. Table 13 presents the committed effective dose coefficients for the unborn and the three-month-old child. The ICRP [I18] has published a range of dose coefficients for in utero exposure of the child following maternal intake by inhalation or ingestion, before or during pregnancy, considering acute and chronic exposure. Account is taken of the retention of activity in body tissue at birth and dose delivered post-natally. The purpose of the ICRP fetal dose coefficients is to allow comparison with doses to other age groups in order to ensure that protection does not neglect doses received in utero [C29, I22].

Table 13. ICRP prenatal and infant effective dose coefficients [I18]

Tritiated compound and mode of intake	Prenatal dose coefficient (Sv/Bq)		Dose coefficients for 3-month-old child (Sv/Bq)
	Acute maternal intake ^a	Prolonged maternal intake ^b	
HTO inhalation	3.6×10^{-11}	3.1×10^{-11}	6.4×10^{-11}
HTO ingestion	3.6×10^{-11}	3.1×10^{-11}	6.4×10^{-11}
OBT ingestion	7.6×10^{-11}	6.3×10^{-11}	1.2×10^{-10}

^a Values are for acute intake by the mother at the end of the tenth week of pregnancy. Acute intake occurring at other times yields lower dose coefficients.

^b Prolonged intake by the mother, beginning at the start of pregnancy and continuing for the duration of the pregnancy.

2. Intake of tritium from maternal milk

159. The ICRP [I21] has developed dose coefficients for newborns for intake of tritium from maternal milk. The approach involved the estimation of the activity transferred to milk as a function of maternal intake for various intake scenarios (acute or prolonged intake regimes, and for various maternal intake times relative to birth). Nursing was assumed to continue for six months after birth, and the ingestion dose coefficients for infants were applied [I14]. Maternal intake (by ingestion and by inhalation) during pregnancy and during lactation was considered.

160. The HTO and OBT models were modified by ICRP [I21] to account for the transfer of tritium to milk fed to infants (up to one year). The rate of OBT transferred to milk was taken to be that of carbon. The ICRP developed dose coefficients on the basis of the assumption of six feeds per day and an average daily milk intake by the infant of 0.8 L. Table 14 shows selected committed effective dose coefficients for nursing infants resulting from maternal intake of tritium.

Table 14. ICRP effective dose coefficients for nursing infant [I21]

Tritiated compound and mode of intake	Dose coefficient (Sv/Bq)	
	Acute maternal intake ^a	Prolonged maternal intake ^b
HTO inhalation	2.2×10^{-11}	2.0×10^{-11}
HTO ingestion	2.2×10^{-11}	2.0×10^{-11}
OBT ingestion	3.5×10^{-11}	3.0×10^{-11}

^a Values are based on acute maternal intake at one week after birth. Acute intake occurring at other times yields lower dose coefficients.

^b Values are based on prolonged intake during the lactation period (up to six months after birth). These dose coefficients are greater than those for prolonged intake during pregnancy.

D. Uncertainties in dose coefficients for tritium

161. Dose coefficients applied for assessment of internal dose for purposes of human radiation protection are defined by ICRP as regulatory parameters without any uncertainty [I23]. They are presented in ICRP publications for reference persons [I7, I19] as values depending on the radionuclide, its physical and chemical form, exposure pathway (inhalation or ingestion) and a person's age [I12, I14, I15, I17, I18, I21]. Uncertainties of ICRP dose coefficients for some radionuclides, including tritium as HTO, are systematically considered in a specific NCRP publication [N4] and by Leggett et al. [L8]. The need for individual values of metabolic parameters arises mostly in cases of emergency intake of large radionuclide activities when probabilities of radiation-induced acute health effects and risk of stochastic effects require consideration on an individual basis in the context of possible decorporation or other medical treatment.

162. For the most common form of tritium, HTO, dose coefficients for adults are determined on the basis of numerous human observations and are, therefore, associated with low uncertainty. Greater uncertainties apply to dose coefficients for children exposed to HTO from the environment. Leggett et al. [L8] considered the sources, quality and completeness of data underlying the biokinetic models for tritium (as HTO) and concluded that the dose coefficient for HTO is known within a factor of two for an adult and between a factor two and three for a five-year-old child.

163. Exchange model parameters for HT inhalation are also derived from human observations, which can generate moderate uncertainty of corresponding dose coefficients. More uncertain are dose coefficients for OBT based on animal experiments and modelling and for tritium aerosols of various types based on both in vitro and in vivo animal experiments [P4, P9].

164. Harrison et al. [H7] reviewed the assumptions used by ICRP in the derivation of dose coefficients for tritium along with their associated uncertainties. The assumptions considered were those related to absorption to blood, the biological half-time of HTO and OBT in adults and children, the transfer to the fetus, the heterogeneity of the distribution in tissues and cells, and the RBE value of the beta particles emitted by tritium.

165. Harrison et al. [H7] estimated uncertainties using ranges on the central values for the incorporation of tritium into OBT in body tissue of 0.01–0.1 and 0.15–0.75 of the tritium activity reaching blood after intake as HTO and OBT, respectively. Biological half-times in adults were taken to vary from about 5 to 20 days for HTO and from about 20 to 200 days for OBT, these ranges being

the 2.5 and 97.5 percentiles of the log-normal distributions. They also considered $C_F:C_M$ ratios ranging from 1.4 to 1.8 based on the relative content of water in the mother and the fetus. The 2.5 and 97.5 percentiles of the log-normal distribution for the OBT transfer and distribution in fetal tissue were taken to be 1.2 and 2. A range of 1–2.5 was used for the RBE value of tritium beta particles compared to gamma rays. This analysis gave median (50%) values for the dose coefficient of 2.3×10^{-11} Sv/Bq for HTO and 5.6×10^{-11} Sv/Bq for OBT for ingestion or inhalation by adults, excluding consideration of RBE value. Table 15 shows probability distributions of the committed effective dose coefficients for adults and for the fetus after ingestion by the mother during pregnancy, including the range of RBE values. Dose coefficients for other age groups were estimated to vary by a factor of two to three for HTO and OBT.

Table 15. Probability distributions of effective dose coefficients from ingestion of HTO or OBT by adults and for fetus after ingestion by mother during pregnancy [H7]

Intakes during pregnancy assumed to take place at 10 weeks after conception

Age	Form	Distributions of effective dose coefficients (10^{-11} Sv/Bq)		
		5 percentile	50 percentile	95 percentile
Adult	HTO	2.1	3.9	6.6
	OBT	3.9	8.7	20
Fetus	HTO	3.7	7.6	14
	OBT	6.9	17	40

166. Hamby [H2], using Monte Carlo sampling, calculated that the dose coefficient for intake of HTO by adults varied by a factor of 15 from its highest to lowest modelled values, with a median value of 2.2×10^{-11} Sv/Bq and a geometric standard deviation of 1.6. This range was most sensitive to the biological half-time, the linear energy transfer (LET), and the reference radiation (i.e. whether X- or gamma radiation). When the quality factor was set to unity, the geometric mean of the dose coefficient was 1.3×10^{-11} Sv/Bq with a geometric standard deviation of 1.4.

167. Melintescu et al. [M10] also assessed the effect of uncertainty on the RBE value of the tritium beta radiation, the retention of HTO and OBT and the presence of tritium in the DNA hydration shell. For the adult male, setting the radiation weighting factor to unity (based on the RBE value) resulted in dose coefficients ranging from 1 to 2.9×10^{-11} Sv/Bq for the intake of HTO and from 5 to 6.7×10^{-11} Sv/Bq for the ingestion of OBT. Accounting for the variability in the radiation weighting factor, the resulting dose coefficient range was from 1.5 to 5.1×10^{-11} Sv/Bq and 5 to 11.3×10^{-11} Sv/Bq for HTO and OBT, respectively. Similarly, the dose coefficient for a one-year-old was found to vary from 2.9 to 6.6×10^{-11} Sv/Bq and 14 to 18×10^{-11} Sv/Bq for HTO and OBT, respectively, when the radiation weighting factor was set to unity.

E. Summary of biokinetic and dosimetric models

168. HTO behaviour following intake into the mammalian body is well understood with regard to both early distribution in the body followed by excretion as part of water exchange (half-time of adult humans 4–18 days) and simultaneous conversion of a small fraction (of the order of 1%) of tritium into OBT with subsequent longer term excretion (half-time of adult humans 23–104 days). The average contribution of OBT to effective dose of adults derived from 17 human observations was 3.0%. The

data on longer term processes with half-times of more than 100 days are highly uncertain and need further study. The ICRP biokinetic model for HTO for all age groups is moderately conservative, with an OBT contribution to dose equal to 9% for adults. The biokinetics of HT following inhalation is also well understood. However, the current ICRP model considers only HTO formed in vivo and does not take account of an additional component of dose to cells of the alveolar-interstitial region of the respiratory tract.

169. The ingestion of food containing OBT by members of the public results in the degradation of a substantial fraction of the OBT to HTO in the gastrointestinal tract and in body tissue by catabolic reactions, and uptake and conversion of the rest of the OBT into tissue macromolecules. Both the fractions and subsequent excretion rates of OBT from tissue depend on food origin and composition. The ICRP model for OBT ingestion by humans is generally consistent with experimental results. However, it does not consider the non-uniform deposition of OBT between various organs and tissues. Physiologically-based OBT models, such as the ones proposed by Richardson and Dunford [R8] and Galeriu and Melintescu [G1], consider non-uniform deposition. Dose coefficients calculated using these models are generally similar to ICRP values.

170. Tritiated biochemical substrates, such as glucose, amino acids, hormones, DNA and RNA precursors, may be directly incorporated into organic molecules in body tissues if absorbed to blood and transported to sites of active metabolism within cells. The extent of incorporation of tritium into specific forms of OBT is determined by such factors as the chemical compound containing tritium, its isomeric form, position of the label in the molecule, and the amount of carrier. OBT formed from tritiated precursors of biological macromolecules is retained in tissue longer than HTO. Catabolism of labelled compounds will result in tritium being partially oxidized and entering the body water as HTO or catabolized and excreted as low molecular weight organic substances. Following intake of tritiated precursors of biological macromolecules, the internal dose to mammal tissue is usually up to ten times larger than the dose from intake of an equal amount of HTO, and the contribution of OBT to dose may dominate.

171. Labelled DNA precursors (e.g. ^3H -thymidine, ^3H -deoxycytidine) entering the mammalian body by various routes are partially degraded to HTO and partially incorporated into the DNA of dividing cells, and thereafter selectively expose nuclei of proliferating cells to beta radiation. ^3H -deoxynucleosides are preferentially incorporated into the proliferating cell systems of embryo and fetus, bone marrow and small intestine at any age and, to a substantially lesser extent, in tissue with lower frequencies of mitoses (e.g. muscle, liver). For both acute and prolonged intake of tritiated DNA precursors, the absorbed dose to nuclei of proliferating cells may be larger by one to two orders of magnitude than the dose from intake of equal amounts of HTO. As the average range of tritium beta radiation is considerably less than the dimensions of the nuclei of mammal cells, the use of average organ or tissue dose in the case of incorporation of ^3H -nucleosides requires careful consideration. The ICRP dose coefficients for OBT should not be directly applied to intake of tritiated DNA precursors.

172. Tritium particles of low solubility (e.g. metal tritides, luminous powder) inhaled by workers in occupational conditions partially deposit in the respiratory tract and may be retained in the lungs for long periods. Material-specific labile fractions of tritium segregate from particles as HTO or as organic molecules that are absorbed to blood and excreted. Effective doses from inhalation of low soluble tritium particles can be assessed by means of the ICRP human respiratory tract model combined with the HTO model. Tritium as HTO or biochemical substrates is easily transported through the placenta to the embryo and fetus and secreted in maternal milk. In conditions of chronic tritium intake by the mother, committed internal doses incurred by the embryo and fetus and by the suckling infant correlate with the dose of the mother and are not substantially different in magnitude.

VI. BIOLOGICAL AND HEALTH EFFECTS

A. Non-radiological effects of tritium in biological systems

1. Transmutation

173. Transmutation is the conversion of one element into another through radioactive decay. When tritium undergoes decay, it becomes helium-3 (^3He), a stable, inert gas. Helium is chemically very different from hydrogen and, therefore, this could make a significant contribution to the effect of tritium when organically combined. If a tritium atom is bound to a DNA molecule when it decays, most of the kinetic energy will accompany the beta radiation as it is ejected from the nucleus, but some energy will provide a kick-back to the ^3He atom as recoil energy. Kacena [K1] determined that the recoil energy was too small (up to 3 eV) to cause ionization of the DNA molecule on its own. However, the resultant ^3He atom would break free from the DNA molecule. In complex molecules, the effect of this conversion to a positively charged carbonium ion would be difficult to distinguish because of the proximity to the deposition of energy and associated events from the beta emission.

174. Myers and Johnson [M26] and Gracheva and Korolev [G8] performed comprehensive reviews of transmutation effects. They noted that the degree of damage caused by transmutation of tritium into helium could theoretically vary significantly, depending on the position of the tritium atom in specific DNA nucleotides. The studies covered several test systems in the S13 virus, in two strains of the bacterium *E. coli*, in *Drosophila Melanogaster* (fruit fly) and in cultured mammalian cells. On the basis of the position of the tritium in the nucleic acid, varying degrees of damage were observed in experiments. The most pronounced mutagenic effect was detected with cytosine-5- ^3H , which in the case of tritium decay converted to uracil. In some simple biological systems (virus, *E. coli*), that transmutation resulted in an elevated mutation rate that was 3–400 times larger than the mutation rate caused by beta radiation only [G8]. The reviewers argued, however, that the increase in the mutation rate in mammals (resulting from transmutation) would not likely exceed 5% of the normal rate and that this was too small to be detected.

175. Carsten [C11] discussed the possibility that such effects would be manifest in humans after ingesting HTO or OBT as food. He suggested that the risk was small enough to pose no significant hazard, primarily because only 2% of the hydrogen atoms in DNA were located at the 5-position of the cytosine ring and damage would be minimal. Feinendegen and Bond [F3] reached the same conclusion—that “the effects of intracellular tritium are overwhelmingly due to beta irradiation of the nucleus” and “transmutation effects do not produce a measurably increased effect under most conditions.” The United Kingdom Advisory Group on Ionising Radiation (AGIR) [H16] came to a similar conclusion. If DNA damage in mammals did occur from transmutation, it is unlikely that it could be distinguished from radiation-induced damage and thus would be already accounted for in measured RBE values.

2. Isotopic effects

176. While chemically similarly to hydrogen, tritium has slightly different physical properties due to its increased mass. Diabaté and Strack [D5] noted that synthetic reaction rates decreased as atomic mass

increased, causing a significant isotopic effect of OBT depletion with tritium compared with HTO from which biological macromolecules are synthesized. In contrast, once fixed to carbon, C-T bonds are cleft more slowly than C-H bonds. In equilibrium conditions of OBT synthesis in plants grown in a medium with HTO, the isotopic ratio of tritium specific activity in hydrogen of OBT in bulk organic matter to that in water was in the range of 0.6–0.8 [D5].

177. Intracellular discrimination between tritium and hydrogen atoms due to isotopic differences (in particular a mass ratio of 3) have been considered in the past (see e.g. [C11, M2]) and concluded to be of little consequence for the risk of tritium. However, contrary to the traditional view of OBT in biomatter, experiments that used denaturing agents have suggested that a proportion of tritium may be designated as “buried tritium”, a tightly bound HTO [B13]. In such a fraction, the buried tritium in biomacromolecules, such as proteins, is in positions where the exchange rates are substantially reduced as a consequence of the three-dimensional structure that arises upon the “folding” of these 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 biomolecules, 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 twofold. While this will certainly result in slightly more beta tracks originating from HTO within and around the DNA, it remains true that the vast majority of beta tracks encountered by the DNA will have originated from HTO outside the DNA since that is where most of the HTO is situated. The effect on radiation dose to the DNA will therefore be small but may increase the RBE value in experimental determinations.

B. Deterministic effects

1. Lethality

178. Brues et al. [B26] investigated the lethality of tritium by giving mice single injections of 0.126–8.4 GBq of HTO. The dose that killed 50% of the population within 30 days ($LD_{50/30}$) was about 9 Gy, which corresponds to an initial activity concentration of tritium of 37 MBq/g of body weight (BW). Furchner [F13] reported an $LD_{50/30}$ of 8 Gy, for HTO given in a single intraperitoneal injection of 33 MBq/g to CF₁ female mice. Yamamoto et al. [Y2] (see also [Y6]) reported an $LD_{50/30}$ of about 8 Gy after a single injection of 0.56 GBq in C57BL/6N female mice and about 13 Gy with an injection of 0.93 GBq in female (C57BL/6N × C3H/He) F1 mice. Overall, these data suggest a $LD_{50/30}$ dose of the order of 10 Gy.

179. Yamamoto et al. [Y2] also investigated the lethality of a continuous oral administration of HTO as drinking water in (C57BL/6N and C3H/He) F1 female mice. The tritium concentration reached a plateau in organs and blood after about seven days. Haematopoietic death typically occurred after two weeks following ingestion of HTO with activity concentrations from 0.15 to 0.6 TBq/L in drinking water. The lowest absorbed dose to cause death was estimated to be about 11 Gy from the continuous ingestion of 0.15 TBq/L of HTO.

180. The dose from tritium necessary to cause death in mice appears to be similar to that from acute external irradiation by X-rays or gamma rays, with tritium $LD_{50/30}$ values of about 6–9 Gy, corresponding to an acute intake of the order of 1 GBq of HTO. In the literature, there are some published historical cases of radiation sickness of workers caused by tritium [M15, O3, S12], including two lethal cases.

181. In 1963, a worker in a radiological laboratory in the former Soviet Union had an intake of about 350 GBq of HTO [O3] due to violation of safety rules. Monitoring of tritium in urine started 25 days later, when the worker had visited a doctor because of deteriorating health. Tritium concentration in urine declined with a half-time of seven days and the committed equivalent dose in soft tissues was assessed to be about 12 Sv. Treatment started immediately after visiting the doctor. Pronounced radiation sickness symptoms were observed during 1.5–2 months after the accident. After about 1.5 months, regeneration of the haemopoietic system began but substantial recovery of leukocyte and neutrophil concentration in blood took more than three months. The patient returned to work after six months. Medical surveillance over 2.5 years showed recovery of working capacity and the absence of substantial adverse effects in internal organs.

182. In the late 1950s and early 1960s, several workers at two European facilities for production of tritiated luminous compounds used large quantities of tritium (4–10 TBq per annum) [M15, S12]. In the course of chemical operations, each worker incorporated substantial amounts of tritium. Measurements of tritium in urine started in the 1960s and were used for dose assessment. In case A-1, tritium concentrations in urine varied in the range of 2–40 MBq/L. From these data, the equivalent dose in soft tissue was assessed as 3–5 Sv over the four years preceding death [S12]. An assistant to A-1 (A-2) received a dose that was about half of that received by A-1 and stopped working with tritium after she showed moderate anaemia. Workers A-3 and A-4, who succeeded A-1 and A-2, worked under improved conditions and incurred lower doses without health effects. In case B-2, the dose incurred over three years before death was assessed from tritium measurements in urine in the range from a few sieverts up to 20 Sv. In both cases A-1 and B-2 there was substantial contribution to dose from OBT, as indicated by measurements made on autopsy samples, and both workers died with clinical signs of an aplastic pan-myelocytopenia complicated by pulmonary or other symptoms [S12].

2. Effects of HTO on animal embryo and fetus

183. Straume and Carsten [S23] reviewed the current literature on exposure to tritium during fetal development. During particular periods of development, some fetal cells will be dividing rapidly and differentiating to form tissues and organs, while other cell types may be showing very little or no cell proliferation. Tritium that is incorporated into OBT of low proliferation cells could result in larger integrated doses to these cells, since the tritium would not be diluted by further cell proliferation. However, uptake will be dominated by those cells undergoing rapid division. Commerford et al. [C26] reported that the dose from tritium incorporated from HTO into macromolecules, such as DNA and histones, of rapidly dividing cells was small compared with that from the same activity of tritium in the form of HTO.

184. In a study by Laskey et al. [L7], rats were continuously fed HTO with activity concentrations of 0.37–370 kBq/mL from conception of the first generation until delivery of the second. The corresponding dose rates were 0.03–30 mGy/d. Exposure to HTO with an activity concentration of 370 kBq/mL resulted in a 30% weight reduction of the testes in the first generation of adult males, but there was no impairment of overall growth or reproductive ability. In the second generation of newborns, decreases in the weight of the brain, overall body weight and litter size were found. An increase in resorption for rats exposed to HTO with an activity concentration at 370 kBq/mL was also found. However, Laskey et al. [L7] did not observe any effects on litter size or resorption at or below an activity concentration of 37 kBq/mL (which corresponds to a dose rate of about 3 mGy/d).

