

INFERENCE OF DOSE
FROM URINE AND SERUM MEASUREMENTS
FOLLOWING ³H-LEUCINE INGESTION
IN RAT, BEAGLE AND WOMAN.

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THE PROBLEM. In 1975, bioassay data from an 18-year-old woman were collected during the course of a bizarre incident in which there were repeated ingestions of some tritium-labeled organic, probably L-leucine. At the time, no one could interpret the rapid 100-fold rises and drops in tritium concentrations in urine and breath water condensate. It was noted that ³H concentrations in serum were higher by 2 to 5 times those in urine.

In order to interpret the human data, and to develop recommendations for the bioassay of tritium following potential exposures to organic forms, ³H-leucine was administered to rats and a beagle dog.

HUMAN DATA. Concentrations of ³H in breath water condensate, urine, and serum are shown as a function of time. Graph A. shows the period of rapid fluctuations on an expanded time scale. It is not known how much activity was ingested or when, but four or more intakes are indicated. Graph B. is the complete data set. The lines are nonlinear least-squares fits of two-component exponentials to the data from Day 38 on, after intakes had ceased.

HUMAN DATA. Urinalysis is usually used to infer doses to workers exposed to tritium, and it is adequate for exposures to HTO or HT. However, urinalysis clearly underestimates the dose to serum. Dose rate is directly proportional to concentration, so these curves represent the the factor by which the dose rate of the fluid in the numerator is underestimated by bioassay of the fluid in the denominator. The green squares and line are the urine to breath ratio from data and from the least squares fits, respectively. The red diamonds and line are the serum to urine ratios, and the blue x's and line are the serum to breath ratios.

BEAGLE DATA. Both urine and serum were vacuum distilled at room temperature, and the distillates and residues were assayed for radioactivity following a single ingestion of ^3H -leucine by an 11.3 kg beagle. Normalized concentrations, the ratio of concentration in a fluid to the activity administered divided by body mass ($[\text{Bq/g of fluid}] / [\text{Bq administered/g body mass}]$), are shown above for total serum activity, total urine activity, and pooled distillate activity. Graph A. shows the first 6 days, during which a metabolite of leucine was concentrated and excreted by the kidney. The lines are least squares fits to distillate and residue data, with 2 exponentials required for distillate, 3 for urine residue, and 2 for serum residue. Graph B shows the full data set.

why distill?

RAT DATA. The beagle experiment was repeated in rats, with the data for one animal displayed here. Early data and least-squares fits are shown in A., and the complete sequence is shown in B. As with the dog, a large amount of activity is excreted by the kidney shortly after ingestion.

RAT DATA. Normalized absorbed doses ($\text{pGy} / [\text{Bq administered/kg of body weight}]$) to various tissues and fluids in rat are displayed here. Those for distillate (D), plasma (P), and urine (U) are the result of direct measurements. Those for blood (Bl), liver (Lv), kidney (K), testes (T), spleen (S), brain (Br), lung (L), heart (H), intestine (I), and muscle (M) are calculated from proportions of organics and water in each taken from the literature, under the assumption that the organics have the same specific activity as those in serum. Clearly the use of distilled or raw urine underestimates doses to most tissues.

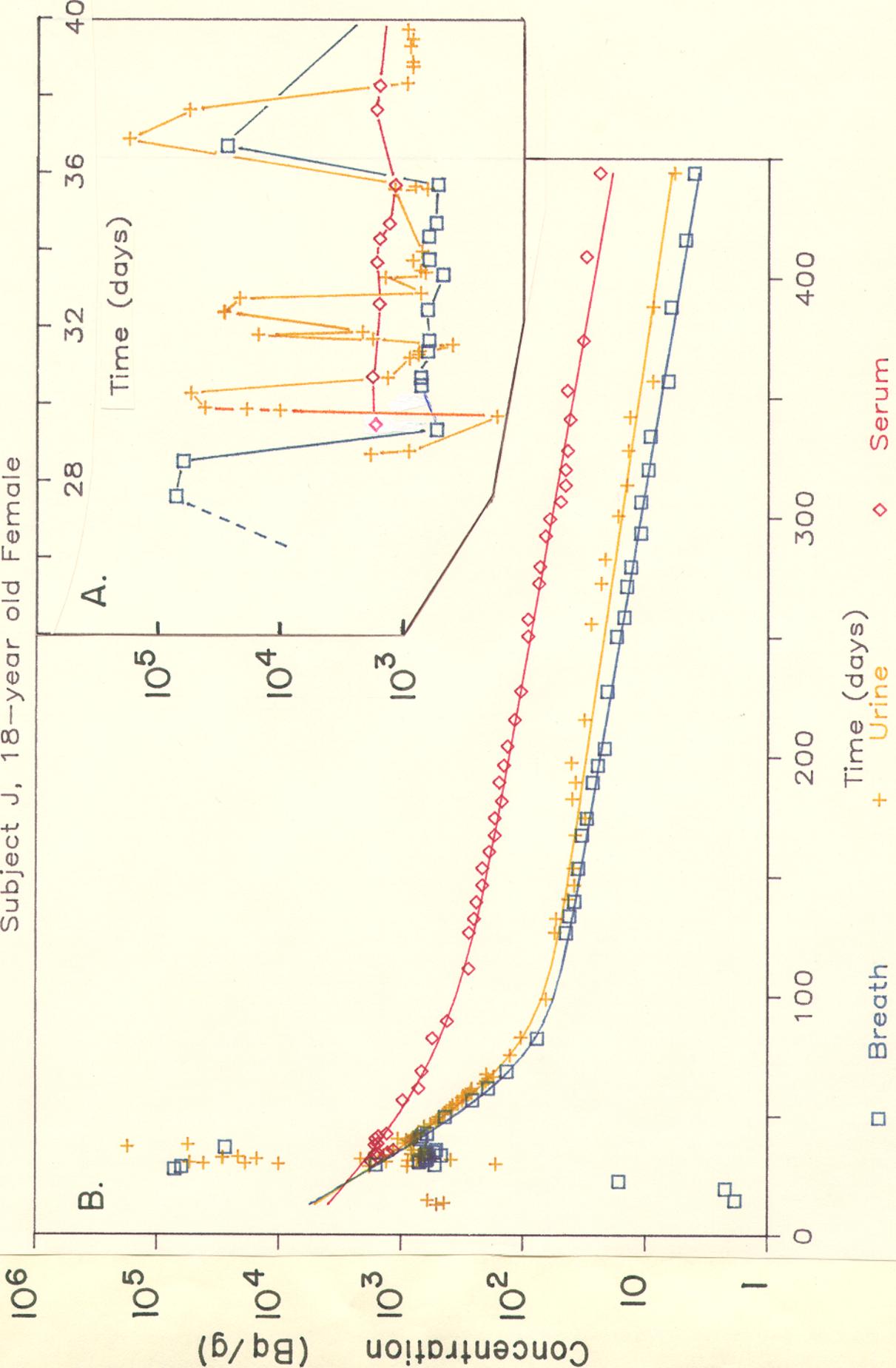
INTER-SPECIES COMPARISON. Normalized absorbed doses to each of three fluids (D = distillate; U = urine; P = plasma; B = breath; S = serum) are shown for the three species. Those for the human are notional, because the dosage (Bq/kg ingested) is estimated by comparing the halftimes in the water compartment for beagle and woman, and also because there were multiple intakes in the woman. However, the relative sizes within each group are correct. The proportion of the dose due to water and to organics are shown. The portion of the urine doses in rat and beagle marked * would be missed if bioassay were delayed for 2 days following ingestion. Such data are not available for the woman.

CONCLUSIONS.

1. The high excursions in the human urine data may be due to the presence of some leucine metabolite, as seen in the dog and rat, not due to the adulteration of samples as was assumed in 1975.
2. The high excursions in the human breath condensate data are consistent with the presence of a volatile leucine metabolite, possibly a ketone.
3. Bioassay for leucine from urinalysis underestimates the doses to most tissues. This is especially serious if the first, rapidly-cleared component is missed due to delay of bioassay.
4. Doses will be further underestimated if urine is distilled or decolorized, as has been past practice.
5. In suspect cases, a small blood sample (25 ug or 1 hematocrit tube) can be used to scale urinalysis to correct doses.

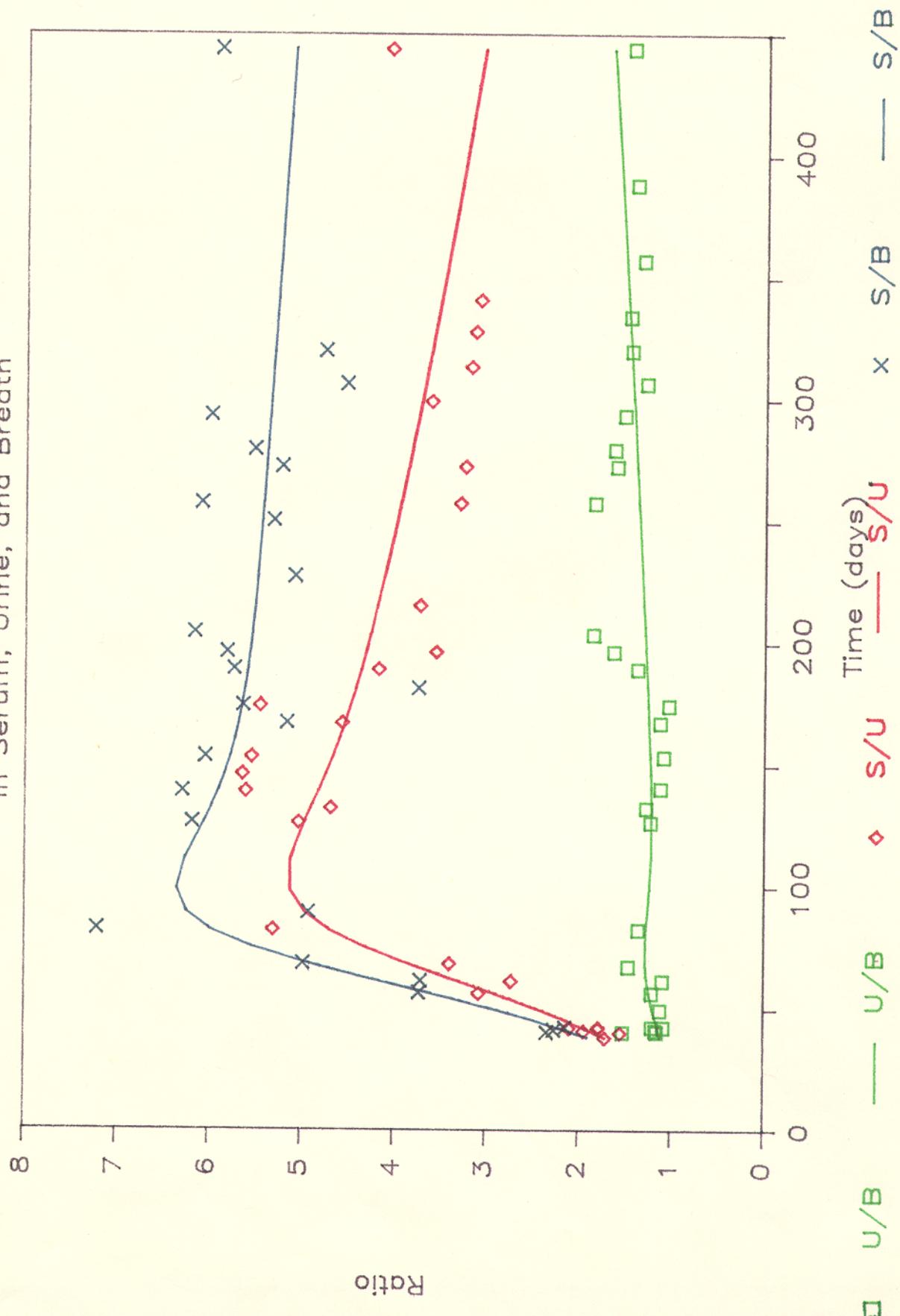
HUMAN FLUIDS (CONCENTRATION)

Subject J, 18-year old Female



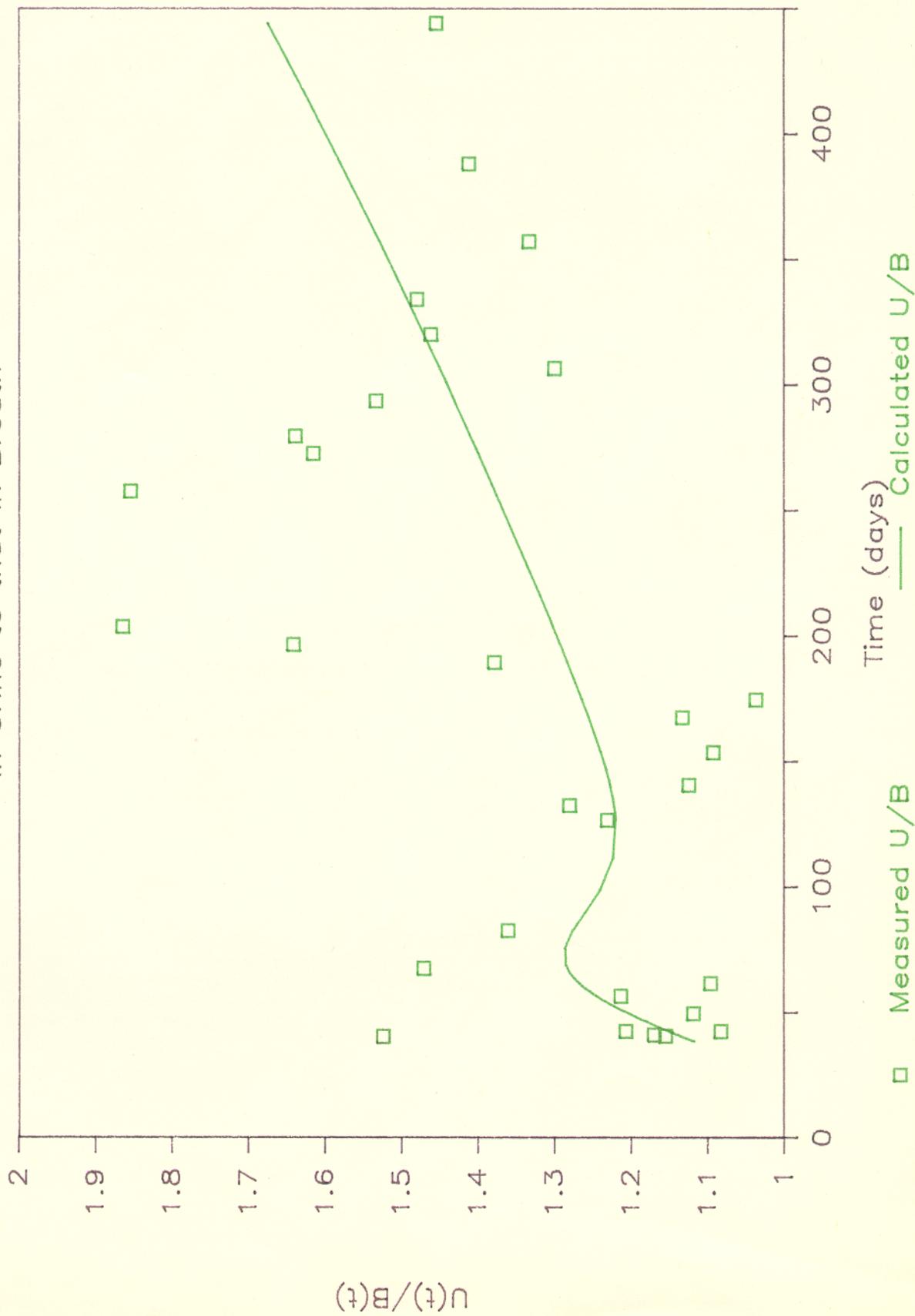
Ratio of Fluid Concentrations

