ENCLOSURE 1

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D. C. 20555

MAR 21 1978 Ref: SA/JOL

MEMORANDUM FOR: I. Craig Roberts, Assistant Director for Site and Health Standards, SD

FROM: G. Wayne Kerr, Assistant Director for State Agreements Program, OSP

SUBJECT: REQUEST FOR ASSISTANCE - EVALUATION OF TRITIUM EXPOSURES

The State of Alabama and Georgia have recently conducted surveys for potential radiation hazards at clock and watch assembly plants which incorporate tritiated luminous dials and hands. These components have been distributed by manufacturers licensed by NRC to distribute them to persons exempt from licensing. The watch assemblers are exempt from licensing.

Smear surveys at one plant have disclosed removable tritium contamination of up to 1925 dpm per 100 cm^2 on incoming packages of tritiated luminous parts, 7,200 to 21,500 dpm/100 cm^2 on watch assembly bench surfaces and up to 84,800 dpm/100 cm^2 on equipment used to hold assembled dials.

The State's observations at the plant are that no special personal hygiene precautions are being practiced by workers at this plant.

Spot urine samples were obtained from 5 workers who are engaged - not full time - in the assembly of tritiated dials. Results were as follows:

Individual	^3H Concentration, nCi/l
A	357
B	315
C	286
D	345
E	312

If the tritium to which these individuals were exposed to was in the form of tritiated water, the associated organ (body tissue) doses would be quite small. However, we are uncertain that this is the likely case for persons handling finished tritiated luminous components. A study by Jones and Lambert suggests tritium may be released from the paint in an organic form (attachment). Ingestion of discrete particles of dried

tritiated paint is also a possibility. In these cases, it is possible the observed tritium levels represent fractions of tritium originally inhaled, ingested or absorbed through the skin in other chemical forms. These forms may be organic or insoluble and, by implication, organs other than body tissue may be the critical organ.

We would appreciate your evaluation of this problem. As additional data becomes available to us, we will forward it. If you believe additional information is needed or should be sought, please contact me.

G. Wayne Kerr

G. Wayne Kerr, Assistant Director
for State Agreements Program
Office of State Programs

ENCLOSURE 2

From the desk of -

ALLEN BRODSKY

To: Chairman, Curtis Graham
Members, Health Physics Society Subcommittee on Internal Dosimetry Standards for Tritium

Enclosed is a slightly revised third draft of Section 8. "Criteria for Determining the Need for a Bioassay Program", and the additional background material, Appendix A, "Derivation of the Criteria for Determining the Need for a Bioassay Program", which I promised you earlier. Section 8, which is intended for incorporation in the next draft of the standard, consists of only two pages, Table 8.1, and three references.

I'm sorry that I could not get the background material to you sooner, but hope that it is still in time to be helpful in preparing for our meeting on June 26. If there is not time to study the entire background material, the last 8 pages, Section A.4, summarizes the derivation of Table 8.1.

Look forward to working with you all at the next meeting.

Allen

Allen
6/6/76

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APPENDIX A

DERIVATION OF CRITERIA FOR DETERMINING THE NEED FOR A TRITIUM BIOASSAY PROGRAM

A.1 Introduction

The need for tritium bioassay of employees depends in general on many interrelated factors such as the nature and amount of tritium in process at any time, the types of processing, the extent of other safeguards or facilities provided to prevent occupational exposures, and the probabilities that significant quantities of tritium may be inhaled or ingested with the particular materials, procedures, and facilities involved.[1] Thus, the choice of an optimum combination of safeguards, including bioassay, is a complex problem and should be carried out in consultation with a professional health physicist experienced in tritium operations. However, experience[2-5] with the processing and use of tritium in various forms now allows the derivation of reasonable standards for determining the need for bioassay sampling and analysis under certain defined circumstances of operation.

The levels of operation with tritiated water above which bioassay checks or routine evaluations have been carried out have varied considerably between institutions.[4] In some instances there is evidence that requirements have been too stringent and have resulted in unnecessary costs for more analysis than a safe surveillance program should have.[4] In other cases, the lack of a suitable bioassay program at an early date may have partly been responsible for serious overexposures.[5] Levels of operation above 10 curies of HTO in volatile or dispersible form, were deemed to require at least occasional bioassay whenever there was a possibility of release and inhalation of the material in process, based on experience with plutonium and scaling up quantities eight orders of magnitude according to the relative dose per unit activity inhaled.[1]

However, experience has shown that tritium as HTO can also penetrate certain protective gloves and be taken in through the skin unless gloves are washed frequently.[2] Also, incidents with smaller quantities of tritium have yielded measurable exposures that some institutions believe should be recorded for radiation monitoring purposes, even though these instances are rare and the cumulative exposures are small.

Experience from accidental releases does indicate that the probability of intake by inhalation would generally be much less than 10^{-5} of the material in process.[7,8] Assuming protection of hands and forearms in the case of tritium, these values from operational experience should also set a practical upper limit to the fraction of tritium inhaled compared to material in process. On the other hand, in many installations, since tritium as HTO can readily be taken up through skin or inhaled, and the intake of only about 5 millicuries could produce 1 rem, routine bioassay is often provided at this level or below for open operations with little or no additional containment. There is considerable opinion that bioassay services at least on a sampling basis should be considered at levels of operation above 10 millicuries per worker in process in order to achieve ALARA exposures, unless the nature of the operation insures additional containment to prevent employee exposure. Thus, in order to balance the apparent differences in practice and opinion, and provide a sounder basis for establishing bioassay programs, the following sections of this appendix consider the available scientific data and accumulated operational experience in order to derive suitable activity levels as a guide for bioassay program requirements.

A.2 Exposure Experience with Tritium in Various Processes

More recent experience with tritiated compounds has shown that the level of 1 curie[1] above which chemical hood operations should be considered, and 10 curies[1] above which enclosed glovebox operation should be considered, are also generally applicable for many tritiated compounds as well as HTO.[2,3,6] Significant fractions of tritium in urine (compared to permissible levels for continuous exposure (28 microcuries per liter[9,10]) or to the derived investigation level of 35 uCi/liter immediately following single intake of 1.5 mCi[12] have been found in employees working within chemical hoods with quantities of tritiated compounds in the range of several curies.[2,3,6,11] Thus, recommendations for bioassay for tritiated compounds, other than precursors of nucleotides, will thus be the same as for HTO except when the compounds may be assured to be of lower volatility, dispersability, or release probability than tritiated water in ordinary chemical processes.

Whenever tritium is in any form (diluted by other materials) so that it can be guaranteed that, even with HTO, a dose equivalent for single intake of no more than 1 rem would be possible from the inhalation of 10 milligrams of the highest specific activity of any material that could be accidentally released into air within 8 hours, then bioassay may not be necessary until higher levels of activity than those in Table 1 are in process. Whenever consideration is given to specific activity of the material in process, an analysis of initial bioassay data and air monitoring data, as well as a written evaluation of the entire procedure, should be carried out by the health physicist in charge. In the case of reactors where the tritium is diluted in a large volume of coolant, the need for bioassay would depend on a large number

of design, operating, and procedural factors. Thus, for reactor installations, the need for tritium bioassays other than the initial and separation samples should be based on a measurement and assessment of air concentrations of tritium to which employees may be exposed.

Radiochemical Industry Experience

Evans[14] has described the types of laboratories required for handling multi-curie quantities of tritiated compounds and for tracer quantities. The need for adequate ventilation when handling tritium is also stressed. Thus, the requirements for bioassay sampling need to be related, as far as possible, to the degree of protection afforded by exhaust hoods and ventilation systems. Evans[14] indicates that when there is 10 mCi or less of tritium in frequent use as tracers, there is little need for preparative work. This may be taken to indicate that experience at the Radiochemical Center has shown there is little likelihood of significant intakes of tritium below levels of 10 mCi in operation.

Luminous Timepiece Industry Experience

In a study of a luminous dial painting plant, Moghissi et al.[15] have found that an employee working in a hood without gloves but under conditions of plant cleanliness and regular changing of surface coverings, will have urine concentrations of about 14 uCi/liter (10 uCi/liter) for a level of processing of 10 Ci of tritium per month (read from Figure 2, Reference 15, which shows a regression analysis of the data). Before plant cleaning and use of bench covers, the comparable average urine concentration was about 34 uCi/liter for 10 Ci per month processed,[15] just below the ICRP derived investigation level.[12]

Experience of the investigators during this study indicated that a major part of the intake in this kind of operation could occur through skin contamination, although general air concentrations could also account for a major portion of the exposure. The operations in this plant of 15-20 dial painters[15] involved painting methods ranging from sophisticated rotary applicators to hand-operated painting machines and manual painting.