185. Bursian et al. [B27] assessed the effects of continuous exposure of rats to HTO from conception to birth. The activity concentrations used were 0, 37, 370 and 3,700 kBq/mL. In utero exposure to doses

as low as 0.66 Gy (corresponding to the highest concentration used) produced measurable and persistent decreases in brain weight and increases in norepinephrine concentrations at 21 and 45 days after birth. No differences from the controls were observed in the rate of turnover or the concentrations of dopamine, acetylcholinesterase or monoamine oxidase.

186. Jones et al. [J8] gave pregnant squirrel monkeys water with tritium levels ranging upwards from 2 kBq/mL throughout gestation. No effects on body weight, body dimensions, organ weights, haematological patterns, or the histology of organs or tissues, with the exception of ovaries, were observed in newborn progeny. However, the number of primary oocytes in female progeny decreased markedly with increasing levels of HTO in maternal drinking water.

187. Yamada et al. [Y1] studied the effect of prolonged in vitro exposure to HTO and ^{60}Co gamma radiation on pre-implantation mouse development after mating female C57BL/C3H F1 and male ICR mice. With the development to blastocyst as the end point, the LD_{50} was 4.4, 8.5 and 15.8 MBq/mL corresponding to beta radiation dose rate of about 10, 20 and 40 mGy/h, respectively, for pronuclear, early two-cell, and late two-cell embryos, respectively. Compared to ^{60}Co gamma radiation, the RBE value of tritium beta radiation was in the range of 1.0–1.7.

188. The effects of tritium on the morphogenesis and development of rats and mice have been studied by several authors. Wang and Zhou [W3] reported modifications in the cognitive function of young rats born to mothers that had been injected with HTO on the thirteenth day of pregnancy that resulted in 0.1 and 0.3 Gy of in utero exposure. Gao et al. [G2] showed decreases in cognitive behaviour and a significant decrease in hippocampal pyramidal cells in the brain's CA1 area with intraperitoneal injections of HTO on the thirteenth day of gestation that resulted in 0.09 and 0.27 Gy of in utero exposure. Sun et al. [S25] reported a decrease in the brain weight of mice exposed on the thirteenth day of gestation to a dose of 0.4 Gy (from the injection of HTO of 964 kBq/g of body weight); both the thickness of the somatosensory cortex and pyramidal cell density were significantly decreased at this dose. Jain and Bhatia [J2] also observed pathological changes in the cerebellum of mice following exposure of the mothers to HTO. An initial injection of HTO was given at 17 days post-conception followed by additional intake of HTO of 111 and 11.1 kBq/mL. The observed damage was dose dependent.

189. Zamenhof and van Marthens [Z3] studied how five generations of rats were affected by pre- and post-natal exposure to HTO. Female rats were given water containing HTO with an activity concentration of 111 kBq/mL beginning in adolescence and continuing throughout pregnancy. This exposure to tritium did not produce any signs of radiation-induced disease in the mothers. The courses and outcomes of pregnancy were also normal, but 60% of the newborn rats exhibited haematomas, oedemas and subdural haemorrhages. None of these effects lasted beyond 30 days. Zamenhof and van Marthens [Z4] subsequently found that there were decreases in the weight and DNA and protein content of the brain in later generations of rats continuously drinking water containing HTO with an activity concentration of 111 kBq/mL (estimated average daily intake for a 60 g rat—the weight of a 30-day-old—was 2.1 MBq, corresponding to an absorbed dose rate of about 1.4 to 8 mGy/d). The effects were generally most evident in all generations (F2–F5) except the F1 generation. In addition, all but the F1 generation showed some recovery over time.

190. In summary, radiation-induced effects on the embryo or fetus (principally neurological or reproductive tissue impairment) have been demonstrated in laboratory animals exposed to tritium. Such effects start occurring at chronic intake of activity concentrations of HTO of about 50–100 kBq/mL of body water and are consistent with similar effects from external photon irradiation. Embryo–fetal effects in animal studies are observed at doses of about 0.4–0.6 Gy from chronic intake of HTO.

3. Immunological effects of HTO

191. The Committee has conducted a number of reviews of the effects of exposure to ionizing radiation on the immune system, the most recent being given in its UNSCEAR 2006 Report, annex D [U12]. The major conclusions from that review were the following:

- “High doses of radiation produce immunosuppression mainly through destruction of cells. Lymphocytes are very radiosensitive, and their destruction is currently used as an early indicator of the level of an accidental acute exposure. Radiation-induced changes in immune parameters seem to be more dependent on total dose than on dose rate. Persisting effects on immune system have been observed after exposure to ionizing radiation.
- At low doses and dose rates, the effects of ionizing radiation on the immune system may be suppressive or stimulatory. The long-term effect of low radiation doses on the immune function in relation to human health needs to be further evaluated.”

192. However, very few studies specifically reference exposure to tritium. Some reports have come from studies of workers exposed occupationally and also from experiments carried out in the *in vitro* or *in vivo* systems.

193. Tuschl et al. [T17] investigated some immunological parameters in ten NPP workers exposed during a four-week period to external radiation (total effective doses ranged from 1.4 to 9.8 mSv) and tritium inhalation (committed effective doses ranged from 1.2 to 2.8 mSv). Twenty-five days after the beginning of the exposure, only the CD4⁺/CD8⁺ T cell ratios were markedly elevated compared to the ratios detected in non-exposed controls and the effect was mainly due to an increase in the absolute numbers of CD4⁺ T helper cells. In five exposed subjects who agreed to give blood samples five months after the first sampling, the CD4⁺/CD8⁺ T cell ratios were still elevated.

194. Milacić [M14] analysed blood samples from 53 workers exposed to tritium. The workers were separated into three groups depending on the duration of occupational exposure: 0–5, 6–15 and 16–30 years. The groups were compared with each other and with a control group. Effective doses were not provided, but the average tritium activity concentration in urine of the exposed subjects was 1.9 kBq/L. Although total leukocyte counts did not differ from the control group, lymphocyte and eosinophil counts were higher in the workers exposed to tritium and varied with the duration of the exposure, being the lowest in the 6–15 years group. Chromosomal aberrations were detected in 49% of workers exposed for 10.5 years and with a significantly higher average tritium concentration in urine (3.5 kBq/L). However, the average tritium activity concentration in the exposed subjects with no aberrations was 0.35 kBq/L. Alkaline phosphatase and myeloperoxidase activities in granulocytes were significantly lower in all exposed workers. The author interpreted the increase in lymphocyte counts as a stimulation of the immune system by tritium and in eosinophil counts as a compensatory reaction of the bone marrow in response to impaired function of granulocytes. The workers had no clinical manifestations of immunity disorders.

195. In 1980, Kirillova and Luzanov [K16] compared prolonged exposure of CBA mice to HTO and external gamma radiation (from ¹³⁷Cs) delivered in equal daily radiation doses (cumulative dose 4.1 Gy). They observed a decrease in the immune response. The antibody and rosette-forming capacity of spleen cells was lower in the group exposed to HTO than in the group exposed to gamma radiation. On the basis of the total immune response observed over the entire treatment period, they concluded that HTO was 1.27 times more efficient in decreasing the immune response than gamma radiation. They suggested that the observed diminution of the immune response was due mainly to damage to the lymphoid tissue and also to disruption of haematopoiesis. Later on, Kirillova [K19] conducted a similar

experiment, but used rats instead of mice. After a prolonged intake of HTO, the decrease in normal killer cells (NK)² activity in rats was less and the recovery was more rapid than observed in mice for the same total dose (about 8 Gy). The authors linked this observation to the higher metabolic rate in mice compared to rats.

196. In another study of changes in the concentration of NK cells as an end point, Kirillova [K17] treated mice to HTO at an activity concentration of 0.37 MBq/g of body mass over six months and compared them with a non-treated group of mice. The exposure to HTO resulted in a decrease in the activity of NK cells by 35–45% in the treated mice when compared with the reference group ($p < 0.05$) at three months after administration of HTO had ceased. Six months later, the NK cell function had recovered and was even higher by a factor of 1.8 in the mice that had been treated with HTO than in the control group.

197. Kirillova et al. [K18] also studied the quantitative and qualitative degree of recovery of the immunological system in mice after prolonged exposure (throughout life; around 725 days for the controls and 650 days for the treated mice) to HTO with an activity concentration of 0.37 MBq/g of body weight giving a total dose of 8.7 Gy. The authors observed a depopulation of cells in bone marrow, spleen and thymus, which persisted until the end of the lives of the animals. They suggested that the disruption in immunological response was caused early in the treatment by a reduction in the numbers of lymphocytes and by a lower activity of B cells and tritium helpers and, later after radiation exposure, by the impairment of tritium helpers function. There was a direct relationship between the immunodeficiency and the dose rate and the total absorbed dose of beta radiation.

198. Smirnov et al. [S14] concluded that prolonged exposure of CBA mice to daily intake of HTO of 0.19, 0.37 and 0.74 MBq/g of body weight up to doses ranging from 0.2 to 1 Gy, resulted in an impairment of humoral immunity at various stages of the immunopoesis at all dose levels. They also showed a direct relationship between the depopulation of colony forming units (CFU) (early precursors of T and B lymphocytes) and dose rate. They concluded that the production of antibody forming cells was a function of the absorbed dose and that a prolonged exposure to HTO resulted in impaired humoral immunity at various stages of immunopoesis. They also demonstrated that the mechanisms generating the immunological response were highly sensitive to the tritium beta radiation.

199. As demonstrated more recently by Umata et al. [U4], a single intraperitoneal injection of HTO to C57BL/6N mice to give a total whole-body dose of 3 Gy significantly increased the number of variants of the T-cell receptor expressed on splenocytes. The frequency of apoptotic cells of the spleen 12 hours after HTO injection increased to 5.0%.

200. In summary, experimental studies carried out in animals indicate that prolonged exposure of animals to HTO associated with relatively high radiation doses (in the range of 1–8.7 Gy) resulted in some diminution in the immune response in animals which, depending on the dose, could be reversed. In contrast, the few studies carried out in workers occupationally exposed to low doses of tritium demonstrate that such exposure can stimulate immune functions, but also increase the frequency of chromosome aberrations in lymphocytes. However, it is not clear whether such effects, even at high doses, had any significant health consequences. More research on the effects of acute and protracted low-level exposure to tritium on the immune system is warranted.

² A cytotoxic lymphocyte.

4. Germ cell effects of HTO

(a) *Effects in females*

201. Because tritium distributes itself throughout the body, it can be taken up by developing oocytes and incorporated into DNA. Tritium incorporated into human oocyte DNA could theoretically irradiate the oocytes over 30 or more years. Because oocytes do not divide until fertilized, there is little turnover of the DNA molecules, which implies that the biological half-time of the tritium embedded in oocyte DNA could approach the radioactive half-life of tritium of 12.3 years. Forell et al. [F8] pointed out that if a biological process were to gradually exchange all the components of DNA molecules—including that of tritium-labelled DNA—it would take 50 years to replace 2–5% of a cell's genome (DNA). The author estimated that in resting lymphocytes 2,000 bases per hour were turned over. Therefore, most of the tritium incorporated into an oocyte will remain there for its whole life. This issue was also discussed by the United Kingdom Health Protection Agency [H16] in relation to the discharges from a radiopharmaceutical plant. They concluded that tritium could be incorporated during pregnancy into the DNA of fetal oocytes and remain there until fertilization decades later.

202. Straume and Carsten [S23], in reviewing the effects of radiation exposure on oocytes, reported that most of the information on radiosensitivity in humans came from autopsies of women who had been exposed to substantial doses of external radiation [L13], and from fertility histories of women who had undergone radiotherapy or had been exposed as a consequence of the atomic bombings in Japan [B5, L14, U5]. In all cases, the data were for short-term external exposure of adult women.

203. In female mice, data suggest that premature oocytes are more radiosensitive than mature oocytes [B3]. This is in contrast to results in human females that demonstrate that from 3 days after birth, all oocytes are equally radiosensitive. In women, exposure of 2.5–6 Gy to X- or gamma radiation will lead to permanent sterility [I11, I20]. There is no temporary sterility in human females as there is in mice.

204. Dobson and Kwan [D6, D7] continuously exposed non-inbred Swiss-Webster mice to HTO and ⁶⁰Co gamma rays during the early period of oocyte development from conception until 14 days after birth. Oocyte survival following tritium exposure decreased exponentially with dose rate with no threshold; the LD₅₀ level was 0.074 MBq/mL of body water corresponding to 4.4 mGy/day. Exposure to ⁶⁰Co gamma rays was shown to be less effective at the same dose and did not follow an exponential relationship. As a result, the RBE value of tritium beta radiation, compared with gamma radiation, increased with decreasing dose and dose rate from about 1.6 at gamma-ray dose of 0.4 Gy to about 3 at lower doses. In studies of both mice and rats, Satow et al. [S4, S5] studied the effectiveness of exposure to tritium in killing immature oocytes. Statistically significant oocyte resorption was found at activity concentrations of HTO of 0.34 MBq/g of body weight and more, corresponding to a total dose of 77 mGy and more.

205. A number of animal studies have investigated the continuous administration of HTO or tritiated thymidine throughout pregnancy and analysis of the subsequent effect on oocytes in the offspring. This method of continuous administration in rats was pioneered by Fliedner et al. [F7] and Schreml et al. [S7] and subsequently adapted by Lambert and Phipps [L6] using mice. Using this method, Haas et al. [H1] studied the effect of HTO infusion in utero on post-natal oocyte development in rats. During the first 21 days of life post-conception, a dose dependent reduction in oocyte numbers was observed. At birth, 54 MBq infused had reduced the numbers by 50% whereas 215 MBq produced total aplasia of oocytes. They suggested that tritiated thymidine was about ten times more effective than HTO for this effect. In a subsequent paper [S8], these authors concluded that this factor was about 3.7 in relation to radiation dose to the oocyte cell nucleus.

206. Lambert and Phipps [L6] exposed pregnant SAS/4 mice to HTO in drinking water and, by constant infusion, to tritiated thymidine throughout pregnancy. A number of parameters were studied in the offspring including oocyte survival at 14 days of life. They concluded that for this parameter tritiated thymidine was about two–three times as effective as HTO in causing oocyte lethality.

207. Pietrzak-Flis and Wasilewska-Gomulka [P8] also studied the effect of constant intake of HTO or tritiated food on oocyte survival in Wistar rats from birth and sampled at ages 21 and 71 days. They found that tritiated food was more effective at reducing oocyte numbers.

208. In summary, the female reproductive system shows great discrepancies between mice and humans. For humans, the reproductive system is radiosensitive to a dose of 2.5–6 Gy given in a single fraction. Exposure to doses within that range will cause permanent ovarian failure due to the killing of oocytes, and will be accompanied by features associated with menopause. It is anticipated that such a dose of tritium in the ovaries would have a comparable effect.

(b) *Effects in males*

209. Unlike oocytes, spermatogonia are continuously produced from stem cells throughout adult life. Like all tissues that are rapidly replaced, there are certain germ-cell stages that are highly sensitive to cell killing by ionizing radiation. Experiments in mice conducted by Oakberg in 1955 and 1959 showed that the most sensitive cells are the type A and B spermatogonia, which can be reduced by 50% with doses of only about 0.3 Gy of acute X-rays (reported in [S23]). The spermatid and spermatozoa stages are much less sensitive than the spermatogonia stage (Oakberg and Clark, 1964 as reported in [S23]). Lambert [L3] found a 27% reduction in spermatogonia of mice injected with tritiated thymidine at an activity concentration of 0.19 MBq/g of body mass and with HTO at an activity concentration of 2.2 MBq/g of body mass (dose to the cell nucleus of 84 mGy and 49 mGy, respectively).

210. Carr and Nolan [C9] studied the reduction of testis mass in mice following single injections of tritiated thymidine (0.037–0.74 MBq/g of body mass) or HTO (0.37–1.48 MBq/g of body mass) and ⁶⁰Co gamma rays (delivered to match the dose-rate vs. time curve in the 1.48 MBq/g HTO group). The radiobiological effect was investigated at times from one hour to 24 weeks after injection. Measurements of the testicular retention of tritium were also made at these times. There was a progressive loss in mass, up to 30% after 4–5 weeks, followed by an irregular recovery, which was more delayed in the case of the animals injected with tritiated thymidine. Time-integrated fractional testis mass loss was a linear function of injected HTO activity. The RBE value of HTO compared with ⁶⁰Co gamma rays was 1.43 at gamma-radiation dose of 0.6 Gy. As only one gamma-radiation dose level was used, RBE dependence on dose could not be assessed.

211. Balonov et al. studied reduction of testis mass in mice following single intraperitoneal injection of HTO (0.4–12.6 MBq/g of body mass) or exposure to ¹³⁷Cs gamma radiation delivered during ten days with exponential reduction of dose rate with a half-time of 2.5 days similar to HTO excretion rate [B10]. The range of tritium beta-radiation dose was 0.12–3.4 Gy and that of gamma-radiation dose was 0.25–3.7 Gy. Statistically significant relative testis mass reduction was observed in the dose range from 0.25 Gy of both tritium beta radiation and gamma radiation. RBE values in terms of relative testis mass reduction increased from 1.9 at mass reduction of 40% (dose of tritium beta radiation 0.8 Gy) to 2.2 at mass reduction of 10% and corresponding lower dose of about 0.2 Gy. In summary, it has been shown by studies using both external radiation and tritium administration that certain stages of spermatogonia development are particularly sensitive to radiation. Most studies concluded that a ratio of effects (mostly lethal) compared to gamma radiation was in the range of 1.4–2.2.

C. Stochastic effects of HTO in mammals

1. Carcinogenicity

212. Many laboratory studies on animals have demonstrated that exposure to tritium, both as HTO and tritiated compounds, can induce cancer although the carcinogenic effect of exposure to tritium has not been studied as extensively as that of gamma radiation and X-rays.

213. Cahill et al. conducted two studies involving the administration of HTO to pregnant Sprague-Dawley rats to term in a range resulting in whole-body doses during gestation of 0.066–6.6 Gy [C1, C2]. In their first study, increased incidence of mammary fibroadenomas was detected in dams exposed at 3.3 Gy and 6.6 Gy, but not at lower doses. In the second study, offspring surviving beyond 30 days were observed throughout their life and neoplasia recorded. Intrauterine exposure to doses of up to 0.66 Gy had no significant effects on overall cancer incidence rate or onset of mammary fibroadenomas. In addition, females exposed in utero to 3.3 or 6.6 Gy had lower incidence rates of mammary fibroadenomas and at 6.6 Gy females had a lower incidence of overall neoplasia compared to the control unexposed rats. These females, however, were sterile and had reduced mean life spans.

214. Seyama et al. [S13] reported on a series of studies involving acute intraperitoneal injections of relatively high levels of HTO to 7–8-week-old female (C57BL/6N × C3H/He) F1 mice at the activities resulting in internal whole-body doses from 2.0 to 10.5 Gy. The animals were observed for up to 750 days and cumulative neoplasia was compared to the effects of chronic irradiation by either gamma rays or fission neutrons. The effect (incidence of cancer) seems to have nearly saturated at the lowest dose level; that is, the total incidence of tumours was similar at 500 days and later in all exposed groups (about 80%) in contrast to the control group (less than 5%). The authors also studied induction of thymic lymphoma in mice that received 7.9 or 10.5 Gy from a single intraperitoneal injection with those that received equal doses in four subsequent injections with weekly intervals. In the latter case, the latent period was much shorter and lifetime lymphoma incidence was significantly higher than after a single injection.

215. Yamamoto et al. [Y3] reported a study involving continuous oral administration of five levels of HTO to female (C57BL/6N × C3H/He) F1 mice from 10 weeks of age resulting in a dose rate to soft tissues of 0.01–0.24 Gy/day. Lifetime tumour incidence approached the maximum level (83%) already at the lowest dose rate (0.01 Gy/day) while spontaneous incidence was 54%. Exposure to larger dose rates accelerated development of most studied tumours, which resulted in substantial life shortening. The main cause of death of mice exposed to higher dose rates (0.096–0.24 Gy/day) was thymic lymphoma. At lower dose rates, non-thymic lymphomas and solid tumours were also observed. Both shortening of the latent period and life shortening due to development of tumours significantly increased with dose rate of tritium beta radiation and the increases were significantly larger than those after irradiation of mice with X-rays or gamma radiation from a ⁶⁰Co source. In a later similar study [Y4], the same authors exposed mice to three lower levels of HTO in drinking water from ten weeks of age resulting in a dose rate to soft tissues of 0.0002–0.0036 Gy/day. The life span was discernibly shortened in the group with a larger dose rate (0.0036 Gy/day) due to shortening of latent periods for tumour development. In the groups of mice with lower dose rates, both this effect and incidence of thymic lymphoma were missing.

216. A study by Johnson et al. [J5] estimated the lifetime incidence of myeloid leukaemia in seven groups of about 750 CBA/H mice each; radiation exposure was approximately 0, 1, 2 and 3 Gy both for HTO and for X-rays. The lifetime incidence of leukaemia in these mice increased from 0.13% in the

control group to 6–8% in groups exposed to higher radiation doses. The results were fitted to various equations relating leukaemia incidence to radiation dose, using both the raw data and data corrected for cumulative mouse-days at risk. The calculated RBE values for tritium beta rays compared to X-rays ranged from 1.0 ± 0.5 to 1.3 ± 0.3 . A best estimate of the RBE value for this experiment was about 1.2 ± 0.3 .

217. Gragtman et al. [G9] estimated RBE for tritium radiation in reference to 200 kVp X-rays, using acceleration of breast tumour appearance in the female Sprague-Dawley rat as the end point. Chronic X-ray doses of 0.3–2.0 Gy were delivered over ten days. Intraperitoneal injections of HTO ranging in concentration from 45 to 370 MBq/100 g of body weight were administered, followed by four additional injections at two-day intervals and half of the initial concentration. RBE estimations were based on various criteria including the tumour incidence per Gy at 450 days post-irradiation and the time required to induce tumours in 50% of the animals at risk. The results suggest that tritium beta rays are about 1.1–1.3 times more effective than chronic 200 kVp X-rays for acceleration of the appearance of rat mammary tumours. However, the uncertainties involved in these calculations are such that the effects of tritium beta rays could not be reliably distinguished from those of chronic 200 kVp X-rays.

218. Revina et al. [R1] described a study in rats which were administered HTO intragastrically five times a week for six months. The effects (leukaemia and other cancer) on these animals were compared with those on a group chronically exposed to gamma radiation delivered in daily doses comparable to the tritium dose rate. The main problems with this study are the high doses and the fact that there was only one dose point in the tritium and gamma exposed groups. An estimate of RBE of about 2.5 was made in this study.

219. Intraperitoneal injection of HTO to male N5 mice several times over 30 days (so that the exposure period comprised all stages of spermatogenesis) to give a total dose of 1.5 Gy resulted in a statistically significant increase of leukaemia incidence among their young (less than 210-day-old, but not yet one-year-old) offspring [D1]. It appeared that the overall leukaemia incidence in the offspring of the HTO-exposed fathers was significantly dependent on the maturation stage of the sperm-forming cells during the HTO exposure. However, in a paper by Balonov et al. [B12] which summarizes Russian studies on tritium carcinogenicity. Mice and rats were given HTO in drinking water at a dose range of 0.24–25.3 Gy. Although most malignancies were increased, the absence of a positive dose–response and occasionally a negative response makes interpretation of these data difficult.

220. Yin et al. [Y5] used 12-day-old male and female pups of C3H/HeN mice that were given a single intraperitoneal injection of HTO at the activities of 0.23, 0.92 and 3.70 MBq/mouse and then observed for 14 months for the development of tumours. In the males, a significantly increased incidence of liver neoplasms was detected whereas in the females, only an insignificantly elevated incidence of ovarian cancer was observed in mice exposed to the highest concentration of HTO.

221. Studies in which administration of tritiated material was compared with the effects of similarly protracted X- or gamma-radiation exposure are the most reliable sources of RBE data. This is important in the absence of such data for human exposure. Four of the more comprehensive studies [G9, J5, R1, S13] were critically examined in the AGIR report [H16] and the conclusion was that, due to deficiencies in the experimental design and statistical analysis, the findings from these studies should be treated with caution. However, taken together, they indicate an RBE value with a central estimate in the range 0.8–2.5 with an upper 97.5 percentile value of no more than about 3.

222. Straume [S22] undertook a literature review of the risks, including cancer induction, from exposure to tritium. Because information was not available for humans, cancer-risk estimates for tritium were derived from experimental animal (mostly mouse) studies. Straume calculated a skewed risk distribution (with a fiftieth percentile risk per unit dose of $81 \times 10^{-6} \text{ mGy}^{-1}$ with a 90% confidence

range of $38\text{--}185 \times 10^{-6} \text{ mGy}^{-1}$) using Monte Carlo methods and distributions of dose-rate effectiveness and multiplying by best estimate RBEs for tritium (based a central value of the RBE of 2–3 ranging up to 4.5). This was comparable to radiation risk estimates in the Committee's UNSCEAR 1988 Report [U6], in the ICRP Publication 60 [I13] and in the BEIR V Report of the Committee on the Biological Effects of Ionizing Radiation [N6].

2. Heritable effects

223. In its UNSCEAR 2001 Report [U10], the Committee noted that no radiation-induced hereditary diseases had (to that date) been demonstrated in humans. Nonetheless, since such effects are seen in plants and animals, the Committee provides an approach for estimating such risks [U10].

224. Russell et al. [R17] studied the incidence of seven specific locus mutations in ($101 \times \text{C3H}$) F1 wild-type male mice using about 40,000 offspring of males exposed to HTO with weighted mean doses of 4.3 Gy to post-spermatogonial germ cells and 6.2 Gy to spermatogonia. The observed mutation spectrum was similar to those following previous exposure to external X- or gamma radiation. The radiosensitivity of post-meiotic cells was similar to that observed for acute exposure to X-rays. For spermatogonia, comparison was made with earlier experiments with low-dose rate gamma radiation showing that the mutation rate was twice as high in the case of tritium exposure.

225. Pomerantseva et al. [P10] studied reciprocal translocations (RTs) in mouse stem spermatogonia induced by HTO and ^{137}Cs gamma radiation. HTO was administered to males by a single intraperitoneal injection and excreted with a half-time of about 2.5 days. In order to adjust exposure conditions, the dose rate of gamma radiation was reduced exponentially with the same half-time. Mean doses of testis cells were 0.5, 1.0, 1.9 and 3.4 Gy of tritium beta radiation and 1.0, 1.9 and 3.7 Gy of gamma radiation [B9]. In the post-sterile period, three–five months after exposure commenced, ten–twelve males from each experimental group and four–five males from control groups were sacrificed. From each male, 100–200 spermatocytes were analysed at the stage of diakinesis-metaphase of the first meiotic division, and the number of multivalents in the form of rings and chains recorded. The groups of animals exposed to beta and gamma radiation at a dose of 2 Gy were also studied over two–eight months and reciprocal translocation frequency did not significantly change during this period. This observation indicates that elimination of cells with translocation from populations of spermatogonia exposed continuously at low dose rates is insignificant. The increase of reciprocal translocation frequency with increasing dose was observed over the entire dose range up to 3–4 Gy. The RBE of tritium in this study was estimated to be 1.8; dose dependence of RBE was not observed.

226. The ICRP Publication 103 [I23] has stated that “there continues to be no direct evidence that exposure of parents to radiation leads to excess heritable disease in offspring”. Nevertheless, on the basis of the results of animal experiments and, citing the Committee's UNSCEAR 2001 Report [U10], ICRP estimated, for protection purposes, a nominal genetic risk of about $0.2\% \text{ Gy}^{-1}$ for up to the second generation (grandchildren). For low-LET radiation, the ICRP value for the probability of severe heritable effects is 0.5% per Gy for the reproductive population, estimated on the basis of mouse data.

227. Straume and Carsten [S23] noted that the heritable effects observed for other low-LET radiation were also present following exposure to HTO. By grouping the RBE studies with genetic end points (such as chromosome aberrations and mutations in mice), they determined that the RBE values ranged from 1 to 3, with the higher values associated with low doses and low-dose rates, largely owing to the curvilinear response for the reference radiation.

3. Germ cell effects

228. This subsection presents effects of tritium exposure of mammalian germ cells in one or several generations that result in progeny death. These effects are interpreted as stochastic, presumably caused by damage to genetic material of a single cell, but not transferred to the next generations because of the lethal nature of the radiation-induced mutation.

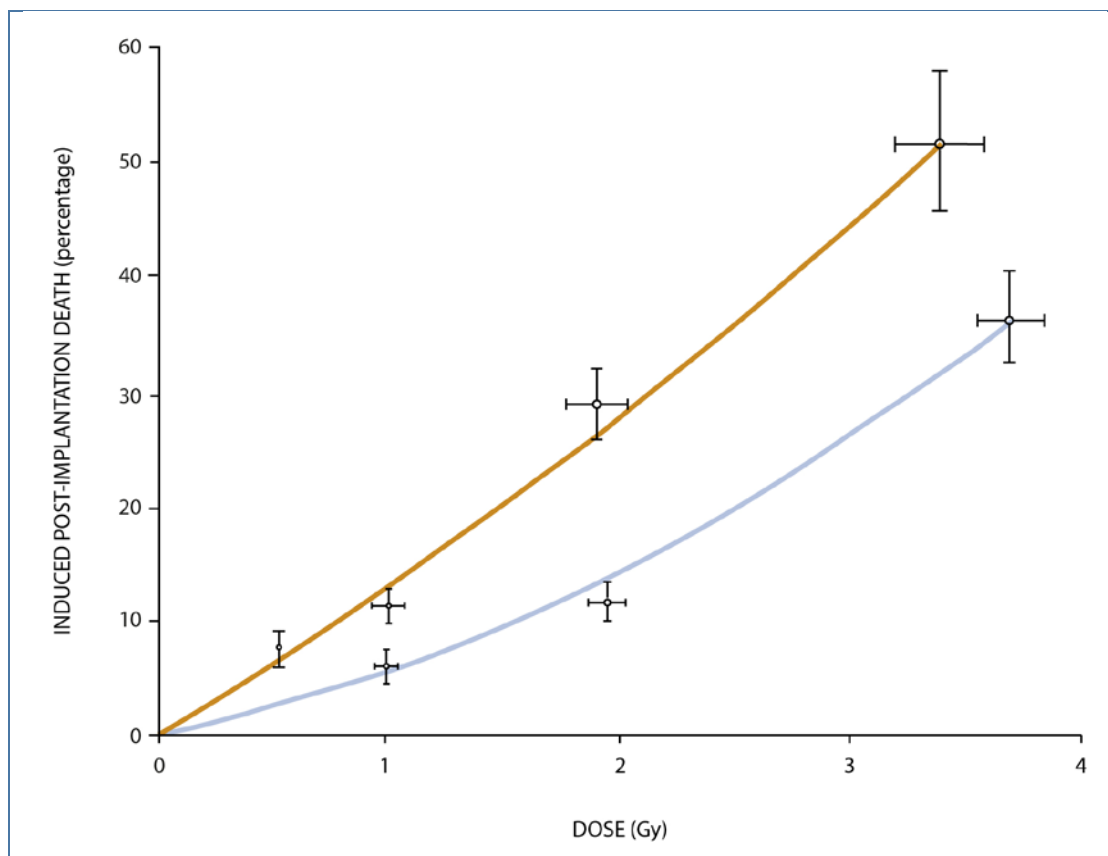
229. Carsten and Commerford studied dominant lethal mutations (DLMs) in Hale-Stoner-Brookhaven strain mice resulting from chronic HTO ingestion [C10]. In a two-generation study, mice were maintained on drinking water with 0.11 MBq/mL HTO. Radiation doses to germ cells of the second generation animals tested for DLMs were 0.28 Gy in females and 0.38 Gy in males. Mice were mated at the age of eight weeks, pairing exposed males and females and exposed and non-exposed. Statistically significant increases in DLM frequency were detected in all the exposed groups compared with the control one. There was no effect of tritium exposure on breeding efficiency.

230. Mewissen et al. [M12, M13] studied cumulative genetic effects following exposure of male C57BL/6M mice to tritium for six and ten generations. At each generation, weaned male breeders aged 35 days either received a single injection of tritiated thymidine (0.037 MBq/g of body weight) or were exposed for five weeks to HTO (0.37 MBq/mL). The dose to male sperm over a 35-day period of exposure in each generation was estimated at 0.037 Gy from HTO. At 10 weeks of age, all breeders were sibling-mated. At the fifth generation, the average litter size was 6.56 and 6.72 vs. 6.92, respectively, in the sibling line receiving tritiated thymidine, exposed to HTO and in the control. The observed variations are significant at the 0.01% level by chi square test. Also, the average weight of mice at weaning consistently decreased through successive generations in the sibling line exposed to tritiated thymidine and to a lesser extent in those exposed to HTO, whereas individual weight remained fairly constant in control mice. F1 and F2 offspring from the ninth generation were studied for litter size and infant mortality. The litter size had decreased and infant mortality increased in experimental groups. DLM frequency (pre-implantation death) had increased in both experimental groups.

231. Balonov and Kudritskaia studied the frequency of DLMs in germ cells of male randomly bred mice induced by HTO and ^{137}Cs gamma radiation [B9]. HTO was administered to males by a single intraperitoneal injection and excreted with a half-time of about 2.5 days. In order to adjust exposure conditions, the dose rate of gamma radiation was reduced exponentially with the same half-time. DLM frequency was estimated from the results of four weekly matings of each male with 2–4 intact females beginning from the tenth day after the exposure launch. At 17–18 days after the beginning of mating, the females were dissected and the number of yellow bodies in the ovaries, places of implantation and dead embryos were counted. It was concluded that HTO beta radiation was more effective than ^{137}Cs gamma radiation (figure XII). RBE values tended to increase with dose and effect reduction: from 1.6 at $D_{\text{HTO}} = 2$ Gy to 2.2 at $D_{\text{HTO}} = 0.5$ Gy. Linear extrapolation of RBE dependence on dose to zero gives $\text{RBE}_{\text{max}} = 2.6$ [B9, B12].

232. In summary, the studies presented here demonstrated that internal exposure of mammal germ cells to HTO can induce DLMs of the progeny at a wide range of radiation doses. RBE estimation showed tritium beta radiation to be more effective than gamma rays for this biological end point by factors of 1.6 to 2.6 [B9, B12].

Figure XII. Frequency of induced post-implantation death of randomly bred mouse embryos depending on dose of ^{137}Cs gamma radiation (lower curve) and of HTO beta radiation (upper curve) [B9, B12]



D. Effects of tritiated biochemical substrates

233. The extent of cellular injury caused by a tritiated biochemical substrate depends largely on where it is incorporated into a cell and the duration of exposure. Tritiated DNA precursors, such as tritiated thymidine, are theoretically more efficient in causing cellular injury because they form part of the basic building block of a DNA strand. This effect was already reported in 1958 by Painter et al. [P1]. On the other hand, compounds containing tritium that are not close to the DNA in the cell, such as fats or some amino acids included in a non-nuclear protein, should pose a lesser risk.

234. Whereas radiobiological studies with HTO aimed mostly at specification of RBE values for either deterministic or stochastic effects in mammals, similar studies with tritiated biochemical substrates aimed to reveal their effects compared with those from HTO. In practical terms, these studies are used for specification of dosimetric models for OBT and tritiated biochemical substrates. It is understood that direct studies of OBT-related biological effects are hardly feasible either in the environment or in experiments on mammals because of low tritium concentration in OBT. Therefore, some tritiated biochemical substrates are used as an experimental surrogate for OBT in food, which is potentially a factor of public exposure.

235. Studies on the effects of nucleotropic forms of tritium such as tritiated DNA-precursors are of special interest because they promote better understanding of radiobiological mechanisms of internal

exposure. In practical terms, their results will be used as scientific bases for future models for the protection of workers dealing with those forms of tritium. However, the number of workers potentially thus exposed is rather limited. Thus, exposure to and incorporation of tritiated thymidine is essentially largely of scientific interest.

1. Studies in vivo

236. In experimental studies on mammals, studies have focused on biological effects resulting from tritiated thymidine, the first synthesized tritium-labelled nucleoside, because of its pronounced intranuclear localization in contrast to uniformly distributed HTO. Effects of tritiated amino acids with varied intracellular distribution and of uniformly distributed ^3H -glucose have been studied to a lesser extent. Deterministic radiation-induced effects were the focus of these studies, except for one series of experiments (table 16) studying stochastic effects in germ cells of male mice, i.e. induction of heritable reciprocal translocations in spermatogonia and non-heritable DLMs.

Table 16. Time-integrated frequency of excess post-implantation embryo death (DLM, % weekdays), frequency of reciprocal translocation (RT) in spermatogonia and relative testis mass reduction (RTMR, %) in one month after injection of HTO and tritiated biochemical substrates in male mice [B9, B10, B12]

Tritium compound	Intake (MBq/g of body weight)	Testis cell dose (Gy)	DLM (%·week)	RT frequency (%)	RTMR (%)
HTO	3.3	1.0	38	0.44±0.20	47±2
Glucose	3.3	0.9	32	0.46±0.16	46±4
Glycine	3.1	1.3	15	0.36±0.11	44±3
D,L-Lysine	3.1	1.5	63	0.38±0.15	51±4
L-Lysine	1.9	2.2	130	0.87±0.22	64±3
Thymidine	0.04	—	10	0.21±0.07	—
	0.4	—	35	0.56±0.20	29±4
	1.1	—	35 ^a	0.44±0.17	—
Deoxycytidine	0.4	—	20	0.12±0.06	14±4
	1.1	—	56	0.26±0.11	35±3
Control	—	—	0	0.025±0.014	0

^a Low fertility.

237. Lambert [L3] found that the number of resting primary spermatocytes per tubule in rat spermatogonia was halved in 72 hours by exposure to HTO and tritiated thymidine concentrations of 2.2 and 0.55 MBq/g of body mass, respectively, given as a single injection. He pointed out that these values should be viewed with caution owing to uncertainties in several factors, such as the time of death of the spermatogonia and, therefore, the dose from tritium that induced it.

238. Baker and McLaren studied effects of tritiated thymidine on the developing oocytes of randomly bred Q strain mice [B4]. Following seven intraperitoneal injections of pregnant mice with ^3H -thymidine (0.15, 1.5 and 15 MBq per injection), tritium label was detected in the ovaries of their progeny. The total number of oocytes in the ovaries was reduced in all the exposed groups proportionally to injected tritium activity. The primordial oocytes were more affected than multilayered follicles. Other functions

(e.g. body weight, fertility, ovarian weight) were affected only in the group with the highest injected activity. It was concluded that mouse oocytes are highly sensitive to beta radiation from incorporated ^3H -thymidine during embryonic life.

239. In the experiments of Carr and Nolan [C9] on reduction of testis mass of the mouse following single injections of tritiated thymidine (0.037–0.74 MBq/g of body mass) or HTO (or exposed to ^{60}Co gamma rays), a significant effect on the testis mass was seen after the injection of tritiated thymidine at 0.037 MBq/g of body mass, which delivered an estimated average absorbed dose to the testis of about 0.035 Gy during 16 weeks. The authors assessed that tritium from tritiated thymidine “fixed” in the testis was about twice as effective as the more labile and uniformly distributed tritium from HTO and that, in terms of injected amount tritiated thymidine, it is unlikely to be more than five times as effective as HTO even at very low injected amounts.

240. Balonov et al. [B12], in a series of experiments on randomly bred male mice, studied both reduction of testis mass and frequency of DLMS in germ cells induced by ^3H -glucose, two amino acids (^3H -glycine and ^3H -lysine) and two nucleosides (^3H -thymidine and ^3H -deoxycytidine) following intraperitoneal injections. Tritiated glucose and amino acids were administered in single injections and nucleosides in six portions during three days. In the post-sterile period, three–five months after exposure commenced, ten–twelve males from each experimental group and four–five males from control groups were sacrificed and reciprocal translocations in mouse stem spermatogonia counted. The effects were assessed in comparison with HTO [B9, B10]. For injected tritiated nucleosides, the concept of tissue or cell dose was not applied. The main results of experiments are presented in table 16. As the time dependence of DLMS was different following administration of HTO and various tritiated substrates, especially the nucleotropic forms, the presented parameter is time-integrated excess post-implantation embryo death.

241. The administration of all the tested tritiated substrates resulted in the production of three radiobiological effects that are qualitatively similar to those observed for HTO. As far as the time-integrated DLM frequency is concerned, the order of effectiveness of the various chemical forms, per unit of injected activity per gram of body weight, is as follows: ^3H -glycine – HTO and ^3H -glucose – D,L-lysine- ^3H – ^3H -deoxycytidine – L-lysine- ^3H – ^3H -thymidine. DLM frequencies induced by labelled lysine, thymidine, and deoxycytidine are five–eight times higher than that from an equal HTO activity. Per unit of testis dose, ^3H -glycine is three times less effective than HTO, ^3H -glucose and ^3H -D,L-lysine do not differ from HTO, and ^3H -L-lysine is more effective by a factor of 1.5. The difference in genetic efficiency will not only reflect different dynamics of retention of bound tritium in the testes but also its different location with regard to the cell nucleus. The nuclear location of ^3H -nucleosides and ^3H -lysine is well established, and the suggestion of a predominantly extranuclear location of ^3H -glycine in germ cells is consistent with observations. In contrast to DLM, reciprocal translocation frequencies in stem spermatogonia reflect late mutagenic effects of tritium. The deterministic effect of testis mass reduction at one month after tritium injection generally agrees with assessed testis doses [B9, B10, B12].