in Serum, Urine, and Breath



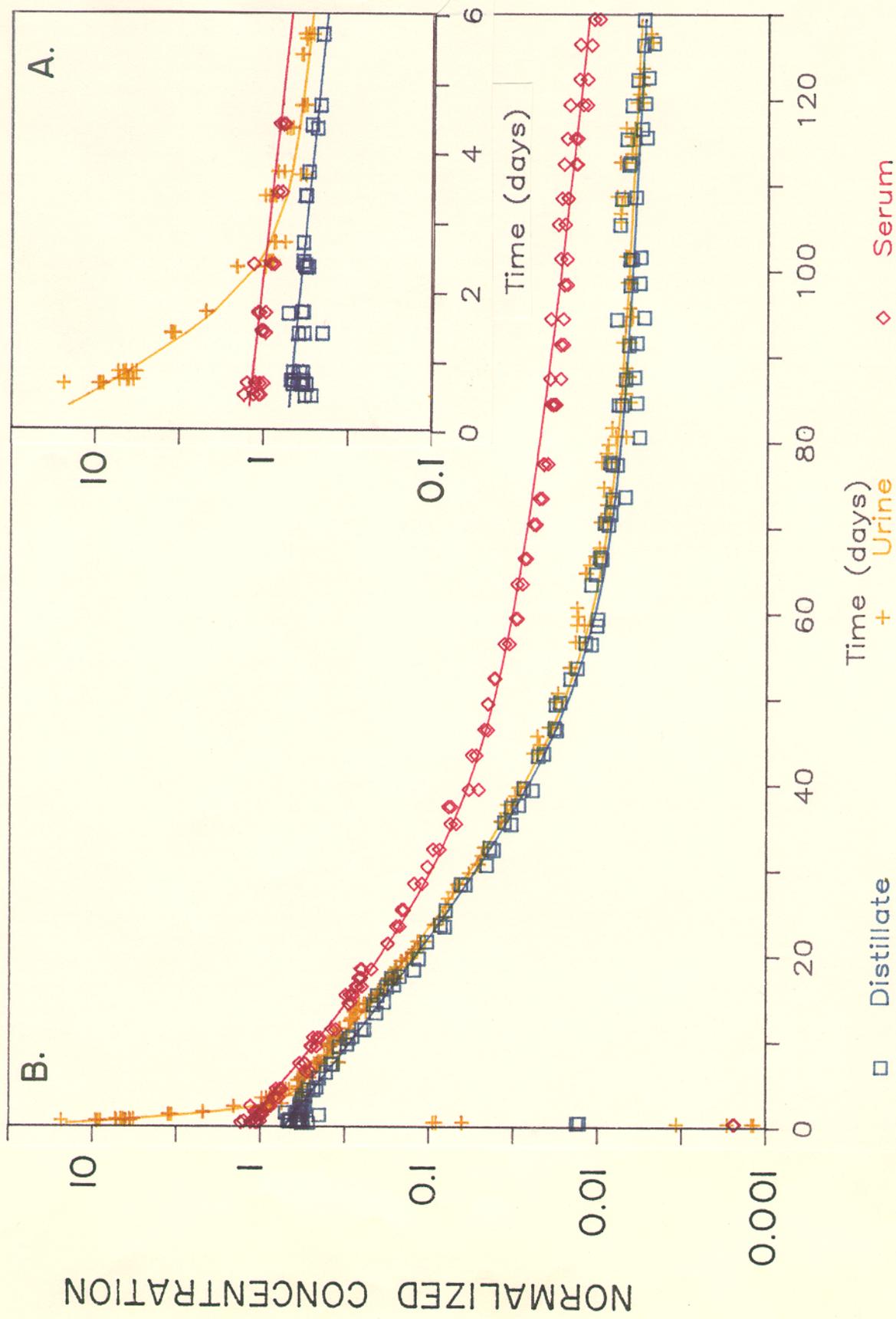
Ratio of Tritium Concentration

in Urine to that in Breath

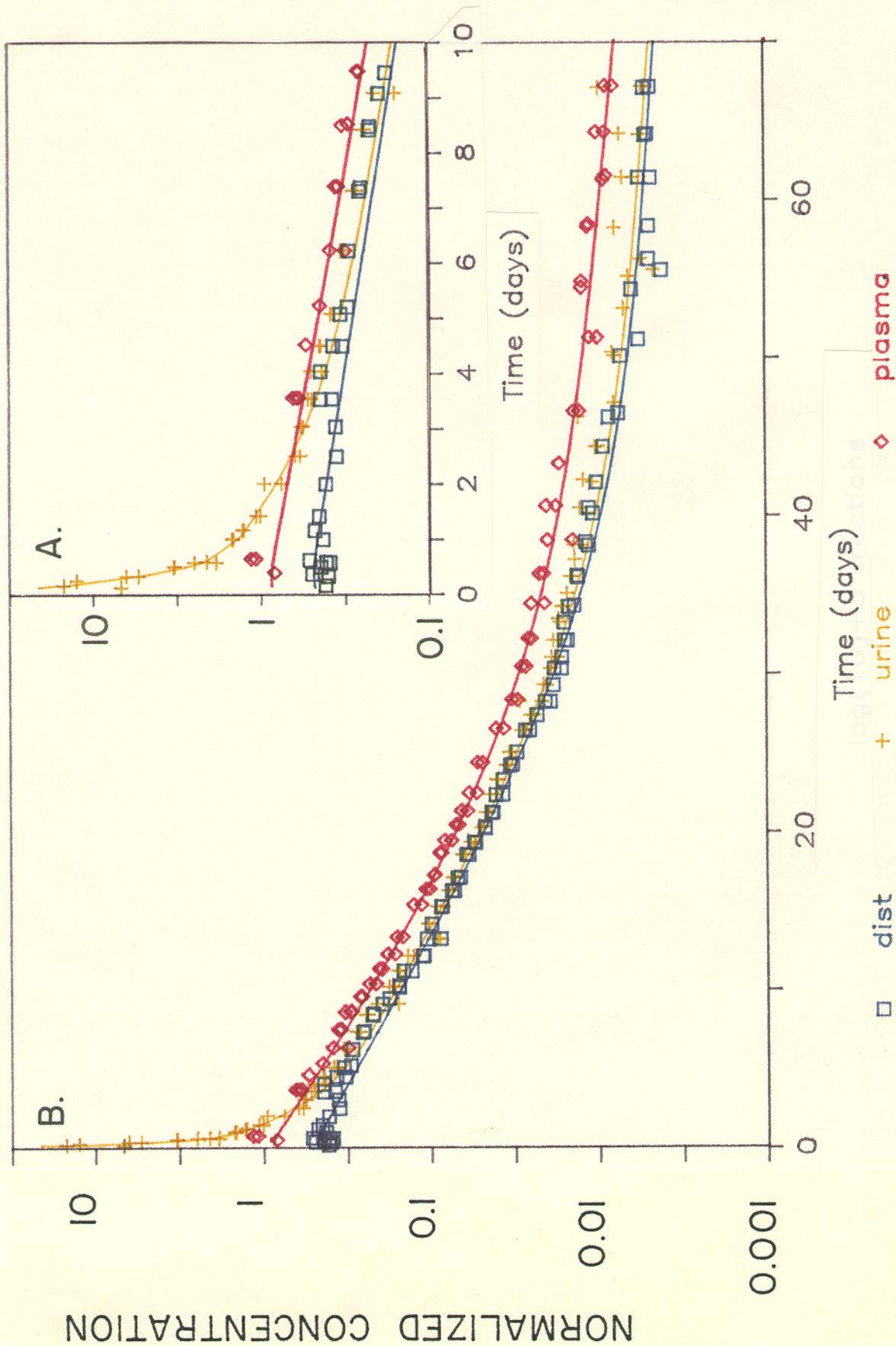


Beagle Fluids (Fraction of Dosage)

after administration of H-3-Leucine

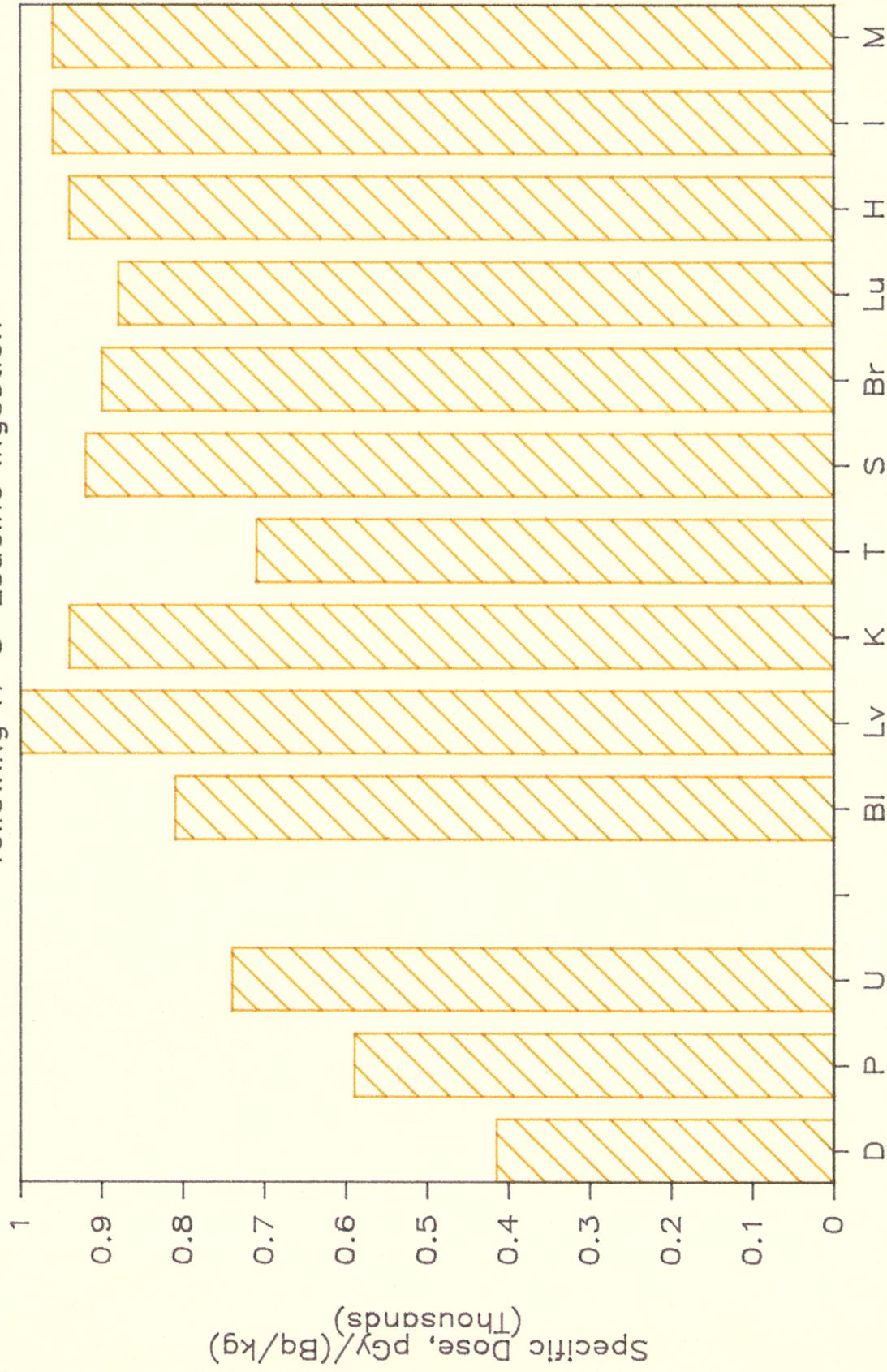


rat fluids fraction of dosage



Specific Doses to Rat Fluids or Tissues

following H-3-Leucine Ingestion



Fluid or Tissue