In a plant with fewer workers, using only closed "pens" with which small amounts of tritium are applied by hand to dials and hands, the processing of 10 Ci/month would lead to about 10-20% of the urinary levels measured by Moghissi, et.al[15] with very rare approach to 35 µCi/liter or above.[16]

Initial preparation and mixing of the tritiated polymer, zinc sulfide and adhesive used to make luminous paint are generally carried out within enclosed gloveboxes vented through absolute filters.[15-17] An employee working on the preparation and mixing process through a single pair of gloves, several hours per week, has shown urine levels of about 20 µCi/liter when processing on the order of 800 Ci/month,[17] which would give a urinary level of 0.25 µCi/liter for 10 curies per month processed. This urinary level is less than 1% of the ICRP derived investigation level, and can be attributed to diffusion of tritium through the glovebox gloves, which could possibly be decreased further through use of frequently changed or washed surgeons gloves inside the glovebox gloves. The tritium paint contains tritium in the form of tritiated polystyrene with specific activities of 250 mCi/gram of paint or less.[15,17] However, the tritium to which employees are exposed behaves in the body in a manner similar to HTO for purposes of dose estimation, and most of the tritium in air is recoverable as HTO.[15] Thus, from experience in the luminous paint

industry the use of gloved boxes or closed systems for handling tritium as HTO or organic compounds may be assumed to provide protection factors of at least 100 above that for operations within hoods, or near local exhaust ventilation.

The need for such large protection factors when handling hundreds or thousands of curies per month is justified by the two cases of deaths[5] attributed, at least in part, to tritium paint production and processing in the absence of safety precautions. Although the workers involved had previously been exposed to unspecified amounts of radium and other nuclides during their careers, Seelentag[5] attributes a causative role to tritium as a result of the similar syndrome in the two cases. These cases indicate that open bench processing of tritium at levels of 100-150 Ci/month can produce urine levels of 140 to 1,120 μCi/liter, showing the need for a protection factor of 100 or more.

Measurements[18] of air concentrations, surface contamination, and urine concentrations of employees in establishments of wholesale timepiece importers, retailers, and refinishers have shown that urine concentrations in these establishments were generally well below 1 uCi/liter. This is true although resuspension factors as measured by the ratio of air concentrations/surface concentrations were relatively high compared to those for other types of radioactive dusts. This implies that surface concentrations from the handling of storage of these timepieces were not sufficiently high (although up to several thousand pCi/100 cm^2) to pose a significant inhalation hazard. In fact, most intake of tritium in storage areas was believed to result from

direct exchange of tritium from the concentrated material on the watch with moisture in the ambient air.[18] The highest urine concentration observed was in a poorly ventilated storage area through which passed about 40,000 watches per year containing 200 Ci/year. The average urine level for this employee was 2.7 uCi/liter giving an estimated 500 mrem per year.[18] Thus, handling 10 Ci/month in importing, retailing, or refinishing establishments should result in less than 10% of the derived investigation level for urinary excretion.

Academic Institution Laboratory Experience

Olson[13] has found no urine samples exceeding 1 uCi/liter out of 102 samples from individuals working in university laboratories (1971-74), presumably always with at least fume-hood protection, but with quantities of 0.2 Ci bi-weekly or 1 Ci per single operation. The range of urinary values is relatively consistent with that to be expected from the experience of watch-dial painters mentioned above,[15-17] who worked with exhaust ventilation and hand-painted using special luminous paint pens. Olson recommends bioassay above 10 mCi in process on an open bench, and above 1 Ci in process in a well-ventilated hood.

An accidental spill was reported by Olson[19] that might be considered a practical upper limit to a single-incident dose commitment to be received from fume hood operations with tritium in research laboratories. About 78 mCi of tritium as HTO was accidentally spilled on the floor of a hood and was immediately wiped up with paper towels by the graduate student involved. Instead of disposing of the towels within a container in the hood, the student allowed the towels to pass close to his face and placed them in a radioactive

waste can outside the hood. In this case, the estimated intake was 0.6 mCi based on a peak urine level of 14 μCi/liter, giving a calculated dose commitment of 100 mrem. Thus, the fractional intake was almost 1%, much higher than any reported by Franke, et.al.[7] However, this incident indicates that 100 mCi processed in a hood would not cause more than 10% of any maximum permissible dose commitment, even in the event of a "maximum credible" accident. The university involved has issued instructions on providing containment for wastes within hoods before removal.

Particle Accelerator Installations

Tritium build-up in activation products from particle accelerator beams is not generally a significant health physics problem,[20] except as a spallation product of ^{16}O for high-energy proton beams,[21] and for the tritium in targets.[22] The build-up of tritium in cooling water of the LAMPF[21] accelerator has reached 1.8×10^{-2} μCi/ml, and a production of 50-100 curies per year is expected in the next few years. However, this level should not pose a serious employee exposure problem with proper handling of wastes and measures to prevent ingestion.

More likely sources of internal tritium exposure from accelerator operations are the tritium and tritiated targets used in (D,T) reactions for fast neutron generation.[22] Exposures of about 0.5 rem/year have been received by employers during the following operation: loading uranium furnaces with T_2 gas (500Ci); transferring T_2 into and out of the target; inhalation exposure during disassembly of accelerator parts that contain absorbed tritium gas; venting of mechanical vacuum pumps, routine maintenance

of vacuum pumps including cleaning and changing oil; and ingestion of tritium from handling surfaces that have absorbed tritium.[22] Tritium concentrations as high as 0.6 Ci/100 cm^2 have been measured by swipe tests on disassembled accelerator parts. Urinary levels rose to as high as 53 μCi/liter during disassembly of the target and removal of the vacuum pumps, although levels of urinary tritium indicated average exposures about 10 per cent of maximum permissible levels for the annual dose commitments of three workers. Weekly or more frequent bioassays were deemed necessary to control the exposure of these workers. Thus, there would appear to be a need for tritium bioassays whenever accelerator parts that have been in contact with more than 100 curies of tritum gas are handled in open operations. However, there was no evidence of personnel exposure when 150 Ci of tritium gas was transferred in a closed system to the furnaces without any disassembly of accelerator equipment.

High Level Operations With Tritium Gas

Up to megacurie quantities of tritium gas have been handled in special facilities designed to minimize the concentrations of T_2O or HTO in the employee's environment.[23] Urine levels in 3800 samples, averaging 600 samples per year taken on a once-per-week frequency (more often for "special" bioassays), showed 90 percent less than the 20 μCi/liter action level, and only four more than 100 μCi/liter. Box gloves were monitored frequently for leaks, and working levels within the gloves of up to 5000 μCi/m^3 did not result in uptakes exceeding weekly permissible levels. If levels

exceeded 5000 μCi/m^3, the gloves were changed. The levels in the box atmosphere did not generally exceed 0.1 Ci/m^3.

Special precautions were taken to properly vent vacuum pumps and carry out equipment decontamination or maintenance with proper protection. Vacuum pump oil was reported to have levels as high as 1mCi/cc, but oil changes by technicians wearing surgeons' gloves, with the pumps placed in hoods, avoided appreciable intakes.

In an incident involving a release of many kilocuries of tritium gas within a hood, while the experimenter's head was in the hood directly over the release point, the experimenter received less than 100 mrem total integrated dose.

This experience[23] and that reported by others[2] demonstrates that, with appropriate equipment and procedures, pure tritium gas can be handled at activity levels thousands of times higher than corresponding levels for tritiated water before appreciable occupational exposure levels will be reached. However, allowance can be made for the lower dose from tritium gas per millicurie inhaled only when there is absolute assurance that significant water or oxygen is not present in the processes of concern. Presence of water or oxygen must be avoided to avoid formation of tritiated water before any potential point of release or dilution of the tritiated gas in process.[24] Also, if there is a possibility of leakage or escape of tritium gas out of an inert atmosphere in curie quantities or more, ventilation protection and appropriate disposal rather than containment within secondary enclosures will help to avoid build-up of HTO and increased exposure potential.[25]

Thus, with appropriate equipment and procedures to guarantee that employees will not be exposed to appreciable quantities of tritiated water, tritium gas may be handled at activity levels several orders of magnitude higher than those for HTO or T_2O before appreciable internal exposures measurable by urine assay will occur from ordinary or accidental releases of the tritium gas in process.

Reactor Operations

In the case of reactor operations, the potential for tritium exposure depends on the reactor design, type and volume of coolant, and the maximum tritium concentrations likely to build up in the coolant.[24,26-28] The dilution of the tritium is such that concentrations of tritium in the coolant of light-water power reactors is not likely to exceed 0.1-0.01 μCi/ml .[26,27] Concentrations of tritium in air within the containment building of a light (LWR) pressurized water power reactor have generally been maintained less than 10^{-6} μCi/ml, and employees entering the containment building for a few hours per week have generally shown negligible or small quantities of tritium in urine, well below the derived investigation level of 35 μCi/liter.[26,27] Experience at a 5 Megawatt deuterium-moderated research reactor has indicated that urine levels of employees will become significant when the coolant exceeds several hundred microcuries per ml.[28] Thus, activity levels in LWR coolant are generally low enough so that large single exposures to employees are unlikely, which is consistent with the suggestion that it is unlikely that quantities of radioactivity diluted to a lower specific activity with more than 10 milligrams of other material will be inhaled during occupational exposure.[29]

There is a lesser likelihood of exposure to tritium at boiling water reactors, and greater at heavy-water moderated reactors.[27] However, for all reactor operations, the need for bioassay sampling is established by monitoring results and/or design and operating factors rather than estimates of exposure potential from total quantities of tritium in process. Generally, pre-employment and post-employment samples are assayed for tritium exposure, and most reactor installations provide some type of routine bioassay monitoring for tritium. Table 1 is thus not applicable to reactor installations, except perhaps for some of the laboratories associated with them.

Fusion Reactors

The maximum release of tritium gas from operations at Sandia's proposed experimental electron beam fusion facility will be 0.1 Curie, as a result of operational restrictions on the amount of tritium used for any single irradiation. The release of 0.1 Curie has been estimated to produce a dose of only 0.188 mrem from inhalation of tritium gas to a standard man working for one hour in the diode preparation room.[30] If the tritium were converted to water vapor form, an estimated dose of 200 mrem would be received.[30] Thus, this reference indicates the assumption of a factor of 1,000 between doses per μCi from HTO and tritium gas. This type of situation, with only limited research levels of tritium, would probably warrant bioassay sampling only in the event of a known release. Later versions of this type of electron beam fusion experiment may require a greater reliance on bioassay sampling for monitoring employee exposure, depending on safeguards for containment and prevention of inadvertent exposures.

For full-scale fusion reactors, a tritium bioassay program would probably be imperative for any reactor design. Operational levels of tritium in such reactors will reach millions of curies, most in the form of tritium gas.[31] Some of the tritium is expected to diffuse through system components and be converted to HTO. The maximum permissible concentration of HTO in air is about 400 times that of tritium gas.[31] Also, tritiated water vapor can enter the body easily through the skin, where the absorption of elemental tritium gas through the skin is negligible and only 1.6 percent of tritium gas inhaled will initially enter the bloodstream.[32] Since even neoprene gloves of 0.36 mm thickness are estimated to offer protective factors of only 340,[32] reliance on protective clothing during maintenance operations will need to be supplemented by bioassay monitoring programs.

Thus, it is likely that for fusion reactor installations, either experimental or commercial, the need for (and type of) bioassay programs will be determined by a wide range of considerations of containment, reactor design, personnel protection provisions and operating procedures. No general guidance would be appropriate or necessary for these installations at this time, so fusion installations are considered outside the scope of this guide.

A.3 Relative Radiotoxicity of HTO, Tritium Gas, and Tritium Labelled Compounds

Although tritiated water has certain features that may make it more difficult to control than other radioactive materials, it is among the least radiotoxic materials per unit activity taken into the body.[2] Thus, it is necessary to consider the quantities of activity taken into the body that produce acute and chronic biological effects in man, as well as the levels of intake below which these effects are expected to be negligible.

Experiments with mice, rats, and rabbits reviewed by Evans[2] show that the LD_{50}^{30} for mice is about 1 mCi HTO per gram by injection, and varies between species somewhat. More than 0.5 mCi/g injected into rabbits results in death to 100% of the animals, after estimated doses of more than 500 rads delivered over 20 days.

Two deaths of humans exposed to tritium, which Seelentag[5] attributes to the tritium exposure despite a history in both cases of unspecified exposure to radium and other bone seekers, appears to occur with accumulated doses that could be on the order of up to several hundred rads, as indicated by urine measurements over periods of several years. In addition, autopsy results indicated components of insoluble organically-bound activity in muscles, kidney, liver, spleen, and lungs.[6]

On the other hand, a 41-year-old male who accidentally ingested about 86 mCi to give a calculated total body water dose of 16 rem (QF = 1.7) showed no clinical side effects.[33] In the latter case, a 2 percent compartment excreted tritium with a half-life of 34 days.[33] In another incident where human urinary excretion could be followed for 450 days, a three-exponential excretion was observed.[34] Sanders and Reinig[34] analyzed this data using

a model with two organic compound compartments exchanging tritium with body water, and calculated lower dose commitments from tritium in the organic compartments than to body water. No immediate clinical effects were reported for this individual. The estimated intake of 45.7 mCi resulted in estimated doses of 3.52 rem to body water and 1.37 rem to the organic-tritium compartments.[34] Long-term but low-level components with half-lives on the order of one year have also been observed in urinary excretion of former employees of the luminous dial industry.[35,36]

Thus, although limited human data confirm that a fraction of tritium as HTO in body water will enter long-term compartments, these data as well as animal data indicate that acute clinical effects are not likely below a 16 rem dose calculated on the basis of energy deposition by HTO in body water, using an RBE or QF of 1.7.

No studies are available on long-term effects in humans at low dose levels from tritium. Such studies would indeed not be feasible, since not only are permissible exposure levels orders of magnitude below levels showing acute toxicity, but industrial experience has shown that the average monitored employee remains far below permissible limits or action levels established for radiation protection design or operations.[24,26-28] The risks from chronic effects may be expected to be of the same low order of magnitude as that from whole-body gamma radiation exposure maintained well below maximum permissible limits. Limited experimental data on chronic effects in animals[2,3] of labelled organic compounds also tend to indicate that the relative risks of tritium exposure would not be likely to be more than 10 times that from gamma radiation under low dose-rate conditions.

Although in recent years there has been an ICRP recommendation[37] to use a QF of 1 for tritium beta radiation, some radiobiological evidence at low dose rates has suggested a QF greater than 1 as appropriate, relative to gamma-ray effects.[2,38,39] Human data is not available to distinguish between these two values, and many references show that action levels and dose calculations in use for radiation protection purposes are still following derived urinary excretion values based on the QF of 1.7.[2,3] A QF of 1 may be more appropriate for estimating the potential for acute biological effects at higher doses, as suggested by the animal data cited earlier,[2] but a more recent experiment with rats resulted in an LD_{50} at four days of 1.86 and 3.72 kilorads for HTO and gamma rays, respectively,[39] as well as QF's greater than one for other macroscopic biological endpoints.

Considering the human and animal data available, the probable variation within a range of 1-2 of QF with dose-rate and type of effect studied,[38,40] the desire for conservatism in establishing standards for radiation protection,[38] the estimate that doses to organic, long-term compartments may be about 1.5 times that calculated for body water,[35,41] and the desirability of avoiding unnecessary perturbations in already-functioning bioassay programs, it seems reasonable to adopt the ICRP[10,12] derived investigation level (DIL) of 1.5 mCi intake as representing a dose commitment of 250 millirem and urinary elimination rates of 35 uCi/liter (initial), 13 uCi/liter at 14 days, and 4 uCi/liter at 30 days after a single intake.[43] The adoption of these DIL's for single intake and the above dose commitment is also consistent with the use of the ICRP[9] maximum permissible continuous body burden of 1 mCi* HTO

*The actual value of 1.2 mCi, giving a calculated dose-rate of 100 mrem/week to 43 kilograms of body water and resulting in an equilibrium excretion rate of 28 uCi/liter of urine (using a 12-day biological half-life[9]), was rounded off to 1 in the ICRP Committee II Report.[9]

for a continuous dose-rate of 100 millirem per week to body water, resulting in an equilibrium excretion rate of 28 uCi/liter.[2] For standard man,[9] a 1 mCi* HTO burden would be sustained by a continuous 40 hour/week occupational exposure to an air concentration of 5×10^{-6} uCi/cc as HTO, or 2×10^{-3} uCi/cc of tritium gas.[2] The corresponding drinking water concentration in equilibrium with 1 mCi* in body water would be 0.1 uCi/ml (100 uCi/liter), allowing for loss of water by exhalation.[9] These ICRP values are consistent with the conversion more recently recommended by Moghissi, Patzer, and Carter[42] for calculating environmental dose commitments to populations from urinary levels of tritium.

Tritium Gas (T_2 or HT)

Anderson and Langham[44] reached the following conclusions[2] from their studies of physiological kinetics and effects of tritium gas and tritiated water:

(a) the hazard from the exposure to tritium gas was at least 1,000 times less than from tritiated water;

(b) the greatest exposure hazard from tritium gas would result from its conversion to its oxide prior to intake;

(c) the beta dose-rate to the 1 μ m respiratory surface of lung is largely ineffective, as indicated by the fact that 135,000 calculated rem to the lung surfaces in mice produced no histological evidence of damage;

(d) there is about equal contribution to whole body dose from dissolved tritium gas in body fluids and from tritium biologically oxidized to HTO.

(e) the doses from bremsstrahlung and auto-oxidation of tritium by its own radiation field can be neglected.

The hazard from exposure to even larger amounts of tritium gas was not judged to be a lethal one.[2] A 10-second exposure to pure tritium gas (2.6 Curies/cc) would result in a dose of only about 6 rem. (At the breathing rate of 20 liters/min of reference man under light activity,[45] the 10 sec exposure would amount to about $\frac{10}{60}$ x 20,000 $\frac{cc}{min}$ x 2.6 Curies = 8,700 Curies.)

It was also calculated[2] that if the air in a room were 10 percent tritium, a 10 minute exposure would result in a dose of about 40 rem. (In a small laboratory of volume 150-300 m^3, a 10 percent tritium atmosphere would correspond to a release of 4 - 7 x 10^7 Ci[2].) (The 10-minute exposure would amount to an inhalation of 0.1 x 20 l/min. x 10 min·2.6 x 10^3 Curies of T_2 per liter = 52,000 Curies of T_2 gas.)

The above estimates of intake may be compared with the data of Pinson and Anderson,[46] which show that a man breathing an atmosphere containing 9 uCi/cc of tritium as HT for 100 minutes reached a urinary level of 14 uCi/liter. Using the ICRP values[10,12] of 35 uCi/liter in urine corresponding to 0.25 rem dose commitment from HTO, the experimenter inhaled a quantity of

9 uCi/cc x 1000 x 20 l/min x 100 =

18 Curies of HT gas,

and received a dose commitment from the HTO produced by biological oxidation of

$\frac{14}{35}$ x 0.25 Rem = 0.1 Rem

Therefore, the inhalation of 52,000 Curies of tritium gas, as postulated in the above example, would give a dose commitment of

$$\frac{52,000}{18} \times 0.1 \text{ Rem}$$

$$= 290 \text{ Rem},$$

(assuming the QF of 1.7).

It is probable that this dose spread out over the effective lifetime of HTO in the body would not be lethal.

Even the 10-second exposure to pure tritium gas involved an inhalation of 8700 Curies. Using Pinson and Anderson's results and ICRP values, this quantity inhaled should give a dose commitment of

$$\frac{8700}{18} \times 0.1 \text{ Rem} = 48 \text{ Rem},$$

in good agreement with the 40 Rem estimate of Anderson and Langham.[2,44] These quantities (and resulting doses) of HTO in the body resulting from inhalation by man of tritium gas are also consistent with the data of Pinson and Langham.[47]

Calculation of Dose from Dissolved Tritium Gas

The solubility of H_2 in water is 1.91 cc/100 g at 25 C or 1.89 cc/100 g at 50 C.[48] Using 1.90 cc/100 g at body temperature and a specific activity of 2.6 Curies T_2* per cc of pure gas at 1 atmosphere pressure, then the solubility

*At 1 atmosphere, the number of T atoms per cc is:

$N = \frac{2 \times 6.023 \times 10^{23}}{22,400 \text{ cc}} = 5.38 \times 10^{19}$, and the activity is:

$A = \lambda N / 3.7 \times 10^{10} = \frac{0.693}{(12.3 \times 365 \times 24 \times 3600)} \quad \frac{5.38 \times 10^{19}}{3.7 \times 10^{10}} = 2.6$ Curies/cc (1.3 for HT)

in body water under equilibrium conditions becomes 0.0494 curies/g. Thus, the concentration per unit volume, relative to that in pure gas in equilibrium with water would be about

$$\frac{0.0494 \text{ Curies/cc water}}{2.6 \text{ Curies/cc}} = 0.019$$

at 25°C, or slightly less at body temperature. This is in fair agreement with the estimate of 1.65% concentration[44] in body tissues relative to concentration of tritium in air. The rate of dissolution of tritium in blood in equilibrium with inspired air may be assumed to follow a 4-minute half-time of uptake,[49] so approximate equilibrium would be reached within 10-20 minutes after exposure to a constant concentration, or the concentration in blood will remain lower than equilibrium concentrations for short exposure times. Solubilities for H_2 gas are assumed sufficiently accurate to use for HT or T_2 gas for dose estimation purposes.[50]

The dose-rate in blood (or body water) at equilibrium with a constant pressure of 1 atm T_2 is

$$0.0494 \text{ Ci/g} \times 3.7 \times 10^{10} \text{ d/sec - Ci} \times 0.0055 \text{ Mev/dis} \times 1.6 \times 10^{-6} \text{ ergs/Mev} = 16 \text{ ergs/g-sec} = 16 \text{ rads/sec}$$

For a concentration of 9 uCi/cc in inspired air, as in the experiment of Pinson and Anderson,[46] the equilibrium exposure rate would be proportional to the partial pressure of tritium gas. Thus, the dose-rate from dissolved HT during the 100-minute exposure period would be approximately:

$$(1/2 \times 16 \text{ rads/sec for HT}) \times \frac{9 \times 10^{-6} \text{ Ci/cc}}{1/2 \times 2.6 \text{ Ci/cc}}$$

$$5.5 \times 10^{-5} \text{ rads/sec,}$$

$$\text{or } 3.3 \times 10^{-3} \text{ rads/minute}$$

Thus, during the duration of the 100-minute inhalation experiment,[46] 18 Curies of HT were inhaled, delivering a dose to blood of about $3.3 \times 10^{-3} \times 100$ = 0.33 rads and a dose commitment from the HTO formed by biological oxidation of about 0.1 rem, as calculated above. This calculation does not take into account tritium compartments resulting from tritiation of organic molecules in vivo or absorbed tritium gas that does not leave the system once the tritium concentration in inspired air is reduced, but the dose from these compartments is expected to be very small due to the rapid elimination of this tritium from the body.

Thus, the internal dose from exposure to HT or T_2 gas would be 5,000 - 10,000 times lower than the internal dose from exposure to the same integrated air activity of HTO. For exposure times of 1 minute or less (typical of single releases in the laboratory), relative doses from tritium gas will be even lower as a result of the finite time required for diffusion of the gas into the blood [49] compared to the instantaneous absorption of inhaled HTO.[2]

Tritium Compounds (Other than Nucleic Acid Precursors)

Although the doses and effects from tritium compounds are more complex to investigate or predict than for tritiated water, many studies have surprisingly indicated that these compounds are usually not much more toxic than tritiatedwater, and are often considerably less radiotoxic as a result of more rapid elimination from the body.[2] Tritiated corticosteroids were found on the basis of estimated organ doses to be 30 times less radiotoxic than tritiated water.[51] Tritiated folic acid was estimated to be twice as toxic as tritiated water based on results from the administration of these

compounds to rats.[52] Shaw[53] has indicated that injections of the tritiated sex hormones oestradiol and testosterone result in smaller doses in all organs of the rats than those from equal injections of tritiated water. There was quoted[2] an absence of appreciable hematologic changes in patients after intravenous doses of 10 Ci of tritiated tetrasodium 2-methyl-1,4-napthaquinol diphosphate.[54] A 10 Ci dose of tritiated water would have been expected to deliver about 1,000 rem to the bone marrow, and would probably have exceeded the more chronic tritium exposures which Seelentag[5] considered the primary causes of death in two cases.

Since tritiated water is the major catabolic product of most of the labelled compounds that enter the body,[41] exposures of workers to these compounds may be monitored by bioassay of urine with the likelihood that a major part of the dose may be interpreted as dose from HTO. This practice has been used in laboratories where employees are exposed to higher levels of tritium during production of these tritiated compounds.[55] Since tritiated compounds are generally less volatile than HTO and less easily absorbed through the skin, it seems reasonable for purposes of establishing criteria for bioassay programs to assume that the relative radiotoxicity of tritiated organic compounds is about the same as that for HTO.

Tritiated Compounds Concentrating in Cell Nuclei

A number of authors have suggested that compounds such as tritiated thymine or thymidine, or other nucleotide precursors that would tend to concentrate in the DNA of cells, might deliver far greater doses than tritiated water and present a far greater hazard per millicurie of intake by persons working with these compounds.[56-60] Barber[61] deduces that tritiated thymidine MPC's should be about 10^{-4} to 10^{-5} times the MPC's for tritiated water, from calculations of an assumed maximum number of permitted disintegrations in the cells of a human composed completely of cell nuclei, using Dewey's[62] finding that 30 disintegrations per cell from tritiated thymidine did not significantly increase chromosomal aberration frequencies. Berry, et.al[58] have suggested, based on cell survival studies, that tritiated thymidine should be regarded as a material of moderately high toxicity, comparable to I-131; this suggestion would place tritiated thymidine in a category requiring about 1,000 times the protection factors applicable to HTO.[63]

Guild[64] calculated that tritiated thymidine can deliver doses to the chromosomes from 50 to 50,000 times those delivered by an equal activity of tritiated water; however, Dewey, et.al[65] suggest that the effectiveness for breaking chromosomes is about the same for thymidine incorporated into DNA as for tritiated water or Cobalt-60 gamma radiation. They[62] also found that 1,700 tritium disintegrations originating in DNA were required to produce one visible chromosome aberration.

Lambert,[66] based on a review of previous literature as well as his own experiments,[66,67,68] concludes that the maximum permissible annual intake of tritiated thymidine is about 20 mCi. This intake of 20 mCi may be compared with the annual intake of 25 mCi of HTO that would give a dose commitment of 5 rem (integrating the intake by standard man breathing at MPC for one year).[9] Thus, since there are conflicting opinions in the literature regarding the relative "radiotixicity" of tritiated nucleotide precursors, some selected experimental results will be examined further here to determine a reasonable upper limit to the assumed relative radiotoxicity of these precursors compared to HTO.

Wade and Shaw[59] have shown that 24 hours after stomach intubation of 1 uCi quantities of tritiated thymidine, the average total body activity was 51 percent of the ingested activity and the non-volatile activity was only 8 percent of the ingested activity. After subcutaneous injection several times more activity was retained in spleen, testes, and small intestine, as measured relative to retention after oral ingestion over days 1,2,4 and 8; about the same relative retention for injection as for ingestion was obtained for liver, kidney, and muscle. The non-volatile activity was assumed to be retained mostly in the cell nuclei of these tissues as reported by others.[69-73] Assuming that the non-volatile activity was dispersed through all cell nuclei, Wade and Shaw[59] calculated the maximum dose to nuclei from their data to be the dose to nuclei of liver, which reached about 0.2 rads per uCi of ingested tritiated thymidine. Scaled up to the body weight of standard man, this would be 0.2 rads/2.8 mCi ingested; for comparison, the calculated dose to body water from ingesting 2.8 mCi of HTO would be 0.28 rads--slightly higher

than the dose to nuclei from tritiated thymidine assuming all of the non-volatile tritium is taken up in all cell nuclei of liver.

Then, assuming that only 5 percent of liver cells actually contain the observed quantity of non-volatile tritium, and adopting the conclusion of Bond and Feinendegen[74] that the RBE of intranuclear tritium is probably close to one, Wade and Shaw[54] calculate a dose equivalent to nuclei of 1.25 rem per 1 mCi of tritiated thymidine ingested. This tritiated thymidine dose is then compared to a stated dose of 1.25 rem per 20 mCi of HTO ingested to conclude that "... tritiated thymidine is more hazardous as an internal emitter than tritiated inorganic molecules such as water or hydrogen gas by at least a factor of 20."[59] However, if the intake of HTO required to give 1.25 rem is calculated from ICRP data,[9,10] but with an RBE equal to 1 and 100 percent uptake of HTO, the comparable dose of HTO becomes 12.4 mCi to give 1.25 Rem -- not 20 as given by Wade and Shaw.[59] Moreover, the assumption[59] that only 5 percent of the nuclei contain the tritium amounts to a proportionate reduction of the numberof cells at risk in the "critical" tissue. Bond and Feinendegen[74,75] as well as Lambert[66] cite evidence that somatic risk may be estimated on the basis of average dose to cell nuclei, or the product of average dose to cells at risk times the number of cells at risk. Thus, if the dose calculated by Wade and Shaw were averaged over all cell nuclei, or equivalently the fractional number of cells at risk were taken into account, then the number of millicuries of ingested tritiated thymidine to produce a dose equivalent of 1.25 Rem for somatic risk evaluation purposes would be increased to 20 mCi, and the relative "radiotoxicity" of tritiated thymidine would actually be <u>less</u> than that of tritiated water.

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Lambert[67] found that tritiated thymidine was 4 times as effective as HTO per μCi injected intraperitoneally for decreasing the production of primary resting spermatocytes in mouse tests.[66] In the same set of experiments, the mice were also subjected to whole body radiation and irradiation of testes alone, with little difference in effect. Also, 50 Kvp (1.2 mm Al HVL) X-rays were as effective as 200 Kvp X-rays (about 12 mm Al HVL). When the dose-rate of 200 Kvp X-rays was decreased at the same rate as that from HTO, the effect of 30 rads of X-radiation was equivalent to that from 20 μCi injected per gram of body weight. The RBE's obtained in these experiments ranged from 1.3 to 2.4. The calculated initial dose-rate from 20 μCi/g body weight would be 20 x 3.6 Rem/week* = 72 Rem/wk. For a biological half-life of 2 days, this would amount to a dose during the 72-hour experiment of

$$\text{Dose (72 hours)} = \int_{t=o}^{72} \frac{72 \text{ Rem/week}}{(168 \text{ hrs/wk})} \, e^{-0.693t/2x24} \, dt$$

$$= \frac{72}{168} \times \frac{48}{0.693} \left[e^{-0.693(0)/2} - e^{-0.693(72)/48} \right]$$

$$= \underline{19 \text{ Rem}} \quad (19/1.7 = 11 \text{ rads})$$

The dose during the earlier 19-hour period when perhaps the spermatogonial cells are in more sensitive stages would be even lower, when averaged over body water. Lambert[67] obtained his doses to cell nuclei

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*Obtained using the ICRP values[9,10] that 1.2 mCi/43,000 g of body water yields a dose-rate of 100 mrem/week; or for a single intake, yields a dose commitment of 100 mrem x 1.44 x 10/7 = 205 mrem using the ICRP 10 values for biological half-life.[10]

from track autoradiographs, correcting to dose in rads absorbed within the nuclear volume, which indicates for tritiated water that spermatagonia cell nuclei receive the same dose from tritiated water as calculated from the average dose to body water. (The calculated dose above, based on an assumed 2-day biological half-life in the mouse gives an RBE = 30 rads/11 = 2.7, close to the higher value given by Lambert.[67]

Although the absorbed tritiated thymidine was contained mostly in cell nuclei,[67] only a small fraction of the administered thymidine reached cell nuclei, so that the relative dose to nuclei per administered microcurie was such that cell effects per unit administered dose were only about 3 times greater for tritiated thymidine than for tritiated HTO.

Thus, the relative radiotoxicity of tritiated thymidine/HTO would be only 3 from these experiments, regardless of RBE or calculated doses to cell nuclei.* Furthermore, although the spermatogonia are particularly sensitive to radiation, and responses may be observed for calculated doses as low as about 2 rads from tritium,[75] these rapidly proliferating cells would perhaps also be more capable of recovery and can sustain considerable depletion without loss of ability to survive or regenerate to full capacity.[67,66]

In another set of experiments, Lambert[68] studied the ingestion of tritiated thymidine in rats, and concluded that tritiated thymidine

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*In a later paper, Lambert[66] states that the relative radiation doses averaged over the testes were in the ratio of 1.5 to 1 for tritiated thymidine compared to tritiated water; for the relative doses to the cell nuclei (of spermatogonia), the corresponding ratio was 6.4 to 1.

administered by ingestion gave the highest dose to bone marrow cells, about 34 times the dose given by tritiated water.

In a further set of experiments studying the effects on production of resting primary spermatocytes, Lambert[66] shows that although high specific activity tritiated thymidine exhibits the greatest (spermatogonia) cell-killing effect per injected microcurie among the several organic compounds studied, the concept of average dose to the mouse testes could be used within a factor of five to estimate the hazard from the compounds studied: tritiated thymidine, uridine, methionine, and HTO. His main conclusion from these and previous experiments is that "....to a first approximation, there is no great difference in cell-killing effects during 90 hours exposure between the compounds studied relative to injected activity."[66] He also reviews previous work of others and indicates that although earlier papers "indicated that tritiated thymidine should be considered several orders of magnitude more toxic to mammalian cell systems than tritiated water.....later work has disproved this concept....," and yet, "....there are still reports published suggesting that, on the basis of dose calculation, tritiated thymidine should be considered an extremely hazardous material." Thus, Lambert concludes both from literature review as well as his own experiments that tritiated thymidine is not more than five times as toxic per injected microcurie as other tritiated compounds or HTO.

Feinendegen and Bond[76] have updated their review[74] of the effects of tritium incorporated in DNA, cell nuclei, and other cell components,

and conclude, consistent with their earlier evaluation, that cell killing effects can be explained on the basis of the average radiation dose delivered to the cell nucleus. The effect of transmutation of H-3 to He-3 after incorporation of tritiated thymidine or cytosine into cell nuclei was estimated to be much lower than the ionization effect from beta decay, and not easily observed.

Tritium bound within the DNA of E. Coli was more effective in cell killing than that bound within the protein around the DNA core. Also, tritium decaying in DNA (^{3}H-thymidine) was about twice as effective in reducing survival of Chinese hamster fibroblasts as tritium incorporated in RNA (^{3}H-uridine). The effectiveness of beta decay was sometimes found to depend on the position of the tritium atom in the pyrimidine ring.(76) Tritium in the 5 position, but not in the 6 position, of cytosine was found effective in mutation induction in E. Coli and bacteriophage.

Tritiated uridine was more effective in inducing mutations in E. Coli at low temperatures (arginine reversion), and in Drosophila, when H-3 was incorporated in the 5 rather than 6 position. The mutation probability in E. Coli for the 6-to-5 position change rose from 0.28×10^{-8} per decay per cell, increasing past the value of 0.67×10^{-8} for tritium-methyl-thymidine in DNA. Since there was no significant difference in lethal effects of the two uridines, the 5 position effectiveness was in this case attributed to a transmutation effect in the 5 to 6% of the uracil that was converted to cytosine and incorporated into the DNA of the nucleus.

Tritium decaying in the 5 position of DNA cytosine in E. Coli was interpreted as producing a coding change from cytosine to thymine, whereas no such change was detected with tritium decaying in the 6 position.[77] Single and double strand chromosome breaks in mouse leukemia cells stored at -196°C were also attributed to the beta-ray dose to the nucleus from incorporation of tritium-methyl-thymidine, rather than H-3 to He-3 transmutation. The decay of two to three tritium atoms in a cell nucleus of 6 to 7 μm was estimated to deliver an average dose of 1 rad to the nucleus; Lambert estimates the dose within a range of 1 μm to be 170 rads.[66]

From the preceding experiments, Feinendegen and Bond[76] conclude that, under normal growth conditions, the calculated dose to the cell nucleus from DNA bound tritium is comparable, for a given degree of effect, to the same dose from external gamma radiation. Transmutation effects do not produce a measurably increased effect under most conditions, and have been detectable at all only under highly specialized laboratory conditions.

Colvin and Everts[78] showed that tritium from luminous compounds could be absorbed through the skin of Chinese Hamsters in proportion to the amount of tritium applied. However, the frequency of chromosome breaks from the compound could have been due to a chemical effect of the compound, rather than the tritium. There was no statistically significant difference in the frequency of chromosomal anomalies between the two

exposed groups of animals, even though they absorbed amounts of tritium a factor of ten apart. The amounts of luminous compound applied (5 mg of compound over 1 cm^2 of shaved skin in each case, for 8 hours) was the same for the two cases, and chromosomal anomolies for the two exposed groups were significantly different from those in the controls. No firm conclusions can be drawn regarding the cause of the anomalies since there was no control group exposed to an equal amount of non-tritiated luminous compound. It appears from the results, however, that the chemical toxicity of tritiated luminous compounds may be much more important than the effects of tritium radioactivity.

Mewissen and Rust[79] have produced cancer in C57 Black/6 mice by injecting subcutaneously 16 hours after birth with doses of 0.3 μCi/g to 1.5 μCi/g and following age-specific mortality and tumor incidence, relative to controls injected 16 hours after birth with cold thymidine. However, the strain of mouse employed in this experiment had a high incidence of spontaneous tumors. The experiments were consistent with the findings of Lisco et. al.,[80] who had established induction of malignancies in CAF_1 mice at dose levels of 1.0 μCi/g. However, tumor incidence was increased even at smaller dose levels in the C57 Black/6 mice, possibly attributable to the earlier age at injection.[79] The dependence of susceptibility on age at initial exposure is further suggested by the negative results obtained by Johnson and Cronkite.[81] They found no change in age-specific mortality rates, nor alteration of incidence or time of onset of neoplasia, in mature BNL Swiss albino mice injected with tritiated thymidine in doses of 1 to 5 μCi/g body weight, at ages varying from 6 to 12 weeks. It should be pointed out

further that the increased incidence of tumors found by Mewissen and Rust was attributable entirely to an increase in lymphosarcomas.[79] Furthermore, an examination of their mortality curves shows that at the highest dose level (1.5 μCi/g) the points indicating cancer incidence return to scatter near the mortality curve for the controls; the authors do not mention or explain this in their discussion.[79]

Thus, these experiments on carcinogenisis indicate that tritiated thymidine injections (which tend to increase dose to the nucleus) can, in some strains, and for very early postnatal administration, produce cancer in susceptible mice at initial dose rates of only about 1 rad/week averaged over cell tissue, or about 4 rads/week to cell nuclei. (These latter dose estimates are adopted from previous paragraphs of this section.) The effect is probably age dependent, may be species dependent, and apparently may disappear for unexplained reasons at the higher dose levels.

In a review of the relative toxicity and permissible concentrations of tritium and its compounds, Osborne[82] has summarized the evidence explaining why, although some of the tritium from HTO and/or other compounds may concentrate tritium in DNA or other cell molecules, the net effect of the exposure has never been observed to be more than about 3 times that expected from a calculation of dose to body water from an equivalent activity of HTO. Osborne[82] suggests, e.g., that although folic acid and tritiated thymidine may give three times the dose to cell nuclei as the same intake to blood of tritiated water,[83] the spatial concentration of that tritium absorbed into cell nuclei is offset by catabolism of most of

the tritiated compound before incorporation into nuclei. Moreover, seven eighths of ingested thymidine would be catabolized in the gut, and additional catabolism of tritiated DNA precursors would take place in tissue before they could be incorporated into cell nuclei.

After intravenous injection of tritiated thymidine at a level of 1 μCi/g body weight (the minimum showing effects on bone marrow cell turnover rates, with no marrow cell depletion in Sprague-Dawley rats) autoradiographic and radiochemical analyses showed that 27 percent of nucleated cells were labelled; the average calculated dose to the nuclei of labelled cells over the effective time until cell killing was 6 rads.[74] If one calculates the dose averaged over all cell nuclei of the nucleated cells, one gets about 1.5 rads. This may be compared to an average dose of about 0.3 rads to all body water (and nuclei as well) if 1 μCi/g were injected as HTO. Thus, the average dose to cell nuclei from injected tritiated thymidine was only about 5 times the average dose to body water (and also approximately to cell nuclei) that would have been delivered from the same injected activity of HTO. Bond and Feinendegen compare (from these experiments) a maximum dose of 25-35 rads to the most highly labelled cell nuclei (young megakaryocytes) with the 46 rads to marrow of mice that would produce definite changes in the DNA content of marrow.[84] However, the mouse marrow endpoint seems more severe than that of Bond and Feinendegen, and the species is different.

In a later review by Cronkite, Robertson, and Feinendegen[75] the authors again confirm earlier conclusions[74] as follows:

"1. The absorbed dose concept holds down to the order of 10^{11} grams or less, and somatic effects can be predicted on this basis.

2. The distribution of tritium atoms incorporated into DNA as tritiated thymidine (and ion pairs from the beta particles) are randomly distributed as far as dose calculations for the purpose of predicting somatic effects are concerned.

3. Every part of the cell nucleus lies within one tritium beta range of some part of a chromatid, and the nucleus contains no sizable contiguous insensitive volume of a radius exceeding the effective range of tritium betas (1 to 2 μm).

4. The origin of tritium beta tracks in, or their close juxtaposition to, the DNA molecule does not appear to enhance the degree of somatic effects."

In this later review, data available on the various types of somatic and genetic effects as produced by HTO and tritiated thymidine are again summarized and seem to indicate that doses to cell nuclei from the tritium beta particles, whether or not they originate from tritium atoms within DNA, can account for the effects produced. Also, the dosage from beta particles originating from DNA-tritium do not seem to be more than about 5 times as effective as the same dose delivered by tritium atoms distributed in HTO within body water (and the water of the cell protoplasm and nucleus). The review emphasizes some uncertainties in measuring beta

particle tracks and calculating doses to cell nuclei. Also, it is not always clear for every experiment described whether the authors are discussing average dose to all cell nuclei of the tissue in question, or the average or maximum dose to labelled cells. However, the analysis above of Feinendegen's findings regarding killing of bone marrow cells, which are again quoted in this later review,[75] shows that the average dose to all cell nuclei is only five times the dose that would be delivered by an equal injected activity of HTO. On this basis, ingested (or even inhaled) tritiated thymidine would be further reduced by catabolism[82] before entering the cell and penetrating the nuclear membrane during the stage of DNA synthesis, and could be reduced in effectiveness even below that of an equal intake of HTO. There seems to be a paucity of actual data, however, on the relative toxicity of HTO and tritiated thymidine when inhaled, ingested, or absorbed through the skin by mammals.

Three studies are cited by Cronkite et. al.[75] in which carcinogenesis was investigated following injection of tritiated thymidine into mice.

Cottier et. al.[85] compared C-57Bl/6J mice injected with 10 μCi/g body weight at each of three weekly intervals against controls given whole-body irradiation. The mice injected with tritiated thymidine did not develop any thymic lymphomas, whereas those given three whole body doses to a total of 480 rads developed the expected number of tumors. (We may estimate that if the 10 μCi/g injections were HTO, the total dose delivered to body water would have been (see p. 27)

$$3\left(\frac{36 \text{ Rem/week}}{7} \times 2 \times 1.44\right) = \underline{44 \text{ rads}},$$

or with an RBE = 1.7, 75 Rem. Thus, the effectiveness of the tritiated thymidine, which did not induce tumors at this injection level, could not be as much as 480/75 to 480/44, or 6.4 to 11 times as effective as HTO would be expected to be in producing thymic lymphomas.)

Baserga, et. al.[86,87] administered thymidine in doses of 0.1 to 10 μCi/g body weight into embryonic, newborn and young mice up to 14 months of age. The higher the dose and the earlier in life it was administered, the higher was the tumor incidence relative to non-irradiated controls.

Johnson and Cronkite's study[81] was also cited[75] in which mice (Swiss Albino) injected with 1 and 5 uCi tritiated thymidine per gram body weight at 6 to 12 weeks of age showed no significant differences in tumor incidence than non-irradiated controls or controls given 400 R of whole body gamma radiation. (Of course, considering the number of animals used in these experiments, detection of small changes in incidence would not be expected.)

Thus, the review of Cronkite et. al.[75] again indicates that tritiated thymidine is not more than 10 times as radiotoxic as tritiated water per injected microcurie, for various biological endpoints in animals including acute and chronic somatic effects, as well as for cytogenetic effects. The relative radiotoxicity might even be lower for ingestion, inhalation, or absorption through skin.

Conclusions

When compared on the basis of equal microcurie intakes under conditions of employment, tritiated thymidine may be assumed to be not more than a factor of ten more radiotoxic than tritiated water. Other tritiated organic compounds may be assumed to be about the same as tritiated water in relative radiotoxicity, for purposes of hazard evaluation and establishing good safety practices. Actual relative radiotoxicities will depend on the type and form of compound taken into the body, the age of the exposed individual and the biological endpoint considered. However, some earlier expectations of a much higher effectiveness of tritiated DNA precursors relative to HTO are not borne out by experimental results. Effects of concentration of precursors into DNA are not as high as originally supposed and the transmutation effect has been judged to be unimportant. Furthermore, catabolism of DNA precursors and other organic compounds after normal modes of entry into the body, rapid turnover of tritium incorporated in DNA with each cell division, repair mechanisms and other factors tend to compensate for the higher nuclear concentration of that portion of tritiated DNA precursors that reach cells during DNA synthesis. Good radiation safety practice and design always provide adequate additional safety factors to allow for uncertainties in these assumptions regarding the ranges of relative radiotoxicities.

A.4 Derivation of Criteria for Establishing Tritium Bioassay Programs

A.4.1 Basis for the Criteria

As indicated in Section A.1, the probability that an employee will inhale or ingest material in his work environment depends on many interrelated factors, such as relative radiotoxicity of the material and its potential for dispersal, types of processes, and safeguards provided through facilities, equipment, and procedures. However, experience with tritium in benchtop or chemical fume hood operations has shown that there are activity levels in certain processes above which the likelihood of intake of measurable quantities of tritium becomes appreciable, and there are higher levels at which the probability of exceeding what the ICRP has considered "derived investigation levels" (DIL) becomes appreciable. Some of these experiences, and empirical data on probabilities of intake, have been summarized in Section A.2

Thus, using the experience and experimentation discussed in Sections A.1 to A.3, the activity levels in Table 8.1 above which tritium bioassay "shall be required" or "shall be considered" are derived as follows:

1. The minimum activity of HTO si determined that could have an appreciable probability of resulting in a n intake of 1.5 mCi, giving a whole-body water dose commitment of 0.25 rem (the ICRP "derived investigation level" (DIL)), if all released within arm's length of an employee working on an open bench (the "maximum credible accident").

2. This level is selected as the value in Table 8.1 (100 mCi) above which some type of bioassay sampling program shall be required for the employee (perhaps only occasional bioassay scheduled after particular operations, as judged by the health physicist).

3. The level at which bioassay "shall be considered" is taken as 10 times lower than that at which it is required, since in the extremely unlikely situation where the total quantity is taken into the body, a dose commitment of about 10 rem (with RBE = 1.7) could be received, and in the opinion of most health professionals doses of such a magnitude exceed the recommended permissible annual limits and should be detected and recorded, even though not likely in this rare instance to cause recognizable harm to the individual or add an amount to his lifetime cumulative dose that would preclude his returning to employment in radiation work. Also, for tritium bioassay the sensitivity of detection of tritium in urine is such[10] that bioassay can be useful in monitoring employee exposures even in more likely exposure situations (more "credible" accidents or routine exposure situations). In keeping with the principle of maintaining exposures "as low as reasonably achievable" (ALARA), a reasonable monitoring program should be provided whenever 10 percent of the DIL may be received, in order to help understand and control sources of exposure as well as document the employee's actual exposure status.

4. The appropriate corresponding activity levels in Table 8.1 for tritiated DNA precursors, other tritium compounds, and tritium gas were chosen by considering operational experiences and radiotoxicity relative to HTO, as discussed in Sections A.1 - A.3.

5. Activity levels in operational processes within fume hoods (even when contained within process vessels that may fail only occasionally) are allowed to be ten times higher than those on an open bench before

bioassay procedures are considerednecessary or useful. An average protection factor of at least ten may be assumed for a ventilated hood, properly used and maintained at adequate face velocities.(1,63)

6.For processes contained within closed, properly designed, gloveboxes or other failure-proof containment systems, no given values can be presented that can be considered reasonable for all situations. The same is true for nuclear reactor installations, or other facilities in which tritium may (or sometimes may not) be diluted to very low specific activities of the material in process (see Section A.1 and A.2). In these cases of extremely reliable containment or assurance of sufficiently high dilutions, the need for bioassay must be evaluated by a professional health physicist in consultation with appropriate supervisors or plant engineers who know the detailed processes, equipment, facilities, work conditions of the specific tasks, and specific qualifications of the employee. The evaluation in these cases may also include the evaluation of pre-employment and initial bioassay samples, air monitoring results, and contamination surveys, as well as the employee's age, health, employment status, training, work history, and history of previous exposure to radiation and other environmental agents. Industrial medical participation in the determination of the need for bioassay may also be appropriate in many instances.

A.4.2 Probabilities of Intake of Radioactive Material in Various Situations

A number of work situations have been discussed in Section A.2 for which the amounts of radioactive material taken into the body have been

related to amounts of radioactive material in process. The maximum reported fractional intake of material in process following an accident actually occurred with a spill of tritium as HTO within a fume hood.[11,13,19] In this case, less than 1 per cent of the HTO in process, which was all spilled onto the hood benchtop, was taken into the body -- presumably because the student involved wiped the spill with paper towelling and violated the ventilation protection by removing the contaminated towels to the outside of the hood and past his face for disposal. Thus, the "maximum credible accident" is taken to result in about a 1 per cent intake of the material in process.

All other accidents reported in the literature showed that fractional intakes were less than about 10^{-6} of the material in process, except for one case of 10^{-5} under conditions of poor ventilation.[7,8,1,14,63] Thus, the assumption of a 10^{-2} fractional intake should be sufficiently conservative for purposes of planning bioassay programs, and yet will also be seen (from Section A.2) to result in criteria that will be reasonable from the standpoint of experiences with intakes from monthly amounts routinely processed. (The values in Table 8.1 are deemed applicable either to single operations with the given amount in process, or to routine, repeated operations for the same integrated amount processed by the given employee over a period of one month. The empirical data and experience presented in Section A.2 allow this fortuitous simplification of Table 8.1 so that it can apply to a broader range of work situations.)

The selection of bioassay sampling frequencies or schedules is discussed in another section of this standard. It may be noted that with

proper selection of the bioassay sampling interval, an adequate sensitivity and sufficient accuracy for the detection of an intake of 1 DIL may be achieved whether there is a single intake during any one month, or whether the 1 DIL is the integrated intake of a series of single intakes or continuous exposures.[10,12,88,89]

It is also interesting to compare in this section the usual range of fractional intakes from accidents, and the levels of tritium in urine for various routine operations discussed in Section A.2, with the estimated annual exposure of a person wearing a tritium-activated luminous timepiece.[90] A luminous watch is worn at about arm's length at a similar distance from the body as the radioactive material in situations discussed in Section A.2. Over the period of a one-year wearing interval, a plastic watch crystal may delay diffusion of a given free HTO molecule from hte face of the timepiece for a few hours, but would not be expected to change appreciably the amount of tritium (exchanged to HTO) that would be emitted from the watch over the one-year period. Thus, it may not be entirely fortuitous that when the average activity per watchdial (about 1 - 5 mCi) is scaled up by a factor of 1,000, the dose to a watch wearer scales up from an estimated dose of 0.15 mrem for a 5 mCi watch[90] to an annual dose of only 0.15 rem per 5 Curies at arm's length. This dose is about the same in magnitude to that observed for workers processing comparable quantities in benchtop operations in some installations. (See Section A.2.)

A.4.3 Derivation of Activity Guide Levels of Table 8.1 Above Which Bioassay May Be Needed or Required

According to the criteria described in Section A.4.1, and using the upper limit estimate of 10^{-2} as the maximum fractional intake of material released (in a single incident or over a one-month interval), the values for Table 8.1 were obtained as follows:

1. For HTO, or T_2O, 100 mCi x 0.01 = 1 mCi, which is almost the DIL of 1.5 mCi intake[10] selected as the criteria above which bioassay shall be required. This extreme intake could result only if the entire 100 mCi were released from process, and the highest fractional intake, 0.01 of released material were taken into the body (see previous section). Assuming that this entire 100 mCi could be released in an open bench accident, it thus becomes the level in process in open-bench operations (within ordinary non-failure proof laboratory vessels) above which bioassay shall be required.

2. The level above which bioassay "shall be considered" is 10 times lower than that above which it "shall be required". As discussed in Section A.4.1, this recommendation provides for maintaining control of operations and maintaining exposures ALARA. The level of 10 mCi is also in reasonable agreement with some present practice and professional opinion,[13,2,91,92] but it is considered too restrictive a level for an absolute requirement for bioassay in some laboratory situations.[4,13,55,63] Evans[14] has indicated that when there is 10 mCi or less of tritium in frequent use, there is little need for preparatory work.

3. The corresponding "shall be required" and "shall be considered" levels were taken 10 times higher for fume hood than for open bench

operations with HTO (1 Curie and 100 mCi, respectively). Properly designed and ventilated fume hoods may be assumed to provide at least a factor of ten protection, as discussed earlier.[1, 63]

4. Tritiated compounds other than DNA precursors were assumed to have the same radiotoxicity as HTO, for reasons discussed in Section A.3.

5. Tritium gas (HT or T_2) was assumed to deliver 1,000 times less dose per microcurie-sec/m^3 of exposure as HTO. Literature[82] and calculations discussed in Section A.3 indicate that the relative radiotoxicity is probably closer to 10,000.

However, values in Table 8.1 for tritium gas are conservative (on the safe side) only when conditions assure absolutely that the tritium can not be oxidized to HTO or T_2O prior to release to the work environment.[25] Experience has shown that megacurie quantities of tritium gas can be handled with proper facilities, equipment, and procedures, without exposing employees to unacceptable doses.[2,23] An accident has even occurred in which an employee released many kilocuries of tritium gas within a hood while his head was over the point of release, and yet he received less than 100 mrem integrated dose. This experience is consistent with the calculations presented in Section A.3, p. 20. On the other hand, in the two cases on record[5,6] where human injury (and death) was presumed from autopsy results to have resulted from large tritium exposures as evaluated from urine bioassays, hundreds of Curies of tritium gas were utilized annually to prepare luminous compounds without proper protective equipment and procedures. In these cases, the bioassay program by itself did not prevent injury. These injuries and deaths resulted from exposures consistent with those that would have

prevailed for the quantities of material in process if the tritium had auto-oxidized, or had been oxidized in the manufacturing processes, before intake by the employees (see Section A.2). These two cases help to indicate that the degree of conservatism provided for HTO and tritium gas in this standard is warranted. They also indicate that standards of facility, equipment, and procedure design for safe handling of radioactive materials[1,2,63,92-98] are not without foundation.

6. Tritiated DNA precursors have been assumed to be ten times as radiotoxic per microcurie inhaled as HTO, for obtaining corresponding values of Table 8.1, for reasons discussed in the literature review and analysis of Section A.3.

The above factors were used to obtain all values in Table 8.1, which provide firm guidance but still require judgment in regard to the types and quantities of material to be processed as well as the other human and engineering factors already discussed. Proper facility and equipment design, adequate training, safe operating procedures, appropriate supervision, and other aspects of a well-planned and organized radiation safety program[1,2,63,92-98] will combine with the recommendations of this standard on bioassay procedures to provide adequate safety factors and reasonable protection to employees at reasonable cost.

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ENCLOSURE 4

GUIDELINES FOR BIOASSAY REQUIREMENTS FOR TRITIUM

Nuclear Regulatory Commission

Division of Fuel Cycle and Material Safety

Fourth revision

October 19, 1977

AB/REA

Final staff position

BIOASSAY REQUIREMENTS FOR TRITIUM

I. Conditions Requiring Bioassay

A. Routine Bioassay is required when quantities processed by an individual at any one time, or total amount processed per month, exceed those for the respective forms of tritium as shown in the attached Table 1.

B. Above 0.1 of, but less than, the levels in Table 1, routine bioassay is required unless a written justification is submitted for not performing bioassays.

C. Except as stated in I.D. below, bioassay is not required for process quantities less than 0.1 of those in Table 1.

D. Special bioassay measurements should be performed to verify the effectiveness of respiratory protection devices and other protective clothing. If an individual wearing a respiratory protective device or protective clothing is subjected to a concentration of tritium in air (in any form) such that his or her intake with no protection would have exceeded that which would result from exposure for 40 hours per week for 13 weeks at uniform concentrations of tritium in air as specified in Appendix B, Table I, Column I, 10 CFR 20,* bioassays should be

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*Multiplying the concentration given in Appendix B, 5×10^{-6} μCi/ml, by 6.3×10^{8} ml gives the corresponding quarterly intake of tritium by inhalation. This is assumed equal to the uptake of tritium (as HTO) by absorption through the skin unless the form of tritium in the air can be demonstrated to have lower uptakes. The total uptake, including skin absorption, would be assumed to be about 6.3 mCi, which delivers a dose commitment of about 1.25 rems to standard man.

performed to determine the resulting actual tritium intake. These special bioassay procedures should also be conducted, for personnel wearing respirators, if for any reason the average tritium concentration in air and the duration of exposure are unknown.

II. Who Should Participate

All workers involved in the processing of tritium, under conditions specified in I above, or sufficiently close that intake is possible, should participate.

III. What Types of Bioassays Should be Performed

A. Baseline (including Pre-employment, or Pre-operational Urinalysis, not more than one month prior to beginning work with tritium requiring bioassay under Section I above).

B. Routine Urinalysis

C. Post-operational. Within one month of last possible exposure to tritium.

D. Diagnostic. Within one week of any sample exceeding levels given as action points in Section V below. See V.A.2.(d).

IV. How Often

A. Initial Routine Samples

Within 48 hours following entry of an individual into an area where operations require bioassay according to Section I.A and

B above, and then every two weeks or more frequently thereafter as long as the individual is working with ^{3}H.

B. After 3 Months

The sampling frequency selected in accordance with Section IV.A above may be changed to quarterly if, after 3 months, the following 3 conditions are met:

(1) The average urinary tritium concentration from specimens obtained during the 3-month period does not exceed 3 μCi/l,

(2) Where measurements of the concentration of tritium in air are required as a condition of the license, the quarterly average concentration (μCi/ml) to which workers are exposed, multiplied by the factor 6.3×10^{8} ml, does not exceed 0.8 mCi, and

(3) The working conditions during the 3-month period, with respect to the potential for tritium exposure, are representative of working conditions during the period in which a quarterly urinalysis frequency is employed, and there is no reasonable expectation that the criteria given in (1) and (2) above will be exceeded.

V. Action Points and Corresponding Actions

A. Bi-Weekly or More Frequent Sampling

1. If urinary excretion rates exceed 5 μCi/liter, but are less

than 50 μCi/liter, the following course of action should be taken:

(a) a survey of the operations involved, including air and area monitoring, should be carried out to determine the cause(s) of exposure and evaluate potential for further larger exposures.

(b) Implement any reasonable corrective actions indicated in the survey that may lower the potential for further exposures.

(c) A repeat urine sample should be taken within one week of the previous sample and should be evaluated within a week after collection.

(d) Any evidence from (a) and (b) indicating that further work in the area might result in an employee receiving a dose commitment in excess of the limits established in §20.101 should serve as cause to remove the employee from work in this operation until the source of exposure is discovered and corrected.

2. If urinary excretion rates exceed 50 μCi/liter, the following course of action should be taken:

(a) Carry out all steps as in 1.(a) to (d) above.

(b) If the projected dose commitment exceeds 5 rems, report the incident to the NRC in accordance with §20.403 of 10 CFR Part 20.

(c) Refer the case to appropriate medical/health physics consultation for recommendations regarding therapeutic procedures that may be carried out to accelerate removal of tritium from the body and reduce the dose as low as reasonably achievable.

(d) Carry out repeated sampling (urine collections of at least 100 ml each) at approximately one-week intervals, at least until samples show an excretion rate less than 5 μCi/liter. If there is a possibility of long-term organic compartments of tritium that require evaluation, continue sampling as long as necessary to ensure that appreciable exposures to these other compartments do not go undetected.

B. Quarterly Sampling

Carry out actions at levels as indicated under A. above, and if the excretion rate continues to exceed 5 μCi/liter, also reinstitute biweekly (or more frequent) sampling for at least the next 6-month period, even when urinary excretion falls below 5 μCi/liter.

TYPES OF OPERATION	HTO FORM (& forms other than those on right-hand cols.)	HT or T_2 GAS IN SEALED PROCESS VESSELS	NUCLEOTIDE PRECURSORS	HTO MIXED WITH MORE THAN 10K_g OF INERT H_2O OR OTHER SUBSTANCES
PROCESSES IN OPEN ROOM OR BENCH, WITH POSSIBLE ESCAPE OF TRITIUM FROM PROCESS VESSELS	0.1 Ci	100 Ci	0.01 Ci	0.01 Ci/K_g
PROCESSES WITH POSSIBLE ESCAPE OF TRITIUM, CARRIED OUT WITHIN A FUME HOOD OF ADEQUATE DESIGN, FACE VELOCITY, AND PERFORMANCE RELIABILITY	1 Ci	1000 Ci	0.1 Ci	0.1 Ci/K_g
PROCESSES CARRIED OUT WITHIN GLOVEBOXES, ORDINARILY CLOSED, BUT WITH POSSIBLE RELEASE OF TRITIUM FROM PROCESS LEVELS AND OCCASIONAL EXPOSURE TO CONTAMINATED BOX AND BOX LEAKAGE	10 Ci	10,000 Ci	1 Ci	1 Ci/K_g

Table 1

ACTIVITY LEVELS OR CONCENTRATIONS ABOVE WHICH BIOASSAY SHALL BE REQUIRED

Quantities present (< 10Kg) may be considered either the amount processed by an individual at any one time (when accidental intake is more likely), or the amount of activity entered into process (throughput) during any one month (when routine handling of repeated batches is the more likely source of exposure). Concentrations in the right-hand column may be used when activity in process is always diluted in more than 10K_g of other reagents, as in nuclear reactor coolant systems.