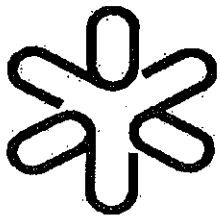

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## URANIUM TRANSFER FROM AN ANIMAL DIET TO ITS ORGANS

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# URANIUM TRANSFER FROM AN ANIMAL DIET TO ITS ORGANS

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## ABSTRACT

The transfer coefficients of uranium to the organs of animals (Wistar rats) were determined as a function of the uranium concentration in food. The experiment initiated immediately after weaning, lasting till maturity. Groups of animals were fed with ration doped with uranyl nitrate at concentrations ranging from 0.5 to 100 ppm. The uranium content in the ashes of liver, kidneys, heart, brain, intestine, skin and testicles, was measured by the fission track counting technique, following neutron irradiation of the biological samples near the core of a research reactor. The most striking result refers to the observation that the transfer coefficients, as a function of the uranium concentration in the food, exhibit a concavous shape with a minimum around 20 ppm-U for all organs. Some possible explanations to interpret this finding are tentatively addressed. Toxicology related effects are reported too.

## 1. Introduction

From the pathways of entry of radionuclides in the human (or animal) body, ingestion is very preoccupating because it is closely related to life-long alimentary (or dietary) habits. Those radionuclides which are able to enter the living cells by either metabolic or other processes give rise to localized doses that can be very high. The evaluation of these internally localized doses are of paramount importance for the assessment of radiobiological risks and radiological protection (Alpen 1990).

As pointed out elsewhere (Karpas et al. 1998), the motivation to study uranium, in particular, is the fact that the daily intake of uranium through food and water may be regarded as chronic ingestion and is a much more common occurrence than generally appreciated, as uranium is normally present in drinking water and in food.

In fact, uranium is a trace constituent in rock phosphate, which is extensively used as source of phosphorus for fertilizers and livestock feed supplements. Di-calcium phosphate (DCP), for example, a source of calcium used as animal feeding supplement, can present concentrations of uranium as high as 200 ppm (Arruda-Neto et al. 1997). Additionally, DCP can be produced by mixing phosphoric acid with calcareous rocks, while the phosphoric acid is frequently obtained from rock phosphate by the sulphuric acid process.

Thus, the investigation of the pathway

uranium (from feeding) → animal → human

is particularly important, as far as the radiological protection of the general population is concerned. In this regard, the calculation of radioisotope burdens requires, as main inputs, the transfer coefficients of radionuclides from the diet of animals, or humans, to their tissues. In fact, once the transfer coefficients are known, and given the amount of a radionuclide present in the diet, it would be possible to evaluate the content of this radionuclide transferred to the tissues. From this last information, internally localized doses could be estimated.

A transfer coefficient, $f$, is usually defined as

$$f\left(d.kg^{-1}\right)=\frac{C\left(Bq.kg^{-1}\right)}{A\left(Bq.d^{-1}\right)} \qquad (1)$$

where $C$ is e.g. the uranium content per $kg$ in a given animal tissue, and $A$ is the amount of uranium daily consumed by the animal during its last, and prolonged, feeding period. The amount of uranium can be expressed by its activity ($Bq$) or by its mass ($kg$).

Experimental determination of transfer coefficients for uranium is scarce, while data on uptake through ingestion, gastrointestinal (GI) absorption, biokinetics and chemical toxicity, are abundant. There are some published works on these issues (Bhattacharyya et al. 1989, Wrenn et al. 1994, and Karpas et al. 1998) but most of the studies so far reported deal with uptake and loss of uranium and their applicability to the determination of occupational exposure. For illustration purposes, we mention the study undertook by La Touche et al. (1987), where the absorption and biokinetics of uranium

were investigated in adult rats (fasted for 12 h) following single oral administration of acute dosages of uranyl nitrate solutions. It was pointed out that this mode of ingestion creates a scenario analogous to the human intake via drinking water after an overnight fast.

However, in the case of animals fed e.g. with DCP as feed supplement (as in the breeding of cattle, chicken, sheep, etc.), we have the following distinct characteristics:

(a) the animals initiate ingestion of uranium (from DCP) immediately after weaning, but could be receiving uranium through the milk;

(b) this ingestion of uranium persists until sacrifice of the animal, following closely, thus, the important stages of its somatic development, and

(c) since food is not withheld until sacrifice, it is an open issue as to what extent the uranium absorption is reduced because the animals have food in their upper GI tract.

Then, the key information of interest to humans, which are consumers of animal products since their childhood, is the content of uranium transferred to the tissues of animals. From this set of data it would be possible to:

(1) evaluate the uranium ingestion by humans from animal products, given their dietary habits; and

(2) estimate the content of uranium transferred to organs, and milk of humans, using suitable and validated models, thus allowing the evaluation of internally localized doses.

It should be pointed out, moreover, that since transfer coefficients are dependent on the type, amount and chemical characteristics form of the contaminant; on the animal species, sex, age, and on some physiological conditions, as well, it is crucial measuring these coefficients as accurate as possible, because they are needed for refinement and validation of biokinetics models. These models are quite useful for the study of radionuclides transport in biological systems (Garcia et al. 1999).

Needless to say how important such a kind of study is. In the present work, therefore, we report on an investigation of a long-lasting uranium ingestion from food, starting after weaning, and lasting until the animal maturity. The mode and time interval of ingestion, in this case, simulate a common real-life scenario, which is valid both for animals and humans. In this sense, the goals of this work are

(i) measurement of the uranium content in organs of animals (Wistar rats);

(ii) the determination of such uranium content as a function of the uranium concentration present in the administered food; and

(iii) observation of possible toxicity related effects, as e.g. renal failure (the most serious one) and behavior alterations as a function, also, of the uranium concentration in the food. There are reports that uranyl nitrate is one of the most toxic U compounds, and that it has often been used in experimental modeling of renal failure (Haley 1982, Pelayo 1983).

## 2. Materials and methods

### 2.1 Animals

Fifteen males Wistar rats, 15 days old and weighing approximately 25-30 g, were housed in 7 metabolic cages, forming 6 groups with 2 animals each and one group, the "control group", with 3 animals. The animals were maintained under natural photoperiod, and fed with rat chow enriched with (per kg): 12 mg of calcium, 10 mg of iron, 60 mg of manganese, 2 mg of copper, 50 mg of zinc, 2 mg of iodine, 0.1 mg of selenium and 10 mg of anti-oxidizing.

Uranyl nitrate was mixed to the food of the 6 groups (with 2 rats each), with the following concentrations (in parts per million): 0.5, 2, 10, 20, 50 and 100 ppm. The animals were sacrificed after an experimental period of 60 days when they reached maturity.

The following procedures and tasks were carried out during the experiment:

(1) daily control, and measurement, of the amount of ingested food and animals weight;

(2) urine and feces were collected and analyzed, intending the control of occult blood, pH, protein concentration, etc.;

(3) frequent evaluation of the animals, aiming the observation of possible clinical variations.

After sacrifice, the animals were dissected, their organs were weighed, wrapped in aluminum foils, and kept at -20°C till processing, which consisted of incineration using a muffle furnace at ~550°C. The organs of the animals were combined in pairs, except for the control group (3 animals), and incinerated together. For a given group of animals, thus, the obtained amount of ashes corresponds to material from two animals (and 3 for the control group).

### 2.2 Quantification of the uranium on the biological material

Ashes of kidneys, liver, heart, testicles, brain, intestine, and skin, were dissolved in nitric acid at 50%. Fractions of these solutions were deposited on foils of Makrofol E (Bayer), 100 $\mu$m thick, circular shape with 2cm of diameter. After evaporation of the liquid phase, a second Makrofol foil was attached and fixed, forming a "sandwich" Makrofol - biological material - Makrofol. Sets of 10 piled up "sandwiches", wrapped with tin aluminum foils, were placed in the interior of "rabbits" (aluminum cylinders, 22mm in diameter and 70mm high). "Sandwiches" prepared with standard solutions of uranyl nitrate were placed in the edges and in the center of each "rabbit". The "rabbits" were sealed by soldering a cap on each. Possible air leaking was checked with a solution of glycerin at 150°C.

The "rabbits" were positