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P-10 RESEARCH PROGRAM IN BIOLOGY

Early in the year recommendations for biological research with tritium were outlined by M. E. Getzendaner in document HW-17059. Since that time, work has begun on many of the preliminary experiments suggested in that document, and further thought has been given to an overall research program designed to secure the information needed to evaluate and control the tritium hazard. Consideration has also been given to the use of tritium oxide as a radiation source in the study of radiation effects in general.

It seems desirable at this time to reformulate the projected research program in this field, more extensively and with a greater degree of confidence than was possible eight months ago. This document will indicate only the scope of desirable investigations, without attempting to spell out in detail the experimental procedures to be followed. Proposed investigations will be

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discussed under four general classifications: (1) studies of water metabolism (2) studies of hydrogen metabolism (3) studies with tritium labelled compounds of biological interest, and (4) studies of the biological effect of tritium radiations. The problems outlined under these headings were chosen on the basis of general scientific interest. In most if not all cases, however, the application to radiation hazard evaluation and control is obvious.

In several instances the desirability of experiments on humans has been indicated. This is to be understood as solely an indication of desirability. The practical feasibility of such experiments will not be considered in this document.

WATER METABOLISM STUDIES

Mode of entry of water into the organism:

For effective evaluation of the hazard involved in the handling of tritium oxide, information must be available as to effective portals of entry. Oral ingestion by animals and uptake through the roots of plants are obvious pathways which should require little further investigation. Less well understood routes will require investigation. Specifically:

1. The efficiency of removal of water vapor from the air by the lungs for small animals and man. This information is essential to the evaluation of the tolerance limit for tritium oxide in air.
2. The percutaneous absorption for small animals and man.
3. The absorption of water vapor from the air by plants.
4. Uptake by other living organisms indigenous to territory.

Gross turnover time for water in the organism:

In order to calculate maximum permissible concentrations of tritium, it is

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necessary to know how long the material will remain in the organism. Investigations along these lines should include:

1. Determination of the turnover time for body water, under normal environmental conditions for small animals and man.
2. Determination of the turnover time for body water as affected by environmental changes (humidity, temperature, forced fluids, etc.)
3. Study of the storage of water in plants under varying environmental conditions.

Turnover time for water in various tissues of small animals:

Should it be found that there is an appreciable holdup of water (bound water) in any tissue (metabolic pool) this knowledge will be of importance in modifying the maximum permissible concentration as calculated from gross body water turnover time.

Incorporation of hydrogen from water into tissue compounds:

A knowledge of the extent to which hydrogen from water is incorporated into other compounds in the organism, and the turnover time for these compounds is essential to the calculation of the maximum permissible concentration. Such investigations would involve:

1. Localization of bound tritium by tissue in small animals and plants.
2. Localization of bound tritium by compound in small animals, plants, and microorganisms.
3. Determination of turnover time for compounds incorporating tritium.
4. Study of mechanism of utilization of hydrogen from water in biological syntheses (particularly in photosynthetic reduction by green plants, and including in vitro studies with isolated enzyme systems).

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Isotopic fractionation of water:

Because of the three-fold difference in mass between tritium and ordinary hydrogen, there is little doubt that the living organism will to some extent differentiate between the two isotopes. A knowledge of the degree to which such fractionation occurs is of fundamental interest and necessary to the proper interpretation of the results of all tracer experiments with tritium. Preliminary information of this sort could be most readily obtained from studies with microorganisms grown in tritium oxide labeled aqueous culture media. The same information should later be obtained for higher plant and animal forms.

HYDROGEN METABOLISM STUDIES

The metabolism of elementary hydrogen has received practically no study except in the case of a few microorganisms. Any proper evaluation of the tritium hazard will require additional information as to the extent of occurrence and mechanism of hydrogen fixation processes.

Mode of entry of hydrogen into the organism:

Investigation of the following should be undertaken:

1. Extent of absorption in the lungs of small animals and humans.
2. Percutaneous absorption in small animals and humans.
3. Absorption by plants.

Mechanism of hydrogen fixation:

Should the absorption of hydrogen prove to be significant, investigations along the following lines should be undertaken:

1. Determination of chemical form in which activity first appears in blood stream of small animals and humans. Is tritium transported as the

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dissolved gas until metabolized by specific enzyme systems, or is it converted to water by catalytic exchange in the lung?

2. Localization of fixed hydrogen by tissue in small animals and plants.
3. Localization of fixed hydrogen by compound in small animals, plants and microorganisms, and determination of turnover time for these compounds,
4. In vitro studies with isolated enzyme systems.

TRACER STUDIES WITH TRITIATED COMPOUNDS

Synthesis of labelled compounds:

Tritium labelled compounds of biological importance should prove useful in a wide variety of investigations. These compounds may have to be prepared synthetically, or it may prove more practical to isolate them from organisms grown in a tritium oxide environment.

Metabolic fate of administered intermediates:

Virtually limitless research possibilities might fall under this heading. Of particular interest in connection with the evaluation of the tritium hazard will be the use of those compounds identified as important intermediates in the normal metabolism of water and hydrogen. Should tritiated hydrocarbons prove to be a significant contaminant in plant operations, it will also be desirable to study the metabolism of such substances. These experiments will fall into the following categories:

1. Determination of turnover times for specific compounds (study of metabolic pools).
2. Study of metabolic pathways
 - a. Localization of tagged products by tissue.
 - b. Localization of tagged products by compound.
 - c. In vitro studies with isolated enzyme systems.

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BIOLOGICAL EFFECTS OF TRITIUM RADIATIONS

Specific tritium hazard evaluation studies:

These investigations will center around the determination of the relative biological effect of the weak beta of tritium as compared to other more thoroughly studied radiations.

1. Acute exposure studies - these will involve:
 - a. The determination of the LD-50 for small animals, and
 - b. Study of the relative biological effect on microorganisms.
2. Chronic exposure studies at or near proposed tolerance levels using small animals, fish and plants.
3. Effects of both chronic and acute exposures on selected biochemical systems may afford a simple approach to RBE determinations.

General Study of Radiation Effects:

Tritium oxide would seem to offer unusual possibilities as a source of radiation in the general study of radiation effects. Its uniform distribution in the organism, the short range of its beta and its ease of administration should make it ideally suited for many purposes including particularly the following:

1. Determination of comparative radiosensitivity of various organisms, organs and tissues using small animals, plants and microorganisms.
2. Study of the effect of radiation in modifying the bacterial flora of animals.
3. Study of the effect of radiation on isolated enzyme systems.

It should be obvious that the program outlined above could well occupy a large group of investigators for a period of many years. It will be the problem

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of the Biology Division to concentrate upon such phases of this program as
will most speedily yield the essential information for the proper evaluation and
control of the tritium hazard.

Ray C. Thompson
Member
P-10 Hazards Control Committee

RC Thompson

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