242. In summary, experiments on rodents with administration of biochemical substrates labelled with tritium confirmed the theoretical consideration that some of them are more efficient with regard to induction of both deterministic (cell death) and stochastic (mutation) effects compared with administration of equal activities of HTO. Per unit of intake, ^3H -thymidine is 5–10 times more efficient than HTO. The experiments also demonstrated elevated efficiency of other nucleotropic forms of tritium, L-lysine- ^3H and ^3H -desoxycytidine. For ^3H -labelled nucleosides, the application of concepts of tissue and cell dose is hampered by lack of data on their distribution in mammalian cells.

2. Studies in vitro

243. In 1973, Snow [S16] showed that tritiated thymidine at activity concentrations between 0.37 and 3.7 kBq/mL (0.01 and 0.1 μ Ci/mL) significantly reduced the number of cells in mouse blastocysts cultivated in vitro after exposure starting during the two-cell stage. Activity concentrations exceeding 3.7 kBq/mL were lethal to the two-cell embryos. Several other authors have published consistent findings [H11, K10, M23, O5, S21].

244. By incubating embryos in solutions of tritiated thymidine, Streffer et al. [S24] found that an activity concentration of 18.5 kBq/mL almost completely inhibited the development of mouse blastocysts and was about 1,000 times more effective than similar activity concentrations of HTO. Similarly, they found that activity concentrations of 1.85 MBq/mL of HTO and 1.85 kBq/mL of tritiated thymidine reduced the yield of fully developed blastocysts to 50–60%.

245. The extreme ratios of “toxicity” reported refer to concentrations of tritium in the culture media rather than dose to cells. In fact, Streffer et al. [S24], when culturing blastocysts, estimated that tritiated thymidine at a concentration of 1.85 kBq/mL resulted in a dose rate to DNA of 70 mGy/h and its effect was similar to that of 1.85 MBq/mL of HTO, which gave a (uniform) dose rate of 60 mGy/h. The tritiated thymidine in these in vitro cultures was available for the duration of the experiment, thus resulting in the labelling of all DNA synthesis in the developing embryo. This situation is different from the situation that might arise in vivo. This was referred to by Furuno-Fukushi [F14].

246. Particularly interesting are those papers that compared the effects of exposure to different tritiated compounds. Clerici et al. [C22] compared the toxicity of tritiated thymidine with that of the toxicity of four tritiated amino acids; arginine, lysine, histidine and aspartic acid with regard to growth and development of two-cell mouse embryos exposed in vitro. Surprisingly, arginine was the most lethal of all the tritiated compounds, requiring 1.1 kBq/mL of medium to kill 50% of the embryos. In comparison, tritiated thymidine had an LD₅₀ of about 3.0 kBq/mL. The LD₅₀ of the other amino acids was 2.2 kBq/mL for lysine, 4.8 kBq/mL for histidine and 14.8 kBq/mL for aspartic acid. The LD₅₀ for tritiated tryptophan (1 kBq/mL) was almost the same as that for tritiated arginine [K12]. The authors commented that this was surprising because tryptophan was not excessively incorporated into histones. However, two non-histone chromosomal proteins with high amounts of tryptophan were identified.

247. Similarly, in vitro experiments performed by Müller et al. [M24] on preimplantation mouse embryos have shown that, given the heterogeneous distribution and specific incorporation into DNA, tritiated thymidine is 1,000–5,000 times more effective than HTO in inducing harmful effects at the same level of applied activity concentration. Müller et al. also found that tritiated arginine, a histone precursor, was more damaging than tritiated thymidine for a number of in vitro end points in the mouse embryo, including blastocyst formation, hatching of blastocysts, trophoblast outgrowth, inner cell mass formation, number of cells per embryo and micronucleus formation. The mice embryos were incubated in vitro in solutions with activity concentrations of 0.37 kBq/mL and 0.93 kBq/mL of both tritiated arginine and tritiated thymidine. The authors postulated that the greater radiotoxicity of the tritiated arginine was due to faster uptake and possibly because histone synthesis is not restricted to the S phase of the cell cycle while thymidine would be incorporated only during DNA synthesis. The latter assumption was confirmed some years later in cell-cycle specific experiments [M25]. These studies emphasize the importance of understanding the intracellular distribution of tritium-labelled biochemicals, with effects relating more directly to nuclear dose than to averaged cell or tissue dose or to levels of administered activity.

248. Furuno-Fukushi et al. [F14] treated lymphocytic leukaemia cells of mice for 50 hours with various tritiated compounds: thymidine, lysine, arginine, leucine, and aspartic acid. Cell doses for HTO

and tritiated amino acids or nucleus doses for ^3H -thymidine ranged from approximately 0.1 to 8 Gy (as interpreted from graphical data). Cell survival decreased exponentially with increased substrate activity concentration in culture medium for all compounds with the effects being greatest for thymidine, followed by arginine, lysine, leucine and aspartic acid whereas cell-mutation frequencies increased linearly. The concentrations for detectable cell killing and mutagenesis were about 37 kBq/mL for tritiated thymidine, 37–370 kBq/mL for tritiated amino acids and 18.5–185 MBq/mL for HTO. When activities in cells were measured and converted to dose in cells for tritiated amino acids and dose in nuclei for ^3H -thymidine, the response both in terms of cell survival and mutation frequency per unit dose was estimated equal for all amino acids; however, elevated by a factor of 2–3 for ^3H -thymidine.

249. Wang et al. [W4] examined the effects of tritiated biochemical substrates on cultured embryonic mid-brain cells of mice using the following tritiated compounds: thymidine, uridine, arginine and glutamic acid. The cells were exposed to different concentrations of these compounds over a 20-hour period. Assays of cell proliferation and differentiation and DNA and protein content were conducted. Contrary to the studies by Müller et al. [M24] and Clerici et al. [C22], Wang and Zhou [W3, W4] found that both tritiated thymidine and tritiated uridine were more radiotoxic than tritiated arginine and tritiated glutamic acid. This was probably due to the different biological end points studied. Table 17 provides a summary of the effects of exposure to the tritiated compounds measured as the tritium activity concentration (ID_{50}) in the culture medium and corresponding dose for cells or nuclei (the latter for ^3H -TdR) necessary to inhibit the cellular processes (proliferation and differentiation) by 50%. Tritiated thymidine behaved very differently from the other three tritiated compounds, with a much steeper dose–response curve. This is evident in table 17 where the ID_{50} for tritiated thymidine is much lower. However, corresponding absorbed doses for cells or nuclei do not vary much whether the tritium-labelled substance is distributed uniformly or concentrated in the nucleus as is ^3H -thymidine.

Table 17. Inhibitory effect of beta radiation from tritiated biochemical substrates on cellular proliferation and differentiation [W4]

OBT	Proliferation		Differentiation	
	ID_{50} (kBq/mL)	Absorbed dose (Gy)	ID_{50} (kBq/mL)	Absorbed dose (Gy)
^3H -Thymidine	29	0.58	21	0.42
^3H -Arginine	193	0.85	163	0.66
^3H -Uridine	193	0.60	141	0.43
^3H -Glutamic acid	525	0.95	438	0.77

250. In summary, incubating mammalian cells and embryos in media containing biochemical substrates labelled with tritium may result in various biological effects, such as death of cells and embryos, cell mutations and inhibited proliferation and differentiation. The radiobiological efficiency of these outcomes, assessed per unit labelled substrate concentration in culture media, varies by a factor of up to 1,000 compared with HTO and by a factor of up to some tens between substrates. These differences reflect the active involvement of labelled biochemical substrates in biochemical processes that lead to incorporation of tritium into cell organelles and subsequent exposure of cells and nuclei (such as in the case of labelled DNA precursors) with tritium beta radiation. However, the radiobiological efficiency of the different substrates is comparable when assessed per unit of cell or nuclei radiation dose.

3. Biophysical models

251. In order to study the impact of tritiated biochemical substrates or OBT, Chen [C14] performed microdosimetric simulations to compare differences in energy deposition between uniform distribution of tritium 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 results from a localized increase in dose to the critical target due to a non-uniform distribution of energy deposition within the cell. However, the extent of any increase would depend on the extent to which OBT preferentially localizes within critical targets.

252. Alloni et al. [A1] simulated radiobiological effects of tritium concentration, depending on its chemical form, either in the cytoplasm or in the nucleus of the target cell. The biophysical track-structure code PARTRAC was used to calculate nuclear doses, DNA damage yields and fragmentation patterns for different localization of tritium in human interphase fibroblasts. For tritium distributed selectively in the cytoplasm but excluded from the cell nucleus, the dose in the nucleus is 15% of the average dose in the cell. In the low- and medium-dose regions investigated in the paper, numbers of double-strand breaks (DSBs) are proportional to the nuclear dose, with about 50 DSB/Gy. These results illustrate the potential for over- or underestimating the risk associated with tritium intake when its distribution at subcellular levels is not appropriately considered.

253. In summary, while many studies have examined how tritiated biochemical substrates are partitioned within the body and within the cell, studies specifically looking at health effects due to exposure to those substances are limited. Those that are available indicate that most organic compounds have about the same effectiveness as HTO, since they are distributed throughout cells and do not lead to preferential irradiation of the nucleus. Incorporation of some tritiated amino acids and tritiated nucleosides (e.g. thymidine), however, can lead to the accumulation of tritium in the nucleus with longer retention times and a proportionately larger dose per unit intake.

VII. RELATIVE BIOLOGICAL EFFECTIVENESS

254. The RBE is the ratio of the absorbed dose of a reference radiation needed to cause a specific biological response divided by the absorbed dose of the radiation of interest that causes the same response. RBE values are experimentally observed values and differ for particular radiation types according to the biological system and end point under consideration, dose, dose rate, and the reference radiation. RBE values are the basis for but have to be distinguished from the concept of radiation weighting factors (w_R) used by ICRP in the calculation of equivalent and effective doses, in which simplifications are made that are considered appropriate by ICRP for protection purposes. In radiological protection, the RBE for stochastic effects at low doses (RBE_M) is of particular interest.

255. RBE data and biophysical considerations (see below) indicate that lower energy electrons (such as those released by tritium) or photons are biologically more effective than higher energy gamma rays for a range of deterministic and stochastic end points. Although ICRP [I13, I23] recognized that there was evidence for a significant variation in RBE values for low-LET radiation (e.g. increasing RBE with decreasing photon energy), it was argued that a more detailed distinction was not warranted for the purposes of radiological protection. Thus, a value for w_R of 1 was chosen for practical reasons to apply to all electrons and photons, including beta particles from tritium [C30].

A. Track structure considerations

256. Tritium decay results in the production of a very low-energy beta particle (average energy 5.7 keV) of short range (average track length in water 0.56 μm) and, as a result, the average ionization density (and LET) produced by the emitted beta particle is significantly higher than that produced by higher energy electrons or photons, such as ^{60}Co gamma rays (see table 18). Lower energy photons or electrons similar to those produced by tritium decay also show a significant shift in microdosimetric energy deposition patterns towards higher lineal energy (y) compared to higher energy photon or electron fields. The 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 [E2]. The results were then interpreted using the earlier site model of the Kellerer-Rossi theory of dual radiation action (DRA) (e.g. [K7]) to estimate the RBE value for limiting low doses. The DRA model simply assumes that the biological effect is proportional to the square of the energy deposited in some small volume, often taken to be about 1 μm in diameter. They 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 1.8 mm Cu), assuming a critical site size of 1 μm .

Table 18. Track average LET, \overline{L}_{Δ} , in water for various radiations based on a cut-off energy, Δ , of 100 eV [I24]

Radiation	\overline{L}_{Δ} (keV/ μm)
^{60}Co gamma rays	0.22
200 kV X-rays	1.7
^3H beta rays	4.7
50 kV X-rays	6.3

257. 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 ionization which can be enfolded within a 2.3 nm diameter sphere compared with photons with energies above 100 keV [M17]. This represents ionization events on the dimensional scale of DNA.

258. A joint task group of ICRP and the International Commission of Radiation Units and Measurements suggested a relationship between what the group called a quality factor, $Q(y)$, and lineal energy, y , defined as the energy imparted in a 1 μm diameter spherical tissue volume divided by its mean chord length [I25]. 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 2 compared to orthovoltage X-rays. This is supported by theoretical calculations performed by Bigildeev et al. [B19] on the basis of similar microdosimetric quantities on the micrometre scale.

259. Morstin et al. [M20] calculated the lineal energy spectra of tritium beta particles for spherical sites with diameters from 1 nm to 10 μm and showed that the mean values varied by more than an order of magnitude over this range. Then, when they applied the assumptions of the site model of DRA 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 <1.1, for assumed 10 nm sensitive sites, to a peak of ~1.5 for 1 μm and then decreased to ~0.6 for 10 μm . The corresponding predicted RBE value of tritium beta radiation relative ^{60}Co gamma rays was ~1.5 for 10 nm sites, ~2.9 for 1 μm and ~1.6 for 10 μm . Morstin et al. [M20] pointed out limitations of the DRA 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 and 20 nm diameter (to represent DNA double-strand break formation) within a gross sensitive volume of 1 μm diameter. By then “assuming arbitrarily (by somewhat questionable analogy to the DRA 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.

260. In a recent theoretical study, Chen [C16] performed microdosimetric simulations to compare dose mean lineal energies for HTO and OBT with that for ^{60}Co gamma rays in the same size range from 10 nm to 2 μm of spherical radiosensitive sites. Compared with ^{60}Co gamma rays, the estimated RBE value varied from 1.3 to 3.5 for HTO and for 2.3 to 5.6 for OBT.

261. Most of the above theoretical calculations of RBE values 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 will not typically provide an adequate description of these patterns [G3, G5, G12, K8].

262. The effectiveness of low-energy electrons, similar to those produced by tritium, can be studied using ultrasoft X-rays (0.1–5 keV) that 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 end points compared to equal doses of conventional X-rays or gamma rays [G6, G7, H10], 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 keV and 8.0 keV, respectively) similar to the average energy of the emitted beta particle from tritium.

263. Hill [H11] reviewed several studies that looked at in vitro end points, such as dicentric aberrations in human chromosomes, micronuclei induction, and mutations over a range of photon energies from ultrasoft X-rays to ^{60}Co gamma rays. He observed a pronounced trend of an increase in RBE values with decreasing photon energy for several biological end points, particularly for the induction of dicentrics in human lymphocytes. He noted that, because of differences in cell types and biological end points, the extent to which lower photon energy caused RBE values to rise was still uncertain. Recent data by Frankenberg et al. [F11] report an RBE_M (maximum RBE value for very low doses) of about 4 for soft (mammography) X-rays compared to 200 kVp X-rays.

264. The percentage of absorbed dose deposited by low-energy electrons (0.1–5 keV) in tissue is ~33% for ^{60}Co gamma rays, ~49% for 220 kV X-rays and rising to ~78% for tritium beta particles [N5]. 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 ionizations and excitations apparently having little biological effect [B24, G6]. The contribution to absorbed dose of these low-energy electrons is large for tritium beta particle compared to orthovoltage X-rays or gamma rays. Therefore, the ultrasoft X-ray data would predict an increase in biological effectiveness as a result of increased clustering of ionization events on the nanometre (DNA) scale leading to an increase in the number of DSB per unit absorbed dose, along with a slight increase in complexity of the breaks due to additional associated damage within a few base pairs.

265. Using Monte Carlo simulation, Moiseenko et al. [M18] modelled DSBs and single-strand breaks (SSBs) in cells exposed to tritium beta particles and low-energy photons. They found that a direct energy deposition of 10 eV could result in an SSB. They further studied base damage associated with DSB and were able to differentiate between simple DSBs and complex DSBs. They later developed a Monte Carlo model to calculate yields of DSBs in DNA after irradiation with ^{137}Cs gamma radiation, orthovoltage X-rays (typically 150–300 kVp) and tritium beta particles [M19]. The RBE values for DSB production for tritium beta radiation (with ^{137}Cs gamma radiation as the reference) was 1.2 for the total DSB yield and 1.3 for complex DSBs. They explained that low-energy X-rays and tritium beta particles tended to deposit energy in a more clustered fashion than ^{137}Cs gamma rays. They concluded that tritium beta particles were more efficient in producing DSBs in DNA compared to ^{137}Cs gamma rays and that their relative effectiveness was even greater for the production of complex DSBs.

266. In summary, track structure considerations suggest that the low-energy beta particles produced by tritium decay are more biologically effective than hard X-rays and gamma rays per unit absorbed dose, at least in producing DSBs in DNA. This is a result of the average ionization density along the track of the tritium beta particle being significantly higher than produced by much higher energy photons. Theoretical calculations based on microdosimetric considerations suggest an RBE value of approximately 2, relative to ^{60}Co gamma rays.

B. RBE literature reviews and experimental studies

267. In studies aimed at deriving values of RBE for tritium beta radiation, there is the potential for the values obtained to depend on the total dose and rate at which dose from both tritium and the reference radiation are delivered. In the case of ^3H , the dose is expected to be protracted in time since the dose rate is dictated by the rate of tritium loss from the body and, to lesser extent, by its radioactive disintegration. Experiments using X- or gamma rays, on the other hand, often deliver dose in a single acute exposure because this is more convenient in practice. It is generally accepted that the same dose delivered in a protracted manner can have a lower effect than an acute dose would, due to the greater opportunity for DNA repair in the protracted case [I13, N3, N7, U7, U8].

268. Most of the lower values for the RBE of tritium reported in the literature are from studies that used higher doses and dose rates of 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 tritium RBE studies was carried out by Ujeno [U2] illustrated this phenomenon. Those studies, which included external reference radiation, showed a tendency for an inverse relationship between dose rate and RBE value. The author concluded that use of a RBE value of 1 would be reasonable for assessing the dose from a very large intake of tritium but that a figure larger than 1 would be more appropriate for environmental and occupational exposure situations. Therefore, the differences in RBE values can be viewed assuming that the response at high acute doses is less dependent upon or is independent of photon/electron energy.

269. In numerous studies of tritium radiobiological effects conducted since the early 1960s, the focus has been on the RBE values for the tritium beta radiation for assessing stochastic health risks (primarily cancer induction and heritable effects) of lower doses in mammals to be used in radiation protection of humans and environment. Those studies were carefully reviewed by several groups of authors over the past two decades [H16, K20, L12, O1, P2, S23].

270. Straume and Carsten [S23] provided a comprehensive review of the literature on the carcinogenic, heritable, developmental and reproductive effects associated with tritium exposure. They identified 33 published studies on the RBE of the tritium beta radiation using HTO: 12 studies used X-rays (200–500 kVp) as the reference radiation; 21 studies used gamma rays from ^{137}Cs or ^{60}Co as the reference radiation. Combining these studies, they calculated an arithmetic mean of 1.8 and 2.3 for the range of RBE values when X-rays and gamma rays, respectively, were used as the reference radiation.

271. The AGIR report [H16], discussed RBE values of tritium beta radiation and also the relationship between RBE value and the dose and dose-rate effectiveness factor (DDREF), the use of different reference radiation, and some experimental studies. They noted that the RBE values for tritium beta radiation using HTO from a wide variety of cellular and genetic studies were generally found to be in the range of 1–2 when X-rays were the reference, and 2–3 when gamma rays were the reference.

272. Little and Lambert [L12] subsequently conducted a comprehensive analysis of several peer-reviewed studies with the intent of determining maximum low-dose RBE values, denoted RBE_M . The biological end points of these tritium studies included carcinogenesis, chromosomal aberration, and cell death. The studies were divided into in vivo and in vitro experiments, and subdivided further according to whether the reference exposure was prolonged or acute. To be classified as a prolonged exposure, the external irradiation dose rate had to be comparable to that for exposure to tritium. The authors concluded that the overall aggregated results implied RBE values with a central estimate in the range of 1.2–2.5 and a 97.5 upper percentile of no more than 3.0. The six studies with prolonged gamma radiation as reference exposure and end points apart from cell survival yielded aggregate RBE values of 2.19 (95% CI: 2.04, 2.33) versus 1.17 (95% CI: 0.96, 1.39) when chronic X-rays were used as reference radiation.

273. A review of RBE values by Kocher et al. [K20] was conducted to support assessments of cancer risk from known exposure to ionizing radiation and estimation of the probability of causation. A defining characteristic of analysis of data on RBEs by these authors was that estimates of radiation effectiveness factors were expressed as subjective probability distributions to represent uncertainty arising from uncertainties in the underlying estimates of RBE values.

C. Factors affecting RBE values

274. The reference radiation types used in RBE studies were 150–250 kVp X-rays, and gamma radiation from ^{60}Co (1,173 and 1,332 keV) or ^{137}Cs (662 keV). However, studies such as those by Bond et al. [B23], Sasaki [S3] and Schmid [S6] reported in the ICRP Publication 92 [I20], demonstrated that orthovoltage X-rays are typically about twice as effective at low doses as are high energy gamma rays and that this difference is consistent with biophysical calculations [E2, K9].

275. Straume and Carsten [S23] discussed this issue, indicating that RBE can vary significantly with changes in dose rate and radiation quality. Furthermore, as noted by AGIR [H16], the dose–response curve for acute doses of low-LET reference radiation is often curvilinear in relation to the response to radiation with higher LET. This curvilinearity of response to reference radiation in the low-dose range means that the RBE between the two types of radiation is maximum at lower doses. The maximal RBE value is referred to as the RBE_M .

276. Cell mutations and chromosome aberrations represent chromosome damage that could lead to cancer development. However, as Little and Lambert [L12] noted, chromosome damage may be only one of many steps in carcinogenesis. Hill [H11] also pointed out that many studies used the induction of

dicentric aberrations as an end point because it was a reliable and repeatable method for comparing biological response, recognizing that this was a short-term effect not directly relevant to quantitative assessment of long-term stochastic effects.

277. The yield of DSBs is considered to be strongly dependent on biological systems and cellular environments and has been used for RBE determinations. After reviewing data on DSB yields for low-energy electrons and high-energy protons of comparable microdosimetric characteristics to those of tritium in the dimensions relevant to DSBs, Chen [C15] estimated that average yields of 2.7, 0.93, 2.4 and 1.6×10^{-11} DSBs/Gy·Da were reasonable estimates of DSB yields for tritium in plasmid DNAs, yeast cells, Chinese hamster V79 cells and human fibroblasts, respectively. If a biological system is not specified, the DSB yield from tritium exposure can be estimated as a simple average over experimentally determined yields as $2.3 \pm 0.7 \times 10^{-11}$ DSBs/Gy·Da in various biological systems.

D. Summary of RBE value determinations

278. In summary, about 50 different experimental estimates of the RBE values for the tritium beta radiation in animals or animal cells have been reported that ranged from 1.0 to 5.0 (centred around 2-2.5) and 0.4-8.0 (centred around 1.5-2) with gamma rays and orthovoltage X-rays as reference radiation, respectively. There is tendency for RBE values to increase with decreasing doses. RBE values derived from stochastic effect studies are generally higher (centred around 2.5-3 compared with prolonged gamma radiation) than those obtained from studies of deterministic effects (cell killing in vivo and in vitro). Considerable variation from one experiment to another exists. Only three experimental studies directly addressed carcinogenic effects in mammals. In addition to experimental uncertainty and the choice of a reference radiation, a number of other factors contribute to this variability, including differences in radiosensitivity of tissues, organs and organisms; differences in the biological end points; variation in dose and dose rate; and choice of in vitro or in vivo test systems.

279. Tables 19 to 22 provide summaries of the studies of the RBE of tritium beta radiation in mammals, the studies being grouped by the experimental condition (in vivo studies in tables 19 and 20, and in vitro studies, including murine and human cells, in tables 21 and 22) and according to the type of radiation used as reference (X-rays in tables 19 and 21, and gamma rays in tables 20 and 22). In all the listed studies, tritium was used in HTO form. Tables 19 and 22 present studies in chronological order with both stochastic and deterministic end points; these are separated in summary table 23. When two or more end points or various exposure conditions were used in the same study, they are presented in tables as separate studies.

280. Using the data from some of these studies, Little and Lambert [L12] recalculated RBE values for the tritium beta radiation and their results are also provided in the tables 19 to 22 and used in summary table 23.

Table 19. In vivo studies using X-rays as reference radiation

<i>Study reference</i>	<i>Biological end point</i>	<i>Exposure conditions</i>	<i>Reference radiation</i>	<i>Dose range (Gy)</i>	<i>RBE values for the tritium beta radiation (95% CI where indicated)</i>
Lambert [L3]	Spermatogonial survival in mice	Single injection of HTO and prolonged X-rays	200 kVp X-rays	0.05 tritium beta 0.11 X-rays	2.3
Gragtmans et al. [G9]	Cumulative incidence of mammary tumours in S-D rats	Five HTO injections every two days and acute and prolonged X-rays	200 kVp X-rays	0.46–3.85 tritium beta 0.57–1.78 X-rays (acute) 0.29–2.00 X-rays (prolonged)	0.68 1.1–1.3
Gragtmans et al. [G9]	Cumulative percentage of mammary tumours in S-D rats	Five HTO injections every two days and acute and prolonged X-rays	200 kVp X-rays	0.46–3.85 tritium beta 0.57–1.78 X-rays (acute) 0.29–2.00 X-rays (prolonged)	0.83 n.a.
Chopra and Heddle [C21]	Chromosome aberrations in peripheral blood in female mice	Single injection of HTO and prolonged X-rays	250 kVp X-rays	2.0–6.0 tritium beta 1.5–6 X-rays	1.14 (0.8–1.5)
Chopra and Heddle [C21]	Chromosome aberrations in spermatogonia in mice	Single injection of HTO and prolonged X-rays	250 kVp X-rays	1.5–4.5 tritium beta 1.5–4.5 X-rays	1.21 (0.8–1.9)
Johnson et al. [J5]	Myeloid leukaemia in mice	Single injection of HTO and prolonged X-rays	200/150 kVp X-rays	0.85–3.04 tritium beta 1.06–2.64 X-rays	1.24 (0.63–1.85)
Kozlowski et al. [K24]	Chromosome aberrations in bone marrow in mice	Continuous intake of HTO and acute X-rays	250 kVp X-rays	0.6 tritium beta 0.5 X-rays	1–2 0.43 (0.20–0.81) ^a

^a Recalculated value by Little and Lambert [L12].

Table 20. In vivo studies using gamma rays (prolonged irradiation) as reference radiation

<i>Study reference</i>	<i>Biological end point</i>	<i>Exposure conditions</i>	<i>Reference radiation</i>	<i>Dose range (Gy)</i>	<i>RBE values for the tritium beta radiation (95% CI where indicated)</i>
Furchner [F13]	Mortality in mice	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	5.3–16.5 tritium beta 12.3–16.5 gamma	1.7
Dobson and Kwan [D6, D7]	Oocyte survival in mice	Continuous intake of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.07–0.88 tritium beta 0.22–1.25 gamma	2.8
Carr and Nolan [C9]	Testes weight loss in mice	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.14–0.58 tritium beta 0.58 gamma	1.43 (1.06–1.80)
Russell et al. [R17]	Seven specific locus mutations in F1 mice from spermatogonia exposure	Single injection of HTO and prolonged gamma	Caesium-137 gamma 0.4 Gy/h	6–9 tritium beta	2.2
Balonov et al. [B10]	Testes weight loss in mice	Single injection of HTO and prolonged gamma	Caesium-137 gamma (tritium simulator)	0.12–3.4 0.25–3.7	1.8–2.2
Balonov et al. [B9, B12]	Dominant lethal mutations in male mice	Single injection of HTO and prolonged gamma	Caesium-137 gamma (tritium simulator)	0.5–3.4 tritium beta 1.0–3.7 gamma	1.6–2.2 RBE _M = 2.6
Pomerantseva et al. [P10] and Balonov et al. [B12]	Reciprocal translocations in mice spermatogonia	Single injection of HTO and prolonged gamma	Caesium-137 gamma (tritium simulator)	0.5–3.4 tritium beta 1.0–3.7 gamma	1.8
Zhou et al. [Z5]	Dominant lethal mutations in female mice	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.04–0.91 tritium beta 0.53–2.7 gamma	2.5 2.94 (2.00–4.28) ^a
Ijiri [I26]	Apoptosis of small intestinal cells in mice	Single injection of HTO and prolonged gamma	Caesium-137 gamma (tritium simulator)	0.0–0.29 tritium beta 0.0–2.9 gamma	2.1 (1.7–2.5) 1.6 (1.2–2.0) ^a
Ijiri [I26]	Apoptosis of descending colon cells in mice	Single injection of HTO and prolonged gamma	Caesium-137 gamma (tritium simulator)	0.0–0.2 tritium beta 0.0–0.4 gamma	1.8 (1.4–2.2) 1.4 (1.2–1.6) ^a
Satow et al. [S5]	Oocyte killing in mice	Single injection of HTO and prolonged gamma	Caesium-137 gamma, (tritium simulator)	0.04–0.25 tritium beta 0.04–0.25 gamma	1.1–3.5
Satow et al. [S5]	Teratogenic effects on rat embryos	Single injection of HTO and prolonged gamma	Caesium-137 gamma (tritium simulator)	2.0–6.0 tritium beta 1.75–6.8 gamma	2.6 1.01 (0.57–1.78) ^a
Zhou et al. [Z6]	Dominant lethal mutations-oocytes	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.7 gamma	2.8–3.4
Zhou et al. [Z6]	Dominant lethal mutations-spermatocytes	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.1 gamma	1.6–3.9
Zhou et al. [Z6]	Dominant skeletal mutations-spermatogonia	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.9 gamma	3.5–3.9

<i>Study reference</i>	<i>Biological end point</i>	<i>Exposure conditions</i>	<i>Reference radiation</i>	<i>Dose range (Gy)</i>	<i>RBE values for the tritium beta radiation (95% CI where indicated)</i>
Zhou et al. [Z6]	Oocyte survival	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.9 gamma	1.4–2.0
Zhou et al. [Z6]	Spermatogonial survival	Single injection of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.9 gamma	2.1–2.8
Zhou et al. [Z6]	Chromosome aberrations-spermatogonia	Continuous intake of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.9 gamma	2.9–3.8
Zhou et al. [Z6]	Primary oocyte survival	Continuous intake of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.9 gamma	1.5
Zhou et al. [Z6]	Spermatogonial survival	Continuous intake of HTO and prolonged gamma	Cobalt-60 gamma (tritium simulator)	0.2–0.6 tritium beta 0.7–2.9 gamma	2.3–2.5
Seyama et al. [S13]	Cancer in mice	Single injection of HTO and prolonged gamma	Caesium-137 gamma (tritium simulator)	2.0–10.5 tritium beta and gamma	2.5 ^b

^a Recalculated value by Little and Lambert [L12].

^b Calculated at 500 days.

Table 21. In vitro studies using X-rays as reference radiation

<i>Study reference</i>	<i>Biological end point</i>	<i>Exposure conditions</i>	<i>Reference radiation</i>	<i>Dose range (Gy)</i>	<i>RBE values for the tritium beta radiation (95% CI where indicated)</i>
Bocian et al. [B20]	Chromosome aberrations in human lymphocytes	HTO (2 h or 53 h) and acute X-rays	180 kVp X-rays	0.28–2.45 tritium beta 0.5–3.0 X-rays	1.17 (1.13–1.21) 1.91 (0.64, 3.18) ^b
Prosser et al. [P14]	Chromosome aberrations in human lymphocytes	HTO (30 min or 24 h) and acute X-ray	250 kVp X-rays	0.2–4.0 tritium beta 0.1–4.1 X-rays	RBE _M =1.13 (0.95–1.31)
Vulpis [V3]	Chromosome aberrations in human lymphocytes	HTO (20 min to 2.5 h) and acute X-rays	250 kVp X-rays	0.25–7.0 tritium beta 0.05–9.0 X-rays	2.6 at 0.25 Gy 1.10 at 7 Gy 8.0 (0.2–15.8) ^a
Little [L11]	Transformation in mouse cells	HTO (5–168 h) and acute X-rays	220 kVp X-rays	0.25–5.0 tritium beta 0.5–4.0 X-rays	<1–2 ^a
Kamiguchi et al. [K3, K4]	Chromosome-type aberrations in human sperm	HTO (~80') and acute X-rays	220 kVp X-rays	0.14–2.06 tritium beta 0.25–3.74 tritium beta 0.23–1.82 X-rays	1.08 max dose 1.96 min dose 1.39 (1.26–1.54) ^a
Kamiguchi et al. [K4]	Chromatid-type aberrations in human sperm	HTO (~80') and acute X-rays	220 kVp X-rays	0.14–2.06 tritium beta 0.25–3.74 tritium beta 0.23–1.82 X-rays	1.65 max dose 3.0 min dose 2.17 (1.73–2.73) ^a
Kamiguchi et al. [K4]	Chromosome breakage aberrations in human sperm	HTO (~80') and acute X-rays	220 kVp X-rays	0.14–2.06 tritium beta 0.25–3.74 tritium beta 0.23–1.82 X-ray	1.14 max dose 2.07 min dose 1.47 (1.33–1.62) ^a
Kamiguchi et al. [K4]	Chromosome-exchange aberrations in human sperm	HTO (~80') and acute X-rays	220 kVp X-rays	0.14–2.06 tritium beta 0.25–3.74 tritium beta 0.23–1.82 X-rays	1.54 min dose 2.81 min dose 1.96 (1.49–2.62) ^a

^a Recalculated by Little and Lambert [L12].

^b Recalculated by Prosser et al. [P14].

Table 22. In vitro studies using gamma rays (prolonged irradiation) as reference radiation

<i>Study reference</i>	<i>Biological end point</i>	<i>Exposure conditions</i>	<i>Reference radiation</i>	<i>Dose range (Gy)</i>	<i>RBE values for the tritium beta radiation (95% CI where indicated)</i>
Ueno et al. [U1]	Cell survival in mouse cells	HTO (20 h) and prolonged gamma	Cobalt-60 gamma	1.3–8.0 tritium beta 2.0–9.0 gamma	1.5 1.3–1.6 ^a
Ueno et al. [U1]	Micronuclei in mouse cells	HTO (20 h) and prolonged gamma	Cobalt-60 gamma	1.3–8.0 tritium beta 2.0–9.0 gamma	2.0 1.8–2.3 ^a
Ueno et al. [U1]	Mutation induction in mouse cells	HTO (20 h) and prolonged gamma	Cobalt-60 gamma	1.5–4.7 tritium beta 1.5–4.7 gamma	1.8
Yamada et al. [Y1]	Mouse pronuclear embryo cell survival	Prolonged HTO and prolonged gamma	Cobalt-60 gamma	0.009–0.07 Gy/h tritium beta 0.02–0.12 Gy/h gamma ^a	1.09 (0.50–1.68)
Yamada et al. [Y1]	Mouse early 2-cell embryo survival	Prolonged HTO and prolonged gamma	Cobalt-60 gamma	0.009–0.10 Gy/h tritium beta 0.02–0.12 Gy/h gamma ^a	1.70 (1.21–2.20)
Yamada et al. [Y1]	Mouse late 2-cell embryo survival	Prolonged HTO and prolonged gamma	Cobalt-60 gamma	0.009–0.19 Gy/h tritium beta 0.02–0.30 Gy/h gamma ^a	1.25 (0.88–1.62)
Matsuda et al. [M3]	Chromosome aberrations in mouse zygotes	HTO (2 h) and prolonged gamma	Cobalt-60 gamma	0.09–0.34 tritium beta 0.05–0.30 gamma	2.0 1.62 (1.30–2.07) ^a
Tanaka et al. [T7]	Dicentric chromosome aberrations in human lymphocytes	Prolonged HTO and prolonged gamma	Cobalt-60 and Caesium-137 gamma	0.14–2.10 tritium beta 0.05–4.0 gamma	2.1–2.3 2.39 (2.20–2.59) ^a
Tanaka et al. [T7]	Chromosome aberrations in human lymphocytes: centric rings	Prolonged HTO and prolonged gamma	Cobalt-60 and Caesium-137 gamma	0.14–2.10 tritium beta 0.05–4.0 gamma	n.a. 3.14 (2.56–3.86) ^a
Tanaka et al. [T7]	Chromosome aberrations in human lymphocytes: dicentrics and centric rings	Prolonged HTO and prolonged gamma	Cobalt-60 and Caesium-137 gamma	0.14–2.10 tritium beta 0.05–4.0 gamma	2.2–2.7 2.52 (2.33–2.72) ^a
Tanaka et al. [T7]	Chromosome aberrations total in human bone marrow cells	Prolonged HTO and prolonged gamma	Cobalt-60 and Caesium-137 gamma	0.13–1.11 tritium beta 0.25–2.0 gamma	1.13 1.30 (0.96–1.76) ^a
Tanaka et al. [T7]	Chromosome aberrations in human bone marrow cells (chromatids)	Prolonged HTO and prolonged gamma	Cobalt-60 and Caesium-137 gamma	0.13–1.11 tritium beta 0.25–2.0 gamma	3.1 4.96 (3.73–6.59) ^a

^a Recalculated by Little and Lambert [L12].

281. The RBE values derived from 48 experiments, on mammals in vivo (28) and mammalian cells in vitro (20), is presented in table 23. The RBE values are presented in three study groups: for all studies, for studies of stochastic effects (carcinogenic, genetic, cytogenetic, cell transformations), and for carcinogenic effect in mammals separately; the latter two compared with effects of prolonged exposure to photon radiation (gamma and X-rays). The latter two RBE sets of values are more relevant to effects of low radiation doses on humans. In line with the work of Little and Lambert [L12], the data presented in table 23 are combined mostly from maximum low-dose RBE values (RBE_M if available).

Table 23. Summary of tritium radiation RBE values from experimental studies using different end points and different reference radiation

Studies	Reference radiation	All studies		Studies of stochastic effects ^a with prolonged reference exposure		Studies of carcinogenic effect in mammals with prolonged reference exposure	
		Number of studies	RBE value (mean/median and range)	Number of studies	RBE value (mean/median and range)	Number of studies	RBE value (mean/median and range)
In vivo	Prolonged gamma	21	2.5 / 2.5 (1.0–3.9)	9	3.0 / 3.0 (1.8–3.9)	1	2.5
	X-rays	7	1.1 / 1.2 (0.4–2.3)	4	1.2 / 1.2 (1.1–1.3)	2	1.3 / 1.3 (1.2–1.3)
In vitro	Prolonged gamma	12	2.1 / 1.8 (1.1–5.0)	8	2.5 / 2.4 (1.3–5.0)	—	—
	Acute X-rays	8	2.4 / 1.7 (1.1–8.0)	—	—	—	—

^a Including carcinogenic effects.

282. In broad terms, the RBE values from all studies ranged from 1.0 to 5.0 (centred around 2–2.5) and 0.4–8.0 (centred around 1.5–2) with gamma rays and orthovoltage X-rays as reference radiation, respectively. Studies show a general tendency of RBE values to increase with lower doses. There is some tendency for RBE values derived from studies of stochastic effects (centred around 2.5–3 when compared with prolonged gamma radiation) to be generally higher than those obtained from studies of deterministic effects such as cell killing in vivo and in vitro (not presented separately in table 23).

283. Only three of the studies identified have used cancer incidence as an end point [G9, J5, S13]. These studies include accelerated cancer incidence, i.e. cancer occurring at an early age, rather than an increase in the overall incidence of disease, as the end point. The small number of studies and ambiguous end points limit the opportunity to come to a clear conclusion regarding RBE values or their range for the carcinogenic effect of tritium in mammals.

VIII. EPIDEMIOLOGICAL STUDIES

284. Epidemiological studies of groups of people exposed (or potentially exposed) to tritium fall into two broad categories: those exposed at work and those exposed in the environment. Workplace exposure generally provides a better opportunity for assessing the tritium-specific risks to health following doses received by particular tissues or organs from internally deposited tritium because monitoring for occupational exposure to tritium will usually have been conducted at the facility where exposure occurred (or potentially occurred) and doses may be estimated from these monitoring results. Further, data from monitoring for other sources of occupational exposure to ionizing radiation are likely to be available if assessments for exposure to tritium have been performed at a facility. Such dose monitoring data are required when tritium-specific risk is estimated to distinguish it from other radiation risk sources. Epidemiological studies of tritium workers have generally been unsatisfactory regarding the use of tritium-specific doses monitoring data. Moreover, studies of occupational exposure involve mainly adult men and do not include children who may be more sensitive to tritium-induced adverse health effects.

285. Members of the public are exposed not only to natural sources of tritium, but also to anthropogenic sources such as tritium produced in nuclear weapon explosions, particularly the fallout from the atmospheric thermonuclear weapon tests of the early 1960s. Public exposure to tritium also occurs as a result of releases from nuclear power and nuclear weapon facilities, or from luminizing, radiochemical and other plants, and from devices containing tritium, such as wristwatches with tritium-based luminous paint or emergency exit signs. Studies of environmental exposure to tritium have the advantage that they usually involve exposed (or potentially exposed) individuals other than just adults who are fit enough to be at work. However, a substantial drawback of such environmental studies is that bioassay monitoring for exposure to tritium is unlikely to have been conducted, which greatly reduces the reliability of environmental studies to assess risks specific to tritium exposure. However, there are some instances where such monitoring has been reported for environmental studies.

286. Any analysis of risk in terms of tritium exposure will need to take account of other sources of radiation exposure, such as penetrating radiation from external sources and from intake of other radionuclides, to appropriately distinguish tritium-specific risks from those arising from other sources of radiation exposure. It is important to ensure, if there is a positive correlation between tritium dose and other radiation doses, that any risk from these other radiation doses are taken into consideration.

A. Studies of occupational exposure

287. Given the variety of sources of exposure to tritium, epidemiological studies of the risks to health from tritium exposure would seem to be attractive, especially in an occupational setting since those workers potentially exposed to tritium are likely to have been monitored for such potential exposure through the analysis of urine samples. The results of this monitoring should have been recorded and, if these records still exist, the data could be made available for scientific use through the production of tritium-specific doses to organs/tissues. Unfortunately, although a number of epidemiological studies of tritium workers have been conducted in various countries, few of these studies have made direct use of tritium monitoring data or have used tritium-specific doses derived from urinalysis data. Studies of exposure to tritium in the workplace are considered below in four broad groupings of studies.

288. All workers at installations with nuclear reactors or reprocessing plants will have been exposed to tritium to some extent because tritium is produced (at a low frequency) in ternary nuclear fission. However, studies of workers exposed to tritium have concentrated on those workers who are likely to have received non-trivial doses from tritium because of certain features of operations at the sites, such as the presence of heavy-water-moderated reactors or tritium production or processing facilities. The epidemiological studies considered in this section focus on studies of workers at such nuclear sites rather than workers exposed to very low levels of tritium because of work at other sites, including light-water-moderated or gas cooled, graphite moderated reactors.

1. Studies of workers at installations where tritium is present

289. The weakest of the epidemiological studies of occupational exposure to tritium are those studies that consider workers at sites where exposure to tritium occurs, but make no distinction between workers exposed (or potentially exposed) to tritium and other workers at the site not so exposed. Both the workers monitored for potential exposure to tritium and at least some of the other workers at a site are likely to have been exposed to other sources of radiation.

290. For example, Cragle et al. [C31] studied mortality among almost 10,000 white male workers employed at the Savannah River Site, United States during 1952–1980, and they noted that around 5,000 workers would have been exposed to tritium with 800 of these having received a dose of at least 0.5 mSv from tritium. The workers were found to have standardized mortality ratios (SMRs) that were generally less than 1.0 when compared to the population of the United States (which is probably a reflection of the “healthy worker effect”), but no distinction was made in the analysis between workers monitored for exposure to tritium and other workers. So, although the results of this study are broadly reassuring as far as workers who have been employed at the Savannah River Site, United States are concerned, they are of limited informative value when assessing the risk arising from exposure to tritium, except that the risk of tritium exposure cannot have been grossly underestimated or this would be apparent in the overall results of the study.

291. In another study, McGeoghegan and Binks [M5] examined mortality and cancer incidence among workers at the Capenhurst site in the United Kingdom, a nuclear installation that has handled tritium in relation to nuclear weapon production. This study did not specifically identify those workers monitored for potential exposure to tritium. McGeoghegan and Binks [M5] reported that radiation workers at Capenhurst had a significantly low SMR for all causes of death and a significantly low standardized registration ratio (SRR) for all incident cancer, but workers at this site were exposed to external radiation and to radionuclides other than tritium and it is not possible in this study to disentangle risk posed by tritium from that posed by other sources of radiation. The findings of studies of workforces at establishments where tritium is present to some extent in non-trivial quantities, but which do not distinguish tritium workers from other radiation workers, are summarized in appendix A, table A1.

2. Studies of workers monitored for potential exposure to tritium

292. The next set of studies embraces those workers who have been monitored for potential exposure to tritium, but for whom tritium-specific doses are not available or, if available, have not been used. These studies typically identify those workers at an installation who have been monitored for potential exposure to tritium and then calculate SMRs for that particular group. For example, in the study of workers of the United Kingdom Atomic Energy Authority (UKAEA), Beral et al. [B17] identified the subset of workers who had been monitored for potential exposure to tritium and calculated separate SMRs.

293. In some studies, the SMRs for the tritium workers are compared with the SMRs for other workers at the installation to generate rate ratios (RRs), which have the benefit of addressing (at least, to some extent) the healthy worker effect that may be present if the analysis is limited to the calculation of SMRs alone and the reference population is the general population of a country or region. For example, in a follow-up study of UKAEA workers, Fraser et al. [F12] not only calculated SMRs for tritium workers but also compared these SMRs with equivalent SMRs for radiation workers at the UKAEA who had not been monitored for potential exposure to tritium, to generate RRs. However, the absence of tritium-specific doses in these studies means that quantitative tritium-specific risk estimates cannot be generated, although the calculation of SMRs and RRs for tritium workers does permit the identification of possible large effects arising from exposure to tritium, as happened when Beral et al. and Fraser et al. [B17, F12] found significantly raised prostate cancer SMRs and RRs for UKAEA workers who had been monitored for potential exposure to tritium. The findings of this group of studies of workers monitored for potential exposure to tritium are presented in appendix A, table A2.

3. Studies of workers using occupational dose estimates

294. Some studies of workplace exposure to tritium have used occupational dose estimates, but have not directly used estimates of tritium-specific doses, if available. Typically, these studies identify workers at an installation who have been monitored for potential exposure to tritium, calculate SMRs and possibly also RRs, and then conduct a dose–response analysis in terms of recorded doses of penetrating radiation from external sources rather than tritium-specific doses. For example, in a nested case-control study of prostate cancer risk among UKAEA workers, Rooney et al. [R14] found that for workers who had been monitored for potential exposure to tritium (or to one of four other radionuclides frequently found in the same workplace environment as tritium), the relative risk of prostate cancer significantly increased with the recorded dose of external radiation, whereas it did not for other workers. For those workers either monitored for potential exposure to tritium or not so monitored but assessed to have the potential for exposure to tritium, the relative risk significantly increased with the assessed level of potential exposure. However, although the significantly increased relative risk was confined to those workers monitored for potential exposure to tritium (rather than those assessed to be potentially exposed, but not monitored) no use was made of the tritium monitoring data to derive tritium-specific doses for analysis [R14]. The absence of tritium-specific doses in this study substantially limits the interpretation of the associations found in terms of tritium-specific risk.

295. Sometimes tritium doses have been derived from monitoring data but are then included with external doses since it is usually argued that tritium produces whole-body doses that are essentially equivalent to (and generally smaller than) doses received from external sources of penetrating gamma rays. For example, in the study of workers of the United Kingdom Atomic Weapons Establishment (AWE), Beral et al. [B18] added the recorded whole-body dose from tritium based upon monitoring data to the recorded whole-body dose from external sources. They found a significantly increasing trend of RR for prostate cancer mortality with increasing whole-body dose (driven by one death with a cumulative external dose >100 mSv), but did not conduct an analysis in which the tritium-specific dose was separated out from the external dose. Any inference concerning a tritium-specific risk obtained from such studies of a positive dose–response for tritium should rely on an assumption of a positive correlation between external doses and tritium doses.

296. Zablotska et al. [Z1] studied mortality in Canadian nuclear industry workers, and added recorded tritium doses derived from urinalysis results to recorded doses from external sources. Again, this did not permit any tritium-specific risk to be identified from the published results because any findings of analyses based on tritium-specific doses were not presented. However, of interest are the results for the

ERR/Sv for leukaemia (excluding CLL) and for all solid cancer, with external doses combined with tritium doses, in comparison with the ERR/Sv estimates using external doses not combined with tritium doses (i.e. for external doses alone): for the combined doses, the ERR/Sv estimates are 18.9 (95% CI: <-2.08, 138) and 2.80 (95% CI: -0.038, 7.13), respectively, and for external dose alone, the ERR/Sv estimates are 16.3 (CI not given) and 2.67 (CI not given), respectively. Therefore, the ERR/Sv estimates show a small increase when the tritium doses are included with external doses but, unfortunately, it is not possible from the published results to derive ERR/Sv estimates for tritium doses alone. The findings of studies that have used records of occupational doses of radiation, but have not used tritium-specific doses for the analysis, are presented in appendix A, table A3.

4. Studies of workers using tritium-specific dose estimates

297. Few studies of workers have tritium-specific dose estimates derived from occupational exposure records and use these doses in a tritium-specific risk analysis. If tritium-specific doses are used in an analysis that appropriately adjusts for any effect of doses received from external sources of radiation (and for any doses received from any other internally deposited radionuclides), these tritium-specific doses should enable estimates to be made of tritium-specific risks, although due account must be taken of the precision of these estimates since the number of workers included in such an analysis may be small, leading to limited statistical power.

298. Zablotska et al. [Z2] conducted a study of Canadian nuclear industry workers and used tritium-specific doses in addition to external doses. However, in most analyses, tritium doses were combined with external doses, so the tritium-specific risk was assessed for only one analysis: the ERR/Sv for all solid cancer was reported as -4.71 (95% CI: <-5.92, 8.58). The wide confidence interval for this estimate is indicative of the limited power of studies of tritium exposure in just one country.

299. Hamra et al. [H4] studied the tritium-specific risk of leukaemia among workers at the SRS and supplemented tritium-specific doses derived directly from occupational monitoring records with annual tritium doses reconstructed from external dose records using tritium monitoring results combined with a job exposure matrix. The authors, in a Bayesian analysis, reported that for leukaemia excluding CLL, the ERR/10 mGy estimate was -0.281 (90% credibility interval: -1.136, 0.548) while if the constraint was imposed that the ERR/10 mGy for the dose from tritium beta particles was greater than that for the dose from penetrating gamma rays, then the ERR/10 mGy estimate became 0.334 (90% credibility interval: 0.049, 0.817). The sensitivity of the results to this constraint and the width of the credibility intervals are notable.

300. Studies of adverse health effects in the offspring of workers exposed to tritium in the preconceptional period, which have made use of tritium monitoring results to calculate tritium-specific doses, have been conducted in Canada [G10, M9] and the United Kingdom [H17, H18]. No association between adverse health effects in offspring and the preconceptional dose derived from tritium monitoring data were found. However, the UK-study illustrated a difficulty in the interpretation of findings based upon the assessed potential for historical exposure to tritium rather than the use of monitoring of dose records. In this regard, a highly significant association between the risk of leukaemia and non-Hodgkin's lymphoma in the offspring of Sellafield workers was assessed to potential for exposure to tritium of fathers in the preconceptional period and was not confirmed by tritium dose monitoring data. This calls into question the reliability of assessed potential for exposure to tritium during historical operations when monitoring of those workers most likely to have received doses resulted in different conclusions. The findings of these studies that have explicitly used tritium-specific doses are summarized in appendix A, table A4.

B. Studies of environmental exposure

301. The situation is much more uncertain in studies of members of the public potentially exposed to tritium because direct measurements of tritium body burdens in non-occupationally exposed people are rare and not undertaken as part of an epidemiological study. Therefore, any individual assessments of likely environmental exposure to tritium for use in epidemiological studies have to rely upon modelling results, such as estimates of intake and consequent doses to people based upon measurements of tritium in environmental media; but the derived tritium-specific doses are generally very small, leading to extremely low statistical power to detect any tritium-specific effects. Some studies rely only on measures of proximity to a source of tritium, such as a nuclear facility, and this inevitably leads to results that have an uncertain interpretation because the relationship between linear distance from the facility and tritium dose has not been established, and the relationship between distance and level of exposure could be very complex and far from being directly proportional if, say, the wind rose is significantly anisotropic. Further, such studies must take other relevant exposure into account, including other sources of radiation. As a consequence, studies of public exposure to tritium have to be examined carefully and their findings need to be interpreted accordingly.

302. In only one epidemiological study of environmental exposure to tritium has individually assessed exposure to tritium been used, and that is in a historical cohort study of cancer incidence during 1986-2005 among residents of two areas near the Pickering heavy-water-moderated CANDU reactor site in Ontario, Canada [W5]. In this study, exposure to tritium at residences occupied in 1985 was estimated from an atmospheric dispersion model that used discharge and meteorological data, and the exposure data were used in an analysis of cancer risk in relation to tritium exposure. Assessed annual individual effective doses from tritium were very low (maximum for an adult, 2.36 μ Sv), and the limited number of cases of cancer available for study presented problems for some of the analyses, so the lack of detection of an effect of tritium exposure upon cancer risk must be viewed in this light. Nonetheless, this study does illustrate what may be done to address tritium-specific risk in a study of environmental exposure, but it also demonstrates the problems of achieving reasonable statistical power in a practicably sized study of such exposure.

303. With only one epidemiological study of environmental exposure to tritium that takes account of assessed tritium-specific doses to individuals, very little can be reliably inferred from studies of health effects in the vicinities of installations producing, processing or storing tritium. Nuclear installations that include nuclear reactors or reprocessing plants inevitably discharge tritium to some limited extent because, for example, ternary fission product tritium will be produced/processed during the operation at such installations, although such discharges are likely to lead to very small doses. Studies around installations that include heavy-water-moderated reactors or tritium production or processing plants are likely to address higher doses from tritium discharges, although even then tritium-specific doses will, in general, be low; few of these studies have been conducted, and they will be briefly considered in appendix A, table A5.

304. One possibility that can be eliminated by environmental studies is that the risk of childhood leukaemia from exposure to tritium has been grossly underestimated, and that this is the cause of excesses of childhood leukaemia incidence that have been reported around certain nuclear installations, as has been suggested by Fairlie [F1]. Substantial quantities of tritium were released into the environment by atmospheric nuclear weapon testing during the late 1950s and early 1960s, particularly by thermonuclear weapon testing in the early 1960s [U8]. If there has been a serious underestimation of the tritium-specific risk of childhood leukaemia then it would be apparent in the rates of childhood leukaemia incidence following this period of intense nuclear weapon testing, particularly in the Northern Hemisphere where most of the testing took place and tritium-specific doses were highest.

Examination of childhood leukaemia incidence rates from around the world has not revealed any evidence for an increase of childhood leukaemia risk that might be attributed to tritium fallout, or that the risk of childhood leukaemia has been greater in the Northern Hemisphere than in the Southern Hemisphere after this period of intense nuclear weapon testing [W1, W2]. It cannot be claimed that the results of this study show that the risk of childhood leukaemia arising from exposure to fallout from nuclear weapon testing is less than predicted by standard radiation-induced leukaemia risk models (or that there is no risk) because the statistical power is insufficient for this purpose, but the study can exclude a risk that is much greater than predicted, as has been claimed.

C. Summary of epidemiological studies

305. The great majority of epidemiological studies of tritium workers have not used estimates of tritium-specific doses in their analyses, which limits the inferences that may be made about tritium-specific risk using the findings of these studies. There is no indication, however, from studies of tritium workers that tritium-specific risks have been seriously underestimated. Some results from a few studies that have used tritium-specific doses are available, which represents progress in the epidemiological approach to tritium-specific risks, but the conclusions that may be drawn about tritium-specific risks to health from these few studies are limited.

306. For scientific purposes, it should not be assumed that the effect per unit absorbed dose for tritium is the same as that for an external source of penetrating gamma rays (i.e. the assumption of an RBE value for tritium beta particles of unity), since this question is a component of the epidemiological study. A separate analysis of risk is required using tissue-specific absorbed doses received from tritium rather than equivalent or effective doses. However, tritium-specific absorbed doses to tissues have only rarely been used.

307. Owing to the limited numbers of tritium workers in particular countries, and limited exposure of most of these workers, it is unlikely that epidemiological studies of individual nuclear facilities, or indeed individual countries, will have sufficient statistical power to have a reasonable prospect of detecting the risks predicted by standard models, or of risks not far removed from those predicted. Consequently, international collaboration is required to provide a study large enough to properly investigate tritium risk. Some studies of tritium workers have already been conducted in Canada, the United Kingdom and the United States. Other candidate countries for studies of tritium workers include France and the Russian Federation, and it is possible that other countries, such as China and India, might be able to contribute worker data. It is clear that a coordinated effort is needed if a serious epidemiological evaluation of tritium risk is to be made.

308. It is unlikely that epidemiological studies of environmental exposure to tritium will produce meaningful tritium-specific risk estimates because such exposure is, in general, unlikely to produce tritium-specific tissue/organ doses that are not low or very low. Further, measures of tritium exposure of members of the public based upon monitoring data are rare, and indirect assessments of tritium-specific doses, particularly those based upon linear distance from a point of discharge, are likely to be associated with considerable uncertainty. Those measurements of the presence of tritium in human tissue that have been made do not indicate that assessments of the amounts of tritium entering members of the general public and being retained have been seriously underestimated.

309. The absence of a discernible impact upon global childhood leukaemia incidence rates of tritium released into the environment by atmospheric nuclear weapon testing demonstrates that the risk of childhood leukaemia posed by tritium has not been grossly underestimated, as has been proposed by some commentators.

IX. RESEARCH NEEDS

(a) *Heterogeneity, concept of mean dose*

310. The biodistribution of organic forms of tritium is heterogeneous within tissues and cells. The issue of the relevance of the mean organ dose concept as a risk indicator therefore arises. There is no appropriate dosimetric model for use in human risk assessment and radiation protection for tritiated nuclear acid precursors. The development of an appropriate microdosimetric approach to better understand the distribution of dose from various organic forms of tritium within a cell and within tissues and organs is of importance. The uptake and long-term retention of heterogeneously distributed organic forms of tritium in tissue and cells is particularly of concern in assessing doses to germ cells, the embryo, the fetus and the infant. Another physico-chemical form of tritium that is a factor of human, mostly occupational, exposure and deserves further study of biodistribution in body organs and tissues and biokinetics is tritium dust and flakes formed in nuclear fusion reactors on carbon, beryllium or tungsten basis.

(b) *RBE studies*

311. Up-to-date methods should be used to gather further knowledge on the RBE of tritium beta particles, especially as OBT, focusing not only on aspects relating to carcinogenesis but also on non-cancer effects. In particular, research is required for the various stages of in utero and early childhood exposure. Research aimed at addressing real or practical situations should be prioritized—for instance long-term intake of HTO/OBT as food. Data regarding the potential induction of heritable/transgenerational effects should be critically assessed. New approaches should be investigated, in the light of the latest advances in biology.

(c) *Mechanistic studies*

312. Mechanistic studies should emphasize cellular damage and notably the types and frequencies of DNA damage caused by tritium beta radiation. Of particular interest is the complexity of DNA damage (that might affect efficiency and fidelity of repair) induced by either DNA synthesis precursors (tritiated thymidine) or tritium-labelled amino acids in chromatin binding proteins, the triggering of (DNA) damage signalling pathways and activation of protective processes (e.g. repair, cell cycle arrest, apoptosis, differentiation) in the context of toxicity, and genome instability. Data are also lacking on the metabolism and biological/mechanistic effects associated with organic tritium (tritiated biochemical substances) in situations of chronic environmental exposure of the public.

(d) *Environmental considerations*

313. Given the still incomplete knowledge on tritium accumulation and behaviour in sediment, targeted multidisciplinary studies with rigorous protocols need to be used to provide experimental verification of the hypotheses regarding the possible influence of the activity of microorganisms in aquatic sediments when organic tritium is remobilized in aquatic animals. In general, the scientific data regarding the conversion of HTO into organic tritium along the food chain should be enhanced. Reliable quantitative estimates are required.

314. Some information on the levels of tritium in the environment is available, but it would be of value to enhance this database. Measurements in targeted environmental media, including those giving a historical record of exposure, such as tree-rings, particularly in the vicinity of tritium-handling facilities, would be desirable to provide additional confidence in the current understanding of tritium behaviour in the environment and its transfer to food.

315. Some measurements of tritium in humans exposed in the environment are available, from urinalysis and measurements in tissue, for example, at autopsy. It would be desirable to expand this rather sparse database by gathering data from urine sampling programmes, particularly in residents near tritium-handling facilities, and from measurements made on various tissues as the opportunities arise.

(e) Epidemiological issues

316. Epidemiological studies are currently very limited in the robustness of their conclusions due to insufficient statistical power and lack of information on tritium-specific doses. It should be noted that recorded tritium doses for workers in presently available reports are of the order of ten milligray, which implies that very large cohorts would be needed to demonstrate a statistically significant increase in cancer risk at conventionally predicted increases in risk. However, there may be facilities not currently included in epidemiological studies at which workers were exposed to relatively high levels of tritium in the early years of tritium production or processing, and it will be important to include such facilities in any international collaboration. Such studies should use available tritium monitoring data, and exposure information may be improved by dose reconstruction methods, such as the job exposure matrix methodology, which has already been used at one tritium production/processing facility. A coordinated international approach based on standardized dosimetric assessments would be required in order to make progress in this field. Such international collaboration is the only realistic prospect of obtaining tritium-specific risk estimates from occupational epidemiological studies.

317. Since tritium will continue to find large-scale use, especially if commercial fusion reactors come into operation, it would be advisable to seriously consider international collaborative projects to investigate risks posed by tritium to workers that make full use of relevant occupational data, and that these studies should be based on a common protocol for the determination of tritium-specific doses from occupational monitoring data.

318. Unless circumstances can be identified in which relatively large numbers of members of the public have been exposed to relatively high levels of tritium, it is difficult to see how tritium-specific risk estimates can be obtained from epidemiological studies. Should a biomarker of tritium-specific exposure be identified and developed, this could provide opportunities for studies but, even then, the very low exposure from industrial tritium releases would be difficult to distinguish from the background presence of tritium.

319. A more realistic approach to assessing exposure and inferring risks to members of the public is careful monitoring for the presence of tritium in the environment in the vicinity of facilities that discharge tritium, and the possible monitoring of tritium in selected members of the public in these areas through, for example, urinalysis. However, monitoring programmes conducted in areas around facilities handling tritium must also record data on the general levels and variability of tritium away from such facilities in order that results can be appropriately interpreted.

X. GENERAL CONCLUSIONS

320. Tritium is a radioactive isotope of hydrogen and thus behaves chemically like hydrogen. Humans are exposed internally to beta radiation emitted by tritium either in occupational settings or as members of the public. Workers are generally exposed to higher levels of tritium, as HTO, HT, metal tritides and dust, luminous compounds, tritiated biochemical substrates and some other anthropogenic chemical forms. The general public is exposed to environmental HTO and OBT in food.

321. Absorbed doses arising from the intake of tritium cannot be measured directly and recourse has to be made to the use of biokinetic and dosimetric models such as those of ICRP for dose assessment based on environmental measurements and of bioassay methods (such as the tritium measurement in urine) combined with models for retrospective determination of doses from individual measurements.

322. The ICRP has developed models for estimating the dose from the intake of HTO, or other tritiated compounds that partially convert to HTO after being taken into the body, for inhalation of tritiated gases and low soluble particulate tritium, and for OBT. The current ICRP biokinetic models for tritium intake by workers and members of the public are reasonably consistent with experimental results, and improved models are under development. There is a practical need for the development of biokinetic models for intake of tritiated biochemical substrates, including nucleotropic forms.

323. Doses, and hence risk, from some tritiated biochemical substrates and OBT are greater than those from HTO, due to their longer residence in the body and potentially also as a result of their localization within cells, specifically their proximity to DNA. Direct studies of OBT-related biological effects are not generally feasible because of low tritium concentrations in OBT. However, there are a few studies looking specifically at biological effects related to tritiated biochemical substrates, most of them using DNA precursors and amino acids. There is no appropriate dosimetric model for use in human risk assessment and radiation protection for tritiated DNA precursors. It should be noted, however, that the number of workers dealing with these forms of tritium is rather limited.

324. In laboratory studies of mammals, tritium has been shown to induce both stochastic and deterministic biological effects, consistent with the effects induced by other types of ionizing radiation, and consistent with its generally uniform distribution throughout body tissue, particularly as HTO. The severity of deterministic effects increases with increasing tissue dose above thresholds, as observed with other radiation. Exposure to tritium can also induce stochastic effects, such as cancer or heritable effects, in laboratory mice and rats. However, to date, there is no epidemiological evidence of stochastic health effects being induced by tritium exposure in humans.

325. A review of the RBE studies of tritium beta radiation indicates a range of values from about unity to several-fold higher compared to gamma rays and orthovoltage X-rays depending on many factors such as biological end point, test system, dose and dose rate and choice of reference radiation. RBE values derived from about 50 in vivo and in vitro experiments on mammals, for different end points, ranged from 1.0 to 5.0 (centred around 2–2.5) and from 0.4 to 8.0 (centred around 1.5–2) with regard to gamma rays and orthovoltage X-rays, respectively. Studies also showed a general tendency of RBE values to increase with lower doses. However, the Committee emphasizes that the ability to draw specific conclusions for carcinogenic effect in mammals is limited because of the lack of pertinent data.

326. A number of epidemiological studies have been conducted of workers or members of the public potentially exposed to tritium. Unfortunately, the majority of these studies do not use the results of tritium monitoring to calculate tritium-specific doses for use in the analyses. This makes it very difficult to reliably interpret the findings of these studies in terms of tritium-specific risk as distinct from risk from other types of exposure, principally external sources of penetrating radiation and other internal

emitters. These limitations apply particularly to studies of members of the public, but also extend to studies of tritium workers, because any occupational tritium monitoring data that might be available have not been fully utilized. Consequently, at present, little information of substance on tritium-specific risk can be derived from epidemiological studies of tritium workers or members of the public potentially exposed to tritium beyond the conclusion that tritium-specific risks have not been seriously underestimated.

327. Epidemiological studies of occupational exposure to tritium offer the best prospect of investigating tritium-specific risk to health, but certain requirements have to be fulfilled if this prospect is to be realized. First, tritium-specific doses derived from tritium monitoring and other occupational data need to be calculated from existing records or reconstructed. Second, exposure to other sources of exposure to radiation—such as external sources of penetrating gamma radiation and intake of other radionuclides—needs to be taken into account so that analysis in terms of tritium-specific doses may be adjusted for the presence of other exposure. Third, since the numbers of tritium workers and the tritium-specific doses they receive are limited, international collaboration is required to achieve reasonable statistical power in studying tritium workers to meaningfully investigate tritium-specific risk, and such international collaboration should use a common protocol for the determination of tritium-specific doses. Fourth, the success of an international collaborative study will depend on the numbers of tritium workers available and the doses they have received, so the chance of achieving meaningful results will depend on the participation of as many countries as possible in such a study.

328. As far as the effects of tritium exposure of the public are concerned, there is effectively no information on tritium-specific risk that can be obtained from presently available epidemiological studies. It is unlikely that epidemiological studies of members of the public potentially exposed to tritium will produce results that are interpretable in terms of tritium exposure with any acceptable degree of reliability. This is because environmental tritium exposure is generally very low, and any effect of such exposure against the background of other risk factors will provide a very small signal of tritium risk against this large background noise.

329. Suggestions that reports of excesses of childhood leukaemia incidence near certain nuclear facilities could be due to releases of tritium from these installations because of a serious underestimation of the risk of childhood leukaemia from exposure to tritium are implausible. Large quantities of tritium were released into the environment by atmospheric nuclear weapon testing in the early 1960s and there is no evidence from childhood leukaemia registration rates following exposure to tritium fallout of any major underestimation of the risk of childhood leukaemia from exposure to tritium.

XI. ACKNOWLEDGEMENTS

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APPENDIX A: TABLES SUMMARIZING STUDIES OF OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO TRITIUM

Tables A1 to A4 present four groups of studies that provide increasing levels of information on tritium-specific risk.

Table A5 presents studies of environmental exposure to tritium released from heavy-water-moderated nuclear reactors or tritium production/processing plants.

Table A1. Studies of workforces that include workers (potentially) exposed to tritium though not explicitly identified

Occupational exposure to tritium at installations with heavy-water-moderated nuclear reactors and/or tritium production/processing plants will generally be greater than exposure at installations where there are very low ambient levels of tritium resulting from, for example, the release of tritium generated in ternary nuclear fission. Consequently, studies of workers exposed to very low levels of tritium at, for example, nuclear power stations with only light-water-moderated reactors are not included in this table

<i>Study references</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Cragle et al., and Cragle and Watkins [C31, C32]	Historical cohort study of mortality among white male workers at SRS, USA, first employed 1952–1975. Total 9,860 workers; 1,722 had died before 1987. SMRs, stratified by employee pay code, calculated using general population of US white males as reference. Mortality trends, particularly for various cancers, with recorded external doses. Annual tritium whole-body doses available, but not used. Various subgroups examined, but not tritium workers	About 5,000 workers exposed to tritium, and about 800 workers had recorded dose >0.5 mSv from tritium. SMRs for all causes and all cancers were less than 1.0, which was the case for most causes of mortality, with no SMR significantly above 1.0. Marginally significant positive trend of leukaemia mortality with external dose	Not possible to derive tritium-specific risk, because tritium workers not analysed separately, and tritium-specific doses not used
Richardson et al., and Richardson and Wing [R2, R3, R4]	Historical cohort study of mortality before 2003 (5,098 deaths) among 18,883 workers at SRS before 1987. Cumulative recorded whole-body doses from external exposure combined with tritium-specific doses from urinalysis. Tritium-specific doses alone not used, and workers monitored for potential tritium exposure not considered separately	SMRs significantly <1.0 for all causes and all cancers. Using nested case-control approach, marginally significant positive trend of leukaemia (excluding CLL) mortality with cumulative whole-body dose; strongest for myeloid leukaemia. Adjusting indirectly for smoking, some evidence for positive trend of lung cancer mortality with cumulative whole-body dose	Not possible to derive tritium-specific risk, because tritium workers not analysed separately, and tritium-specific doses not used
McGeoghegan and Binks [M5]	Historical cohort study of mortality (1946–1995) and cancer incidence (1971–1991) among 12,540 workers at Capenhurst, UK. Tritium had been processed before 1988. Annual external whole-body radiation doses were included in the analysis. Unclear how many workers exposed to tritium. Tritium workers not analysed separately and internal doses, such as tritium, were not considered	Most SMRs and SRRs <1.0; several significant association between bladder cancer incidence and cumulative external radiation dose when dose lagged 20 years	Tritium workers not analysed separately and tritium-specific doses not used, so not possible to derive tritium-specific risk
McGeoghegan and Binks [M6]	Historical cohort study of mortality (1955–1995) and cancer incidence (1971–1995) among 2,628 workers at Chapelcross, UK. Tritium production from 1980. Annual external whole-body radiation doses used. Unclear how many workers exposed to tritium. Tritium workers not analysed separately and internal doses not considered	Most SMRs and SRRs <1.0; several significant trends with cumulative external radiation dose found for prostate cancer; no case monitored for tritium and only 2 at Chapelcross after tritium production started	Tritium workers not analysed separately and tritium-specific doses not used, so not possible to derive tritium-specific risk

<i>Study references</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
McGeoghegan et al., Douglas et al., Omar et al., and Smith and Douglas [D8, M7, O5, S15]	Historical cohort study of mortality (1947–1992) and cancer incidence (1971–1986) among 14,319 workers at Sellafield, UK. Tritium released from reprocessing from 1952, and tritium production during 1955–1962. Doses from external radiation and Pu included in the analyses, but not tritium-specific doses. Tritium workers not identified or analysed separately	SMRs for all causes and all cancers <1.0 for radiation workers. Significant trends of mortality and incidence for leukaemia (excluding CLL) with increasing cumulative external dose	Tritium workers not analysed separately and tritium-specific doses not used, so not possible to derive tritium-specific risk
Carpenter et al. [C7]	Historical cohort study of mortality during 1946–1988 (13,505 deaths) among 75,006 workers at Sellafield, UKAEA and AWE; 40,761 monitored for external radiation (6,900 deaths). Tritium doses at Sellafield, AWE and Harwell generally included with whole-body external dose, but excluded for Winfrith and Dounreay. Tritium workers not considered as a separate group	SMRs for radiation workers and other workers significantly <1.0 for all causes and all cancers. The mortality from leukaemia (excluding CLL) increased significantly with increasing cumulative whole-body dose. No analysis performed for tritium-specific doses and tritium workers not considered as a separate group	Although tritium workers included, not considered separately and tritium-specific doses not analysed alone, so not possible to derive tritium-specific risk
Johnson et al. [J7]	Historical cohort study of mortality before 1997 (6,516 deaths) among 22,543 workers at AWE, UK during 1951–1982. Tritium-specific doses combined with external radiation doses; no analysis of tritium-specific doses alone. Tritium workers not considered separately from other internal dose workers	SMRs for all causes and all cancers significantly <1.0 for all workers, all radiation workers, and all workers monitored for internal emitters. For all internal dose workers, the SMR for kidney cancer was significantly raised. Significant positive trends with cumulative external (plus tritium) dose for mortality from multiple myeloma, bladder cancer and lung cancer (doses lagged 11 years). No mention of prostate cancer [B18]	Neither tritium workers nor tritium-specific doses considered separately, so not possible to derive tritium-specific risk
Muirhead et al. [M22]	Historical cohort study of mortality (26,731 deaths) and cancer incidence (11,165 cases) before 2002 among 174,541 radiation workers included in the UK National Registry for Radiation Workers (NRRW). Analyses for recorded external doses. Internal doses (including tritium) not included; internal dose workers identified and either excluded or presence adjusted for in subsidiary analysis. Tritium workers not identified and not separately analysed	SMRs significantly <1.0 for all causes and all cancers. Significantly raised SMR for pleural cancer. Leukaemia (excluding CLL) and all other cancers significantly increased with increasing external dose. Exclusion of internal dose workers increased slopes for other cancers, but alternatively adjusting for internal monitoring had little impact	Tritium workers included but not analysed separately and tritium-specific doses not used, so not possible to derive tritium-specific risk
Gribbin et al. [G11]	Historical cohort study of cancer mortality during 1956–1985 (227 deaths) among 8,977 male workers employed by Atomic Energy of Canada Limited (AECL) during 1956 to June 1980. Analyses for recorded external doses. Tritium-specific doses not considered. Tritium workers not analysed separately	SMRs significantly <1.0 for all causes and all cancers. Marginally non-significant positive trend of mortality from leukaemia excluding CLL and cumulative external dose	No tritium-specific doses and no separate analysis of tritium workers, so not possible to derive tritium-specific risk

<i>Study references</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Sont et al. [S19]	Historical cohort study of cancer incidence during 1969–1988 among 191,333 Canadian workers monitored for exposure to radiation during 1951–1988, using the Canadian National Dose Registry (NDR). Tritium doses estimated from routine urinalysis and added to whole-body external radiation doses. Tritium-specific doses not analysed separately and tritium workers not considered as a separate group	Collective cumulative dose of 1,144.5 man Sv from external gamma radiation compared with that of 122.6 man Sv from tritium. For nuclear workers, mean cumulative tritium dose received from tritium of 5.56 mSv compares with 26.43 mSv received from external exposure; for analysis these two components were combined. SIRs for all cancers significantly <1.0 for males and females. ERR/Sv whole-body dose for all cancers significantly raised	Tritium-specific doses combined with external doses and not considered separately, and tritium workers not considered as a separate group, so not possible to derive tritium-specific risk. Caution needs to be exercised because of problems with the NDR data (see also [Z2])
Metz-Flamant et al. [M11]	Historical cohort study of mortality during 1968–2004 (6,310 deaths) among 59,021 nuclear workers in France during 1950–1994. Analyses of recorded external photon doses. Tritium-specific doses (and other internal doses) not included. Tritium workers not analysed separately	Significant trend with external dose for myeloid leukaemia	Tritium workers not treated as a separate group and tritium-specific doses not used, so not possible to derive tritium-specific risk
Azizova et al., Hunter et al., Moseeva et al., and Sokolnikov et al. [A7, H20, M21, S18]	Historical cohort study of mortality and disease incidence among workers of the Mayak complex in the Russian Federation. Tritium-specific doses not used and tritium workers not considered separately	Study principally concerned with risks from external radiation and from Pu; doses from this exposure were high in the early years of operations at the Mayak complex	Tritium-specific doses not used and tritium workers not identified, so not possible to derive tritium-specific risk
Cardis et al., Fix et al., and IARC [C3, F6, I5]	Historical cohort study of mortality (15,825 deaths), in particular cancer mortality (3,976 deaths), among 95,673 workers at Sellafield, UKAEA and AWE in the UK, Hanford, Rocky Flats and Oak Ridge National Laboratory (ORNL) in the USA, and AECL in Canada (the “IARC 3-country study”). For workers at all sites (except Winfrith and Dounreay) tritium-specific doses included, but combined with recorded external doses. Separate analysis with tritium-specific doses not done and tritium workers not considered separately	ERR/Sv cumulative dose for all cancers excluding leukaemia was 0.07 (90% CI: –0.39, 0.30) while ERR/Sv for all leukaemia excluding CLL was 2.18 (90% CI: 0.13, 5.7)	Neither tritium worker nor tritium-specific doses considered separately so not possible to derive tritium-specific risk

<i>Study references</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Cardis et al., Thierry-Chef et al., and Vrijheid et al. [C4, C5, T11, V2]	Historical cohort study of mortality among 407,391 nuclear industry workers from 15 countries (the "IARC 15-country study"). Total of 18,993 deaths included, 5,233 from cancer. Photon doses obtained from records at individual installations. Tritium-specific doses included with whole-body doses, and no separate analysis conducted. Tritium workers not considered separately	Significant association between cumulative (lagged) radiation dose and all-cause mortality (ERR/Sv=0.42), mainly due to a dose-related increase in all cancer mortality (ERR/Sv=0.97). Among 31 specific types of malignancies, significant association for lung cancer (ERR/Sv=1.86) and borderline non-significant associations for multiple myeloma (ERR/Sv=6.15) and ill-defined and secondary cancers (ERR/Sv=1.96). Stratification on duration of employment had a large effect on ERR/Sv estimates, reflecting a strong "healthy worker survivor effect" in the contributing cohorts	No information on tritium-specific doses provided and no separate analysis of tritium workers conducted, so not possible to derive tritium-specific risk. 15-country study has to be treated with caution because of problems with the Canadian worker data (see also [Z2])
Hamra et al., Leuraud et al., Richardson et al., and Thierry-Chef et al. [H5, L9, R5, T12]	Historical cohort study of mortality (66,632 deaths) among 308,297 radiation workers from nuclear installations in USA, UK and France. Doses used derived from recorded external radiation doses. Tritium-specific doses not included in the study (although in some tritium doses included with external doses). Tritium workers not analysed separately	ERR/Gy for all cancers excluding leukaemia 0.39 (90% CI: 0.12, 0.67), all leukaemia excluding CLL 2.96 (90% CI: 1.17, 5.21). Intended that tritium-specific doses excluded from doses used in analysis; seems likely that for some installations and for some years tritium doses included in external dose records	No analysis conducted for tritium-specific doses and tritium workers not considered as a separate group, so not possible to derive tritium-specific risk
Daniels et al., and Schubauer-Berigan et al. [D2, S9, S10]	Nested case-control (1:4 matching) study of leukaemia mortality before 2006 (369 deaths) and radiation exposure among 105,245 workers at six nuclear sites in the USA. 66 (17.9%) cases and 227 (15.4%) controls were exposed to tritium. Internal doses to red bone marrow (RBM) from urinalysis results were included with recorded external photon doses. No separate analysis using tritium-specific doses and tritium workers not treated as a separate group	ERR per 100 mGy (total low-LET radiation dose to RBM) 0.09 (95% CI: -0.17, 0.65) for leukaemia excluding CLL (ERR per 100 mGy for exposure 6–14 years prior to diagnosis 1.9 (95% CI: <0, 8.0)). Tritium-specific doses to RBM available (mean 0.2 mGy; maximum, 85.1 mGy) but not used alone	Tritium-specific doses alone not used, and tritium workers were not considered as a separate group, so not possible to derive tritium-specific risk

Table A2. Studies of workers monitored for (potential) exposure to tritium, identified and investigated as such, but tritium-specific doses not available or not used

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Beral et al. [B17]	Historical cohort study of mortality (3,373 deaths during 1946–1979) in 39,546 workers at UKAEA. Exposure to tritium occurred at UKAEA sites. Of 20,382 workers exposed to external radiation, 1,418 also potentially exposed to tritium, and tritium workers were considered separately. Only doses from external radiation used, not tritium doses (apart from Harwell from 1977 when tritium included in whole-body exposure)	Tritium doses not quantified. All causes SMR for tritium workers significantly low at 0.59, and all cancers SMR non-significantly low at 0.77. On the basis of 6 deaths, prostate cancer SMR significantly raised, at 8.89; all 6 deaths with cumulative external doses ≥ 50 mSv (SMR=12.77)	Absence of tritium-specific doses does not permit a reliable conclusion on the potential role of tritium in the raised prostate cancer SMR for the group of tritium workers
Carpenter et al. [C8]	Historical cohort study of mortality (4,149 deaths) during 1946–1988 among 40,761 external radiation workers at Sellafield, UKAEA and AWE. 4,111 workers monitored for tritium analysed separately, but tritium-specific doses not used, only a flag indicating tritium monitoring	For tritium workers, SMRs for all causes and all cancers significantly < 1.0 , and compatible with other radiation workers. SMR and RR for prostate cancer non-significantly raised; testicular cancer the only cancer with significantly elevated RR buccal cavity and pharynx the only cancer with significantly reduced RR. Little evidence that RRs varied with period since, or age at, or calendar year of first monitoring or with age at first monitoring. For UKAEA or AWE workers, data available on duration of monitoring; among tritium-monitored workers, for prostate cancer, significant variation with number of years monitored (highest in workers monitored in 2–4 years). Significantly raised RR for lung cancer among tritium workers with external dose < 10 mSv, but not ≥ 10 mSv. Non-significantly raised RR (=1.39) for prostate cancer among tritium workers with external doses ≥ 10 mSv	Absence of tritium-specific doses does not permit a reliable conclusion about tritium-specific risk

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Gillies and Haylock, and McGeoghegan et al. [G4, M8]	Historical cohort study of mortality (19,613 deaths) and cancer incidence (10,411 cases) before 2006 among 64,956 workers employed during 1946–2002 by British Nuclear Fuels plc (BNFL) at Sellafield, Springfields, Capenhurst and Chapelcross. 42,431 external radiation workers, and 22,675 workers also monitored for tritium, Pu and U. 1,757 workers were monitored for tritium, 1,062 for tritium only. Analyses with external doses only, not internal doses (including tritium), but workers flagged for tritium monitoring. In some analyses, tritium workers considered separately	SMRs for all causes and all cancers significantly <1.0 for both radiation and non-radiation workers, but RRs <1.0, significantly for all causes of death. All causes and all cancers RRs for internal radiation workers vs. other radiation workers did not differ significantly from 1.0. Mortality from both cancer and non-cancer increased significantly with increasing cumulative external dose; for cancer trend significantly less for internal radiation workers than external only radiation workers, and same pattern for cancer incidence. For tritium workers, SMR for all causes significantly <1.0, but SMR for all cancers non-significantly >1.0 (contrasting with SMR of 1.0 for Pu workers and SMR significantly <1.0 for U workers). Tritium worker SMRs significantly >1.0 for pleural and female breast cancer. RR comparing all cancer SMR for tritium workers vs. external only radiation workers significantly >1.0. Mortality RR for female breast cancer significantly >1.0 (2 deaths among tritium workers) and also for all smoking-related cancer. All cancer SIR for tritium workers non-significantly >1.0 (and non-significantly greater than SIRs for Pu and U workers). SIRs for pleural, testicular and non-melanoma skin cancer significantly >1.0. Incidence RR for all cancers significantly >1.0 for tritium workers vs. external only radiation workers, and incidence RR significantly raised for non-smoking-related solid cancer and for solid cancer excluding lung, liver and bone. Tritium workers stated to have significantly increasing incidence of digestive cancer with increasing cumulative external dose	Tritium workers considered separately, and all cancer risk (both mortality and incidence) significantly greater vs. external only radiation workers. However, tritium-specific doses not used so not possible to draw reliable conclusions about tritium-specific risk
Boice et al. [B22]	Historical cohort study of mortality during 1944–2009 (3,681 deaths) among 7,270 workers at the Mound nuclear facility, USA, during 1944–1979. 4,509 workers monitored for external radiation. Tritium processed at Mound during 1954–1997; 4,134 workers monitored for tritium (1,125 with positive urinalysis result). Tritium doses estimated on assumption that intake was HTO, and added to the doses from other sources. Tritium-specific doses alone not used in analysis	Mean tritium dose for workers with positive monitoring result 8 mSv and maximum 195.5 mSv. (Mean external dose 26 mSv and maximum 939.1 mSv.) For workers with non-zero tritium dose, SMRs for all causes and all cancers significantly <1.0. For specific cancers, SMRs were generally <1.0, including prostate cancer and (significantly) lung cancer. For dose-response analysis, with tritium doses included in total organ/tissue doses, significant positive trend for oesophageal cancer and negative trend for liver cancer	Tritium workers did not have unusual patterns of mortality. Tritium-specific doses incorporated into total organ/tissue doses in analysis, so that tritium-specific risk cannot be derived

Table A3. Studies of workers monitored for (potential) exposure to tritium, identified and investigated as tritium workers, and occupational dose records used, but tritium-specific doses not available or not explicitly used

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Beral et al. [B18]	Historical cohort study of mortality during 1951–1982 (3,115 deaths) among 22,552 workers at AWE, UK, before 1983. 9,389 workers monitored for external radiation; 1,562 also monitored for tritium. Whole-body doses from tritium added to recorded external doses. Tritium workers considered as a separate group for some analyses, but tritium-specific doses not used	<2% of workers had a tritium dose >10 mSv. SMRs for tritium workers vs. other radiation workers not unusual: RRs of 1.02 for all cancers and 0.97 for other causes (did not vary notably with different dose-lagging periods). Tritium workers had a significant trend of prostate cancer with cumulative whole-body dose compared with workers not monitored for tritium exposure (on the basis of 3 deaths; trend driven by 1 death with cumulative whole-body dose ≥100 mSv). For tritium workers, SMR for prostate cancer non-significantly elevated at 2.50 with RR 1.27 vs other radiation workers	Very few prostate cancer deaths for tritium workers, and no analysis with tritium-specific doses alone, so reliable conclusions cannot be drawn about tritium-specific risk
Fraser et al. [F12]	Historical cohort study of mortality during 1946–1986 (5,509 deaths) and cancer morbidity during 1971–1984 (1,594 cases) in 39,718 UKAEA workers, including 1,702 workers monitored for tritium, considered separately. Only recorded external doses used (except tritium doses at Harwell from 1977 included in whole-body doses)	SMRs for tritium workers compared with SMRs for other radiation workers significantly raised RR only for prostate cancer, with SMR in tritium workers 2.82 (7 deaths) (see also [B17]). Significant association of prostate cancer mortality with cumulative external radiation dose for tritium workers – all 7 deaths with cumulative external doses ≥100 mSv (SMR 5.31). High case fatality for most cancer led to cancer morbidity results similar to mortality	Tritium-specific doses not quantified, so no reliable conclusion on tritium-specific risk of prostate cancer (or other cancer) can be reached. Cannot assume that external dose gives an acceptable measure of tritium dose
Rooney et al. [R14]	Nested case–control study (1:3 matching) of 136 UKAEA workers diagnosed with prostate cancer between 1946 and 1986, and 404 matched controls. 65% of study subjects had been monitored for external radiation (a matching criterion). Monitored and assessed exposure to tritium (and a number of other radionuclides) included in analysis. Although assessed level of tritium exposure used in some analyses, tritium-specific doses derived from monitoring data were not used	Risk of prostate cancer significantly increased in men monitored for tritium, with RR 14.26 (95% CI: 3.09, 133.16). Significantly raised RR for men working >10 years with heavy-water-moderated reactors. Significant trend of RR with increasing external dose for those men likely to have been exposed to tritium or one of four other radionuclides (Cr-51, Fe-59, Co-60 or Zn-65). Assessed potential for tritium exposure, and likely level of exposure, gave significant trend of risk with assessed degree of exposure. When only men assessed as potentially tritium exposed, but not monitored for exposure, included in analysis, no significant increase in prostate cancer RR. Owing to multiple, not possible to disentangle the independent effects of tritium, Cr-51, Fe-59, Co-60 and Zn-65	Exposure to tritium could not be separated from exposure to four other radionuclides. Absence of tritium-specific doses prevents a reliable estimate of the tritium-specific risk of prostate cancer

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Atkinson et al. [A5, A6]	Historical cohort study of mortality before 1998 (10,249 deaths) among 51,367 UKAEA workers before April 1996; 26,395 monitored for external radiation. Some tritium-specific doses included with recorded external doses, although not for Dounreay and Winfrith. Tritium workers considered separately in some analyses. Tritium-specific doses not used	SMRs for all causes and all cancers for non-radiation workers, radiation workers and internal dose workers all significantly <1.0. For tritium workers, no SMR significantly raised, but prostate cancer SMR for tritium workers significantly higher than for other radiation workers. Previously reported significant positive trend of prostate cancer risk with cumulative external dose for tritium workers [F12]. No longer significant and no trend with external dose for 1980–1997	Absence of tritium-specific doses, so little can be derived about tritium-specific risk
Ashmore et al. [A4]	Historical cohort study of mortality during 1951–1987 (5,426 deaths) among 206,620 Canadian radiation workers during 1951–1983, using Canadian NDR. Tritium doses from urinalysis added to whole-body external radiation doses. Tritium-specific doses and tritium workers not considered separately	For all causes of death, when tritium doses included with whole-body external doses, ERR per 10 mSv, 2.6 (90% CI: 1.6, 3.6), with tritium doses excluded (i.e. external doses only) and, ERR per 10 mSv, 2.5 (90% CI: 1.5, 3.5). Risk estimates for tritium doses alone not given. The group of workers monitored for potential exposure to tritium not considered separately	ERR/Sv for all causes of death did not change substantially when tritium doses included with external doses. Separate results for tritium-specific doses alone not presented, so little can be concluded about tritium-specific risk. Caution needs to be exercised because of problems with the NDR data used (see [Z2])
Zablotska et al. [Z1]	Historical cohort study of mortality during 1957–1994 (1,599 deaths) among 45,468 Canadian nuclear industry workers (from AECL, Ontario Hydro, Hydro Québec and New Brunswick Power) during 1957–1994, using Canadian NDR tritium doses from urinalysis and added to recorded external radiation doses. Tritium-specific doses and tritium workers not considered separately	Mean cumulative dose 13.5 mSv; among workers with non-zero doses, mean 19.7 mSv. SMRs for all causes of death and all deaths from cancer significantly <1.0. ERR/Sv total cumulative dose marginally non-significantly positive for all solid cancers combined and marginally significantly positive for all leukaemia excluding CLL; ERR/Sv show small increases (from 2.67 to 2.80, and from 16.3 to 18.9, respectively) when tritium doses included with external doses	ERR/Sv for all solid cancers and all leukaemia did not materially change when tritium doses excluded from whole-body doses, but tritium-specific doses alone not used, so not possible to draw reliable conclusions about tritium-specific risk. Caution needs to be exercised because of problems with the NDR data used (see also [Z2])
Schubauer-Berigan et al. [S11]	Historical cohort study of mortality (41,508 deaths) among 119,195 radiation workers at five nuclear sites in the USA. Tritium-specific doses from urinalysis added to recorded external doses but separate analysis with tritium-specific doses alone not done – separate analysis for all cancers and all haematopoietic and lymphatic cancers with both neutron and tritium doses excluded from cumulative doses. Tritium workers not considered separately	SMRs for all causes and all cancers significantly <1.0. ERR per 10 mSv whole-body dose 0.14% (95% CI: –0.17%, 0.48%) for all cancers combined and 2.0% (95% CI: 0.71%, 3.5%) for all haematopoietic and lymphatic cancer. When neutron and tritium doses together excluded from the whole-body dose, ERR per 10 mSv became 0.18% (95% CI: –0.14%, 0.53%) and 2.0% (95% CI: 0.73%, 3.7%), respectively	Absence of tritium-specific doses alone, and tritium workers considered separately, so little can be derived about tritium-specific risk

Table A4. Studies of workers monitored for (potential) exposure to tritium, identified and investigated as tritium workers, and tritium-specific doses available and used in analyses so that tritium-specific risk may be examined explicitly

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Hazelton et al. [H8]	Historical cohort study using a biologically-based analysis of lung cancer incidence during 1969–1988 (400 cases, 322 in men) among 191,042 Canadian radiation workers during 1951–1988, making use of Canadian NDR. Tritium-specific doses used in analysis, mainly in combination with whole-body gamma-ray doses	Of collective dose from external gamma radiation and tritium combined, tritium contributes 9.0%. 95,430 males, 60,677 with non-zero doses (mean cumulative gamma plus tritium dose, 18.2 mSv), 9,013 with non-zero tritium doses (2 253 with tritium doses >14.95 mSv). Significant dose–response for men with gamma-ray and tritium doses combined, and with gamma-ray doses alone, but for tritium doses alone dose–response only marginally significant. Allowing RBE for the tritium absorbed dose to vary did not improve fit significantly. When dataset restricted to 69,826 men not flagged for neutron exposure, dose–response for tritium doses alone not significant. For 95,603 women (44,238 with non-zero radiation doses, mean cumulative gamma plus tritium dose 3.8 mSv), dose–response non-significant, but consistent with dose–response for men. For men, modelling predicts ~31 cases attributable to gamma radiation and ~2 cases to tritium exposure	Analyses performed with tritium-specific doses alone, although most results for gamma and tritium doses combined. Modelling predicts ~2 lung cancer cases attributable to tritium exposure. Caution needs to be exercised because of problems with the NDR data used (see [Z2])
Zablotska et al. [Z2]	Review by Canadian Nuclear Safety Commission of employment and dose records for Canadian nuclear workers led to corrections and improvements to records. Mortality (489 cancer deaths during 1956–1994) in revised historical cohort of 45,468 nuclear workers (originally studied by [Z1]) reanalysed. Particular attention paid to accuracy of records for AECL workers before 1965. Tritium doses from urinalysis. Summary doses for whole-body external (gamma) and internal (mainly tritium) radiation used for risk analysis. Workers with neutron or high internal exposure excluded. Tritium workers not considered separately	42,228 workers first monitored since 1965 had no significant ERR/Sv for solid cancer (-1.20) or leukaemia (14.4, p=0.28). This contrasted significantly with ERR/Sv for solid cancer in 3,088 AECL workers first monitored during 1956–1964: ERR/Sv=7.87 (p <0.01) (but no dose-related risk of leukaemia). Very likely that dose information in Canadian NDR incomplete for early AECL workers. Mean cumulative tritium dose in revised cohort 3.02 mSv, 14% of mean cumulative total dose; 809 workers had tritium doses >50 mSv. When in revised cohort tritium doses added to risk model for solid cancer with gamma doses as second linear term, fit of model did not improve; in model with two separate dose terms, for gamma component ERR/Sv was 2.56 (95% CI: -0.11, 6.79), while for tritium component ERR/Sv was -4.71 (95% CI: <-5.92, 8.58). For individual cancer types, adding tritium doses to risk model did not improve fit, and risk due solely to gamma doses	Analysis of mortality from all solid cancers, individual solid cancers and leukaemia showed risk due solely to whole-body gamma doses and that the addition of tritium doses did not improve fit of the model. Study provides estimates of tritium-specific risk, but uncertainties associated with estimates are large due to generally low tritium doses received by a limited number of workers

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings relating to tritium</i>	<i>Relevance for this report</i>
Hamra et al. [H3, H4]	Reconstruction of tritium-specific annual doses for workers at SRS, USA, using tritium urinalysis data, recorded external doses, and a job-exposure matrix approach [H3]. Reconstructed tritium-specific doses used in a study of tritium-specific leukaemia risk [H4], using Bayesian approach informed by experimental studies of tritium	From 75,523 dose records for 1954–1978 the proportion of the whole-body dose from tritium was calculated for various jobs, areas and time periods, and tritium doses assigned for 43,590 person-years. Under a strong assumption that the leukaemia risk per 10 mGy from tritium is always greater than that from external gamma radiation, authors derived ERR per 10 mGy of 0.298 (90% credibility interval: 0.027, 0.702) for leukaemia and 0.344 (90% credibility interval: 0.049, 0.817) for leukaemia excluding CLL. Risks obtained without the restriction that the leukaemogenic effect of tritium is always greater than that of external gamma radiation leads to values of 0.141 (90% credibility interval: –0.323, 0.649) and –0.281 (90% credibility interval: –1.136, 0.548), respectively	Illustrates what may be done using occupational records to derive tritium-specific doses for use in epidemiological analysis. Tritium-specific leukaemia risk is uncertain because of limited data, and the dependence of leukaemia ERR/Sv upon the strong assumption that the risk per unit absorbed dose from tritium is always greater than that for gamma radiation means that the findings must be treated with caution
HSE [H17, H18]	Case-control study investigating exposure of fathers working at Sellafield before the conception of their children and an increased risk of leukaemia and non-Hodgkin's lymphoma (LNHL) in these children. Exposure considered included tritium, both assessed potential for exposure and doses derived from contemporary tritium monitoring data	Highly significant association between risk of LNHL in offspring and assessed potential for paternal exposure to tritium in preconceptional period. Association not reproduced when doses derived from measured exposure to tritium based on contemporary monitoring data used	Paternal preconceptional tritium doses derived from monitoring data do not indicate raised risk of LNHL in offspring. Risk indicated by assessed potential for tritium exposure must be treated with caution given difficulties of retrospective assessment of potential for historical tritium exposure
McLaughlin et al. [M9]	Matched case-control study (1:8 matching) of childhood leukaemia (112 cases during 1950–1988) and paternal preconceptional exposure of workers in Ontario, Canada. Analyses included external and tritium doses from occupational records	No association between childhood leukaemia risk and paternal preconceptional radiation dose found for either recorded external whole-body dose or tritium dose. For tritium exposure, no father of an affected child was recorded as exposed while 14 control fathers had preconceptional exposure	No indication of measured paternal preconceptional tritium exposure increasing the risk of childhood leukaemia in offspring
Green et al. [G10]	Matched case-control study (1:1 matching) of congenital anomalies in offspring of workers of Ontario Hydro. Preconceptional tritium doses based on monitoring data	No association between risk of congenital anomalies and the tritium dose received during the preconceptional period	Tritium doses received prior to conception did not increase the risk of congenital anomalies in the child

Table A5. Studies of environmental exposure to tritium released from heavy-water-moderated nuclear reactors or tritium production/processing plants

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings related to tritium</i>	<i>Relevance for this report</i>
Wanigaratne et al. [W5]	Historical cohort study of cancer incidence 1986–2005 using data from the Ontario Cancer Registry, among people living near Pickering heavy water CANDU nuclear reactor site in Ontario in 1985 and in comparison area (north Oshawa) further from site. Atmospheric tritium concentrations estimated for each 1985 residential location using atmospheric dispersion model with tritium discharge and meteorological data. Model predictions compared with monitoring results. In addition to all cancers combined, leukaemia and cancer of the lung, thyroid, female breast and of childhood examined	More than half of Pickering and all north Oshawa residents experienced modelled average tritium concentration levels <2.9 Bq/m ³ , representing annual effective dose of 0.47 µSv for average adult. The all cancer SRR significantly less than 1.0 for both cohorts. Effect of emigration from Ontario not assessable. Only for female childhood cancer in Pickering, SRR significantly raised. For Pickering residents living at the same address in 1985 as in 1979 (“non-movers”), assessed tritium exposure not associated with risk of lung cancer or female breast cancer (other cancer case numbers too small for this analysis)	This study used assessed tritium-specific exposure residents at the same address for at least six years for analysis of cancer incidence. However, doses based on residential histories not reconstructed. Tritium-specific dose estimates very small (maximum annual effective dose, 2.36 µSv), and number of cancer cases (available for just one installation) limited, so power of study to detect any risk was low. Nonetheless, study attempts to address tritium-specific cancer risk, not done in any other environmental exposure study
Grosche et al. [G13]	Comparison of childhood leukaemia incidence around Krümmel nuclear power station, Germany and SRS, USA. Study conducted because of suggestion that tritium discharges from Krümmel (a boiling (light) water reactor) responsible for marked excess of childhood leukaemia cases in the vicinity of the site. In contrast, SRS produced/processed relatively large quantities of tritium for weapons	If releases of tritium from Krümmel site responsible for excess childhood leukaemia cases in immediate vicinity, then the much larger releases from SRS would detectably increase childhood leukaemia risk in neighbourhood. Around SRS, however, statistically non-significant deficit of childhood leukaemia incidence found. Therefore, theory of childhood leukaemia excess around Krümmel due to tritium exposure not supported by this study	Absence of human monitoring data and assessed tritium-specific doses from this study limits possible conclusions on tritium-specific risk. Nonetheless, absence of a detectable increased risk of childhood leukaemia around SRS does not support serious underestimation of the tritium-specific risk of childhood leukaemia
Cragle et al., Cragle and Watkins, and McLaughlin et al. [C31, C32, M9]	Geographical study of childhood leukaemia incidence (1964–1986) and mortality (1950–1987) within 25 km of nuclear installations in Ontario, Canada, in particular, the heavy-water-moderated CANDU reactor power stations	For children born within 25 km of the nuclear power stations, (marginally) non-significant excess of childhood leukaemia mortality and a non-significant excess of childhood leukaemia incidence. Non-significant excess of childhood leukaemia mortality among those resident within 25 km of the nuclear power stations	In the absence of assessed tritium-specific doses to individuals, little may be concluded from this study about the tritium-specific risk of childhood leukaemia
Johnson and Rouleau [J6]	Geographical study of birth abnormalities, perinatal and infant mortality during 1971–1988 within 25 km of Pickering heavy-water-moderated CANDU reactor site in Ontario, Canada. Health outcome data analysed for airborne and waterborne tritium emissions from the site, and using ground-monitored airborne tritium concentration data	No unusually high mortality or abnormality rates found in study area. Only association between tritium release levels and birth abnormalities was for CNS abnormalities, but not reproduced using ground monitoring data. Although some evidence of elevated risk of Down’s syndrome around Pickering, no consistent associations with tritium release levels and ground monitoring data found	Lack of assessed individual exposure to, or doses from, tritium means no substantial conclusions on tritium-specific risk may be drawn from this study

<i>Study reference</i>	<i>Summary of study</i>	<i>Summary of findings related to tritium</i>	<i>Relevance for this report</i>
Richter and Stockwell [R10]	Cancer mortality (during 1980–1991) among residents of Lamar County, Mississippi, near the Salmon (underground) nuclear test site, following two nuclear tests in 1964 and 1966. Residents worried that tritium released due to these two explosions detectably increased cancer risk in vicinity	No increase in environmental tritium levels as a result of the nuclear tests detected. Observed cancer mortality rates for Lamar County no different from those expected for all Mississippi. No association between cancer mortality rate and distance from detonations	Lacking measured increases of exposure to tritium resulting from the nuclear tests, this study provides no information on tritium-specific risk. Conducted as a public reassurance exercise

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