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LUNG ABSORPTION OF HTO BY MAN UPON INSPIRATION OF HTO WATER VAPOR

Work done by:

Ernest A. Pinson
Ernest C. Anderson
Virginia Lotz

Report written by:

Ernest A. Pinson

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ABSTRACT

Five experiments on three human subjects exposed to HTO water vapor in inspired air showed that between 98 and 99 per cent of HTO vapor inspired was absorbed through the respiratory system into the body and that only 1 to 2 per cent of the inspired HTO was expired during the exposure. Thus for radiation exposure purposes when estimating HTO uptake by men exposed to an atmosphere containing HTO vapor, one must assume that essentially all HTO inspired is absorbed into the body.

Twenty-five to 30 minutes was required for the HTO activity in expired air to come down to a level equal to that in the venous blood and urine. This sustained high activity in expired water vapor after exposure was thought to be due to adsorption of HTO on the lining of the upper respiratory tract during exposure where it comes into equilibrium slowly with other body fluids.

After exposure to HTO vapor in inspired air the activity in venous blood rose sharply for a few minutes and then declined exponentially in about 80 min to a level indistinguishable from ultimate equilibrium by the sensitivity of the analytical methods used. The half-time for the exponential decline in activity in venous blood was found to be about 12 min which indicated that 99 per cent of ultimate equilibrium would be reached in about 80 min.

With high rates of urine secretion after exposure to HTO vapor in inspired air the activity in urine showed the same pattern as that observed for venous blood. However, the activity in urine rose higher than that in venous blood and remained measurably higher for about 2 hr after exposure. The exponential decline in activity in urine at high rates of urine secretion had a half-time of about 20 to 22 min which indicated that about 2-1/2 hr was required to reach 99 per cent of equilibrium. At slow rates of urine secretion the rise in activity with time following exposure was slow, and the maximal activity was recorded 25 to 40 min after exposure. After reaching this maximum, the activity declined slowly to equilibrium.

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1. INTRODUCTION

Previous experiments indicated that when rats[1] or mice[2] inhaled HTO vapor, they absorbed between 86 and 100 per cent of the inspired activity. The present experiments were conducted to determine the percentage of HTO activity inspired by man which is absorbed into the body. This information is useful in calculating the concentration of HTO in the body of man which will result from an exposure of any given length of time to any known concentration of HTO or T_2O in the atmospheric environment. On the basis of these data it is possible to predict the time-concentration relationships which will introduce tolerance or lethal quantities of tritium into the body from breathing air which contains HTO or T_2O vapor.

Whereas the main purpose of these experiments was to determine the ratio of HTO inspired to that absorbed into the body through the lungs, measurements were made which elucidate some basic physiological principles involved in water exchange between the body and the environment through the lungs, in water exchanges within the body, and in the excretion of water through the kidneys. These factors are useful to physiologists in studies of water balance and water exchanges in animal systems.

2. METHODS

Subjects inspired for periods of 4 or 5 min oxygen which was saturated with HTO water vapor by passage through saturating chambers containing liquid HTO of known activity. Expired gas was passed through a dry ice trap for condensation of expired water vapor and through a wet test meter for measurement of the volume of gas expired during the exposure. A diagram of the apparatus used to effect the exposure is shown in Fig. 1. The oxygen flow through the HTO water in the first saturating chamber and into the balloon was adjusted to keep the balloon nearly full and was relatively constant at about 7 to 9 liters/min, depending on the minute volume of respiration of the subject. The balloon acted as a storage reservoir for oxygen saturated with HTO vapor from which the subject could inspire intermittently a tidal volume of gas without having to exert objectionable suction on inhalation. The tidal volume of all subjects was kept between 500 and 600 ml during the exposure. From the balloon the oxygen passed through the second saturating chamber, over a thermometer sensitive to $0.1^{\circ}C$, through a one-way valve, and to the subject.

The subject expired through a water vapor condensing trap immersed in dry ice, through a one-way valve, and through a wet test meter for measurement of tidal volume and total gas volume expired (Fig. 1). Exposures began with a normal inhalation and ended with a normal exhalation so that the total volume expired during the exposure also represents the

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volume inspired during the exposure, assuming no change in reserve and residual air in the lungs between the beginning and end of the exposure period.

To ascertain the degree of saturation attained in the saturating chambers, oxygen was passed through the saturating chambers at a constant rate of 9 liters/min when the outlet to the subject was connected directly to the water vapor condensing chamber. When the quantity of water collected in the condensing chamber was related to the temperature and volume of gas passed through the system, the results indicated that a saturation of 99 per cent or better had been attained.

The HTO activity in water condensed from the saturated gas with the above arrangement showed an activity of only 1.16 mc/ml compared to the 1.32 mc/ml activity in the water in the saturating chambers. An isotope fractionation effect is to be expected in this situation due to the fact that the vapor pressure of T_2O at $25^{\circ}C$ is about 19 per cent less than the vapor pressure of H_2O at the same temperature.[3] If one assumes a vapor pressure for HTO at $25^{\circ}C$ intermediate between that for H_2O and T_2O, then one may expect an isotope fractionation in the condensed vapor of about 9.5 per cent. Therefore according to theory one should find an activity of 1.20 mc/ml (1.32 x 0.905) in the condensed water vapor. This corresponds fairly well with the 1.16 mc/ml activity actually measured in the condensed water vapor.

In these experiments the HTO inhaled by the subject during the exposure period was calculated from the volume of gas inspired during the exposure period, the temperature of the gas inspired assuming complete saturation at that temperature, and the activity of HTO per unit weight of water vapor in the gas. The HTO expired by the subject was calculated from the activity in the expired water vapor condensed in the dry ice trap and from the quantity of water vapor expired, assuming saturation of expired gas at $36^{\circ}C$. The HTO retained in the body during the exposure was obtained by subtracting the HTO expired from the HTO inspired. The percentage of inspired HTO retained was obtained by dividing the former by the latter and multiplying by 100 (Table I).

An independent check on the amount of HTO retained in the body during the exposure was made by determining the increase in HTO activity in body fluids after equilibrium had been reached following the exposure and multiplying by the dilution volume for HTO in the body (Table II). The body dilution volume for HTO had been measured previously in each of the subjects by ingestion of a known quantity of HTO. The ingestion experiments and the measurements of body dilution volume for HTO in these subjects have been reported separately.[4]

Venous blood and urine samples were collected just prior to exposure and at intervals

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for 3 to 5 hr after exposure. HTO activity measured in water evaporated from these samples showed the change in HTO activity taking place in these fluids with time following the exposure as well as the activity in urine and blood at equilibrium.

The analytical methods for measurement of HTO activity in fluids have been previously described.[1]

3. RESULTS

Table I shows the results obtained in five experiments on three subjects in which HTO vapor inspired during periods of 4 or 5 min was measured and compared to the HTO vapor expired during the same period. The results indicate that the specific activity of expired water vapor during the exposure period was less than 1 per cent of the specific activity of the inspired water vapor during this same period. These data show that between 1 and 2 per cent of the total HTO inspired appears in the expired water vapor during the exposure, which indicated that 98 to 99 per cent of the inspired HTO was absorbed through the respiratory tract and retained in the body during the exposure period. It may also be observed (Table I) that it made little difference in the percentage of inspired HTO retained in the body whether inspiration was through one nostril and expiration was through the other or whether inspiration was through the nose and expiration was through the mouth. The high percentage of HTO retention observed indicates an almost complete exchange of water vapor in inspired air with that of the respiratory tract during the normal respiratory cycle.

The data presented in Table II give an independent measure of the amount of HTO retained by the body during the exposure and substantiate the high percentage of absorption of inspired HTO indicated in Table I. In Table II the HTO appearing in the body is compared with the quantity inspired. The average of the values for percentage absorption of HTO given in Table II is 99.2 compared to an average of 98.7 per cent in Table I. The figures for percentage absorption given in Table I are more accurate because precise measurement of HTO specific activity is less critical in their calculation.

During three of the experiments, samples of expired water vapor were collected at intervals after exposure until the HTO activity in the expired water approximated that prevailing in the venous blood and urine. These results are shown in Fig. 2. The data show that HTO activity in expired water vapor dropped rapidly from the level prevailing during the exposure. Twenty-five to 30 minutes was required however, for it to reach a level approximating that prevailing in the urine and venous blood. The persistence of high HTO activity in expired water vapor after the exposure period may be due to adsorption of HTO on the walls of the upper respiratory tract where it is diluted with the moisture on the bronchial surfaces

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and where it comes into equilibrium only relatively slowly with circulating fluids. It seems unlikely that this higher activity would come from the alveoli of the lungs inasmuch as HTO must diffuse quite rapidly across the thin membranes of the alveoli and equilibrate with the blood circulating through the lungs. The HTO activity prevailing in the blood and urine a few minutes after the exposure ended indicated that the major portion of the activity absorbed during the exposure was already being distributed and equilibrating in body fluids in general.

The changes in HTO activity in venous blood, taken from the anticubital vein, and in urine in relation to time following exposure to HTO in inspired gas are shown in Fig. 3. The HTO activity in venous blood increased rapidly during the exposure and slowly for a few minutes after exposure, and then it declined exponentially with time and reached equilibrium in about 1-1/2 hr. The HTO activity in urine samples collected at a urine secretion rate of 1 ml/min rose more slowly than that in venous blood and reached a maximum 25 to 40 min after the exposure. During the first 25 min the activity in urine was lower than that in venous blood. From 25 min to about 2 or 2-1/2 hr after exposure the activity in urine was a few per cent higher than that in blood. Thereafter the two activities were the same so far as could be detected by the analytical method used.

The slower rise of activity in urine may be due, at least in part, to urine remaining in the urinary system which cannot be voided so that any particular collection represents urine secreted by the kidneys since the last collection. If this supposition is true, then it should be possible to record a more rapid rise in HTO activity in urine following the inspired exposure if the urine secretion rate is increased. The effect of urine secretion rate on the change in HTO activity in urine with time after exposure was studied in two experiments on the same subject. In one experiment the urine secretion rate was 10 ml/min, in the other 1 ml/min. The data are presented graphically in Fig. 4. At the higher secretion rate the activity in urine rose rapidly during and after exposure, reached a maximum a few minutes after the end of exposure, and then declined exponentially with time until equilibrium was reached. In this experiment the change of activity in the urine samples with time was quite similar to the change in activity in venous blood although the activity in urine was a few per cent higher than that in venous blood from a few minutes after exposure until about 2 hr afterward. It may be that the activity in urine approximates more closely the activity in arterial blood rather than in venous blood. Other observers[5] have shown that after injection of D_2O into the anticubital vein, the concentration of D_2O in arterial blood is much higher than in venous blood for an hour or more after injection. Thus, while equilibrium is being established, there may be significant differences in the activity in arterial blood, venous blood, and urine.

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Another subject with a high rate of urine secretion was exposed to HTO by inhalation. The changes in urine activity with time following exposure are graphed in Fig. 5. Again the rapid rise followed by exponential decline after the exposure was observed. The activity measured at equilibrium in this experiment was subtracted from the activity measured during each of the short intervals after the exposure. A semilogarithmic plot of the results is shown in Fig. 6. These data show that the decline in urine activity is exponential with time and that at least two rate constants are involved. The half-time corresponding to the slower rate constant involved in the equilibration of excreted urine was found to be about 19.5 min. A faster rate constant corresponding to a half-time of about 5 min was also found. A similar treatment of the data shown in Fig. 4 gave a half-time of 22 min for the slower component and 3 min for the faster one. The interpretation and significance of these two rate constants are not clear from the present data.

The data in Fig. 3 for the equilibration of inhaled HTO with venous blood show an equilibration half-time of about 12 min. On the basis of the half-time found for venous blood and for urine (22 min) it is possible to estimate the time required to attain 99 per cent of ultimate equilibrium (7 half-lives). For venous blood the calculated value is 84 min and for urine 154 min. The calculated equilibrium times compare favorably with the actual observed times from the data in Figs. 3, 4, and 5.

4. SUMMARY

Five experiments on three human subjects exposed to HTO water vapor in inspired air showed that 98 to 99 per cent of HTO vapor inspired was absorbed through the respiratory system into the body and that only 1 to 2 per cent of the inspired HTO was expired during the exposure. Therefore for radiation exposure purposes when estimating HTO uptake by man exposed to an atmosphere containing HTO vapor, one must assume that essentially all HTO inspired is absorbed by the body.

Twenty-five to 30 minutes after the end of exposure the HTO activity in expired air came down to a level equal to that in the venous blood and urine. The sustained high activity in expired water vapor after exposure is thought to be due to adsorption of HTO on the surfaces of the upper respiratory tract during exposure where it comes into equilibrium slowly with other body fluids.

After exposure to HTO vapor in inspired air, the activity in venous blood rose sharply for a few minutes and then declined exponentially in about 80 min to a level indistinguishable from ultimate equilibrium. The half-time for the exponential decline in activity in venous blood was about 12 min, which indicated that 99 per cent of ultimate equilibrium would be

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reached in this fluid in about 80 min.

With high rates of urine secretion the activity in urine showed the same pattern as that observed for venous blood. However, the activity in urine rose higher than that in venous blood and remained so for about 2 hr. The exponential decline of tritium activity in urine as a function of time after lung exposure to HTO showed the presence of two rate constants at high rates of urine secretion. The longer half-time was about 20 to 22 min which indicated that about 2-1/2 hr was required to reach 99 per cent of equilibrium. At slow rates of urine secretion the rise in activity with time following exposure was slow, and the maximal activity was recorded 25 to 40 min after exposure. After reaching this maximum, the activity declined slowly to equilibrium.

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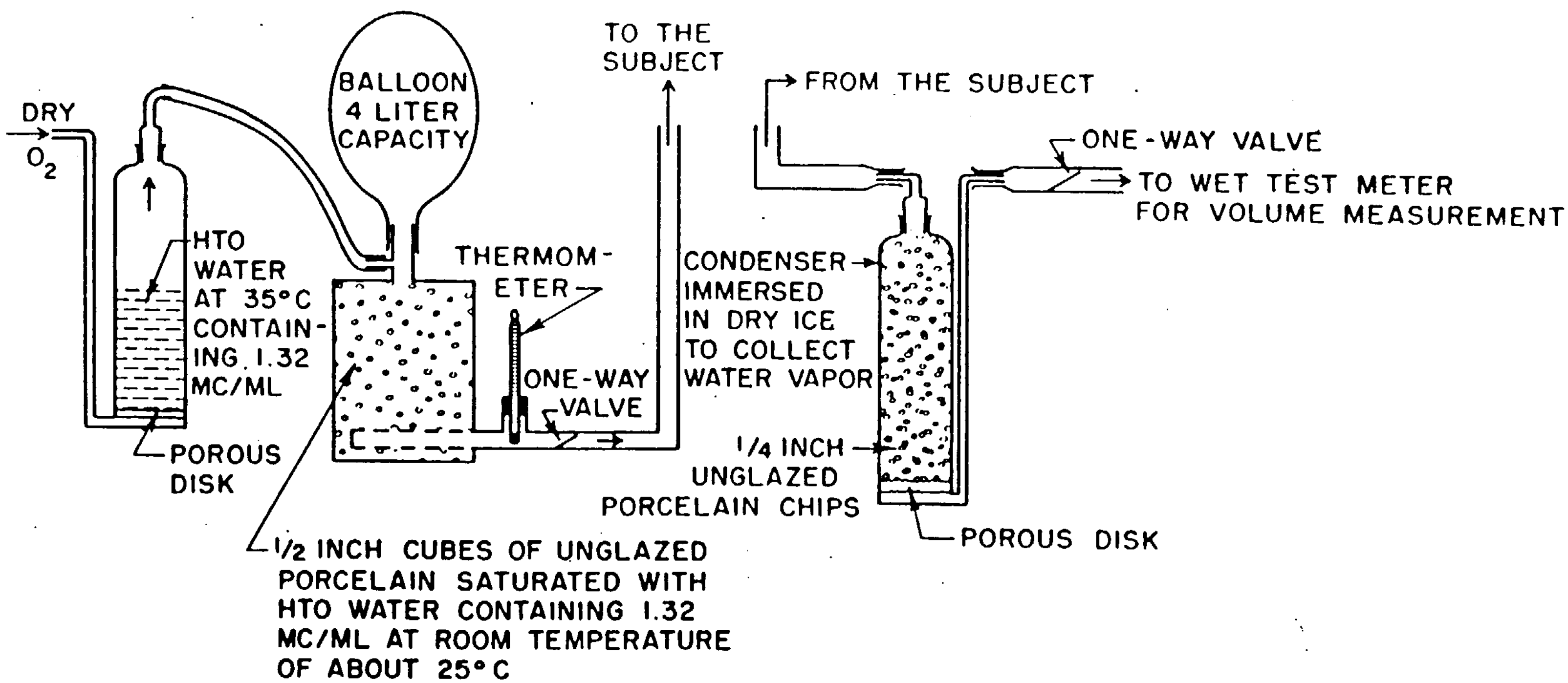

Fig. 1. Diagram of apparatus used for saturating inspired gas with HTO at a measured temperature, for condensing expired water vapor, and for measuring expired volumes.

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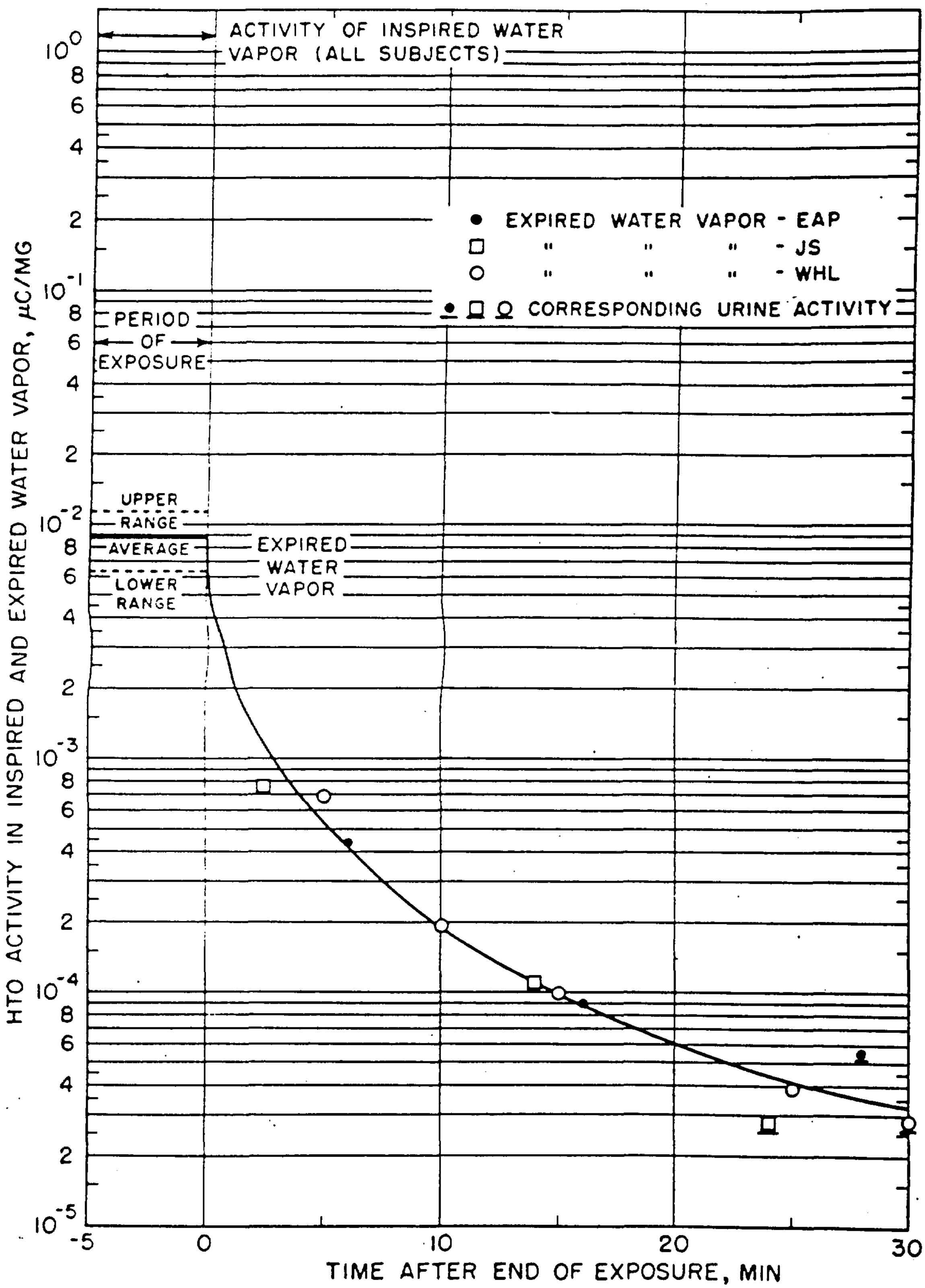

Fig. 2. HTO activity in expired water during and following exposure to HTO vapor in inspired air.

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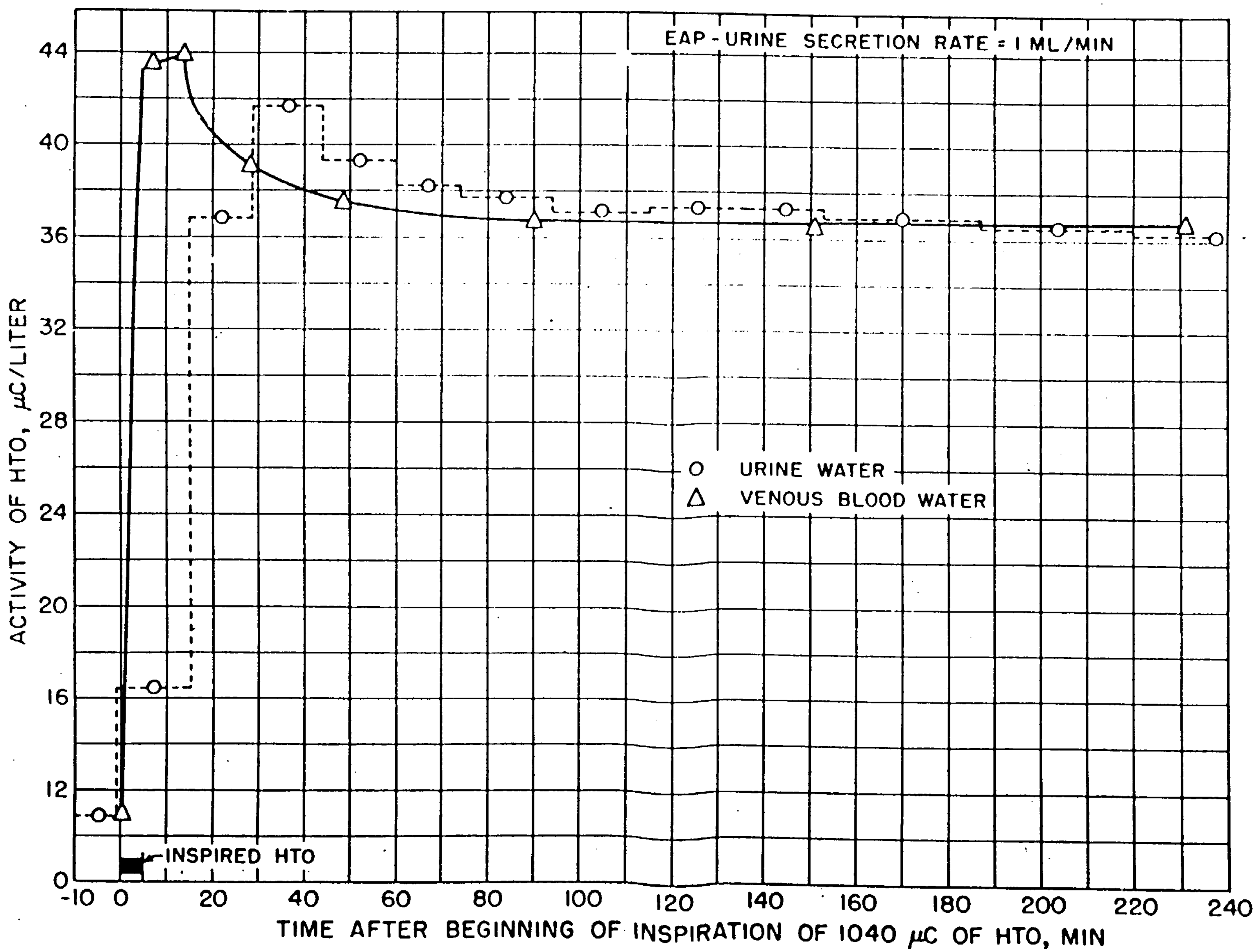

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Fig. 3. Changes in HTO activity in the water of venous blood and urine with time following 5 minute exposure to HTO vapor in inspired gas.

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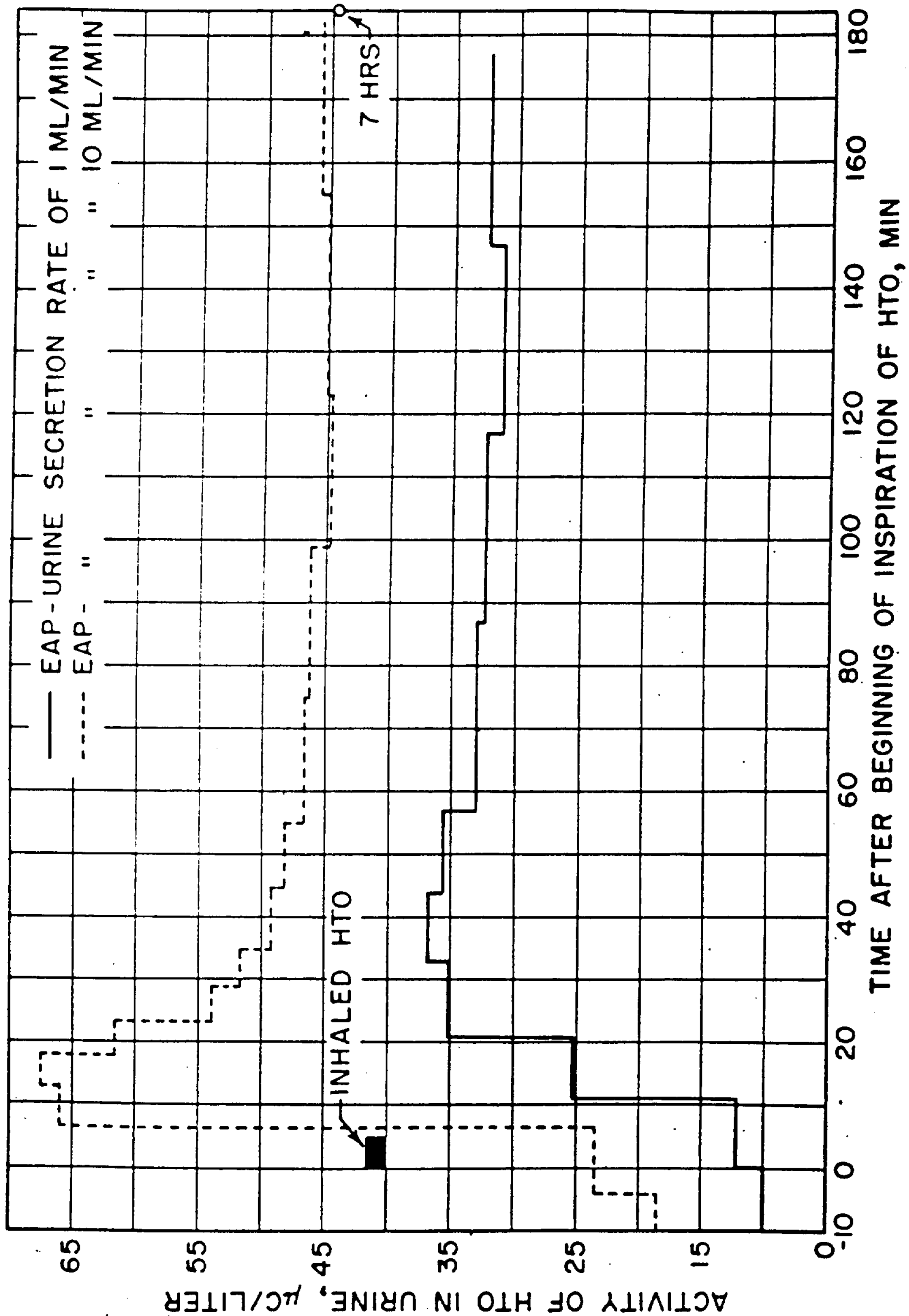

Fig. 4. Comparison of changes in activity in urine water at high and low rates of urine secretion following exposure to HTO in inspired gas.

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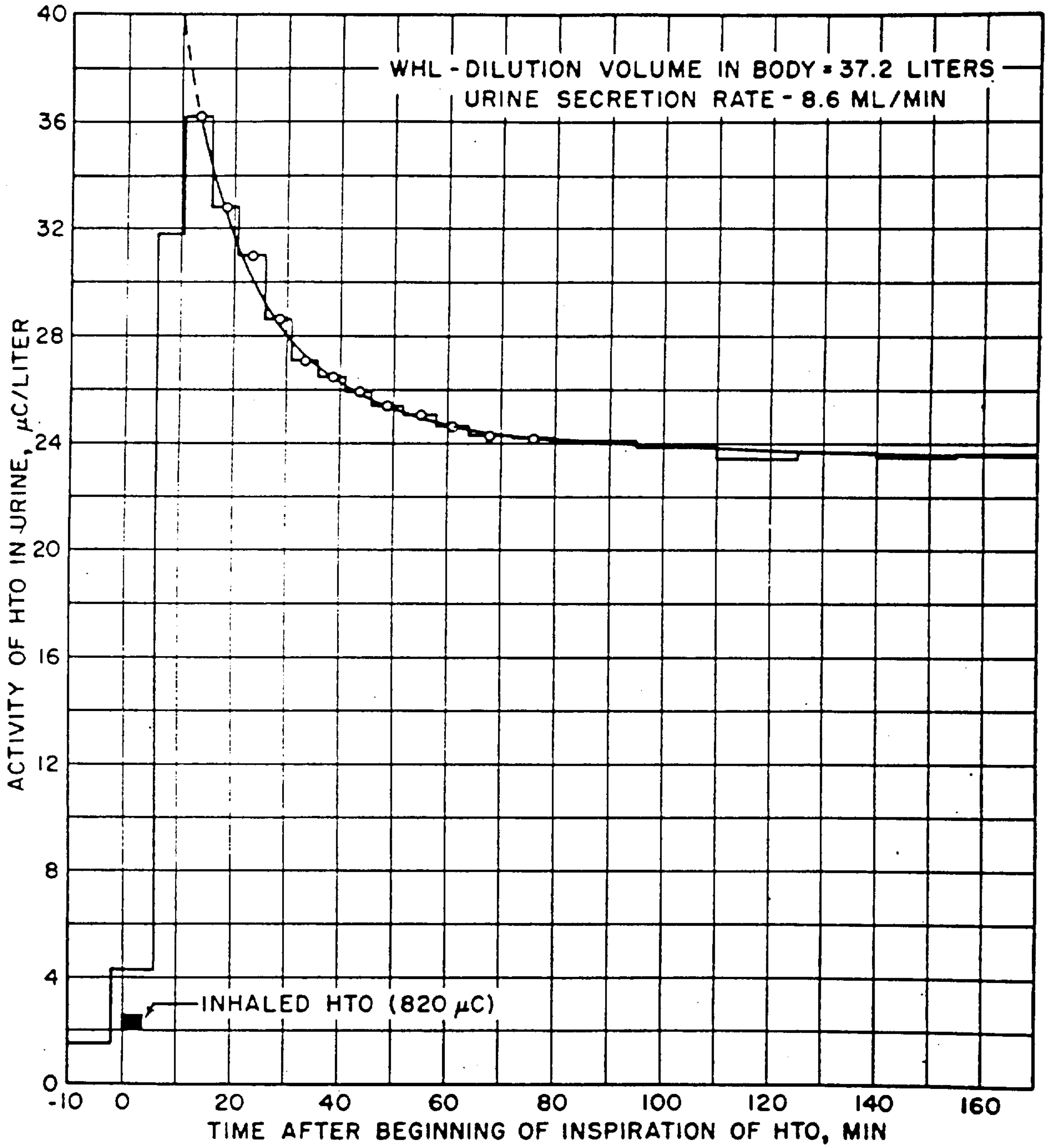

Fig. 5. Changes in the activity in urine at a high rate of urine secretion following exposure to HTO in inspired gas.

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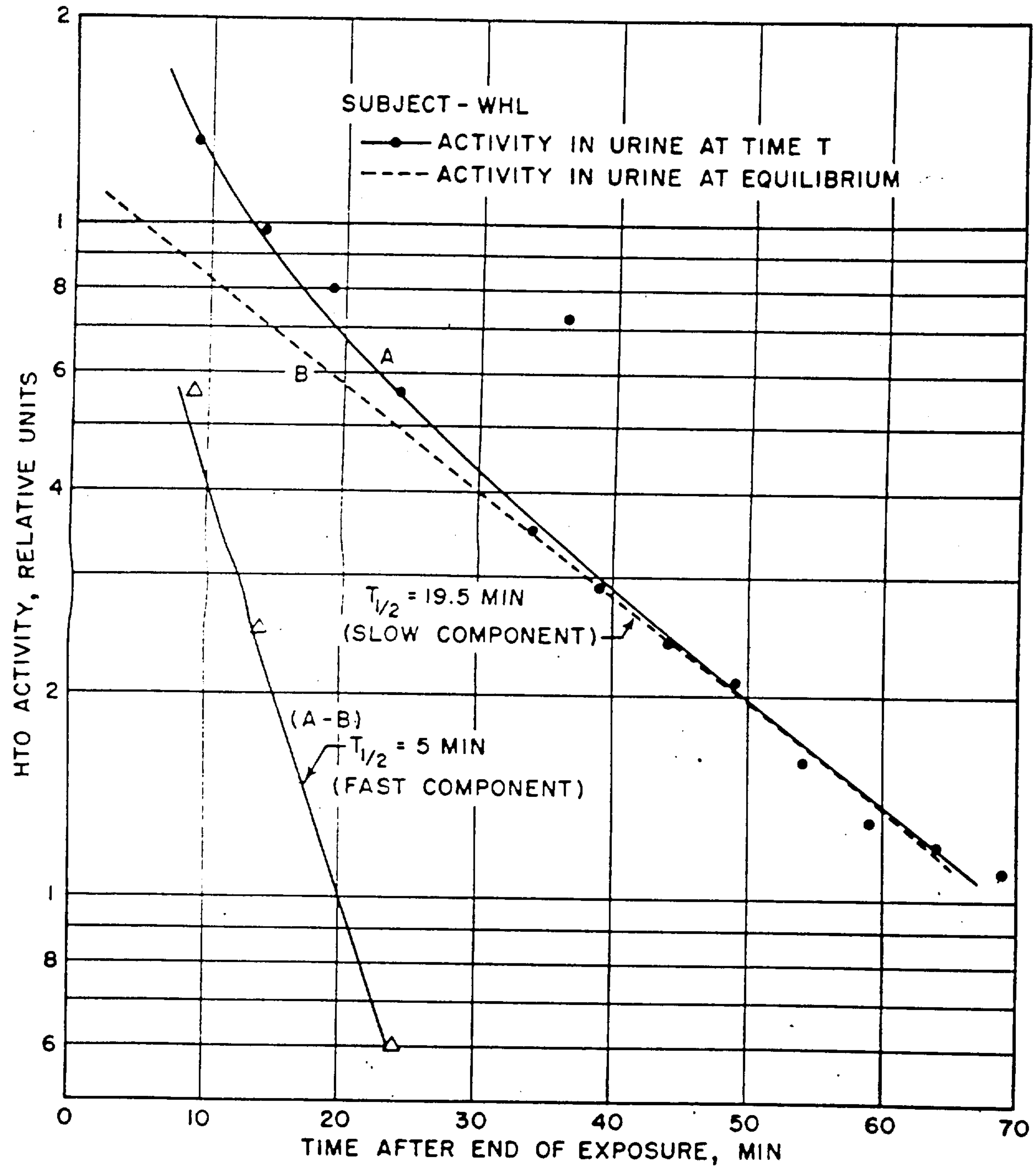

Fig. 6. Exponential decline of HTO activity in urine with time after exposure to HTO in inspired gas.

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Table I

COMPARISON OF HTO INSPIRED TO HTO EXPIRED BY MAN
DURING EXPOSURE TO HTO VAPOR IN INSPIRED GAS

Subject	Inhalation exposure period, min	Air Inspired During Exposure			HTO Activity		Water vapor expired during exposure, mg[c]	HTO Activity		HTO retained in the body during exposure, per cent
		Volume, liters	Temp., °C	Water vapor content, mg/liter	In inspired water vapor, μc/mg	Total inspired, μc		In expired water vapor, μc/mg	Total expired, μc	
EAP[a]	5	36.5	23.8	21.32	1.20	934	1510	0.0071	10.7	98.9
EAP[a]	5	43.2	22.7	20.04	1.20	1040	1785	0.0105	18.7	98.2
EAP[b]	5	38.3	25.0	22.80	1.20	1047	1578	0.0088	13.9	98.7
JS[a]	5	37.4	26.0	24.11	1.20	1083	1545	0.0114	17.6	98.4
WHL[b]	4	29.8	25.3	23.20	1.20	830	1230	0.0063	7.8	99.1

a. Inspiring through the nose; expiring through the mouth.
b. Inspiring through one nostril; expiring through the other nostril.
c. Calculated for saturation of expired air at 36°C.

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Table II

INCREASE OF HTO IN THE BODY COMPARED TO THE AMOUNT OF HTO INSPIRED AS VAPOR

Subject	HTO in body fluids at equilibrium, μc/liter[a]	Body dilution volume of HTO, liters[b]	Calcd. increase of HTO in body, μc	HTO activity inspired, μc	Inhaled HTO appearing in body fluids, per cent
EAP	22.2	40.7	904	934	96.7
EAP	25.7	40.7	1045	1040	100.5
EAP	26.6	40.7	1080	1047	103.2
JS	22.6	46.4	1050	1083	97.0
WHL	22.0	37.2	819	830	98.7

a. Equilibrium value assumed as that value measured 2-1/2 hr or more after inhalation.
b. Previously measured by ingestion of a known quantity of HTO and observing the dilution resulting at equilibrium.[4]

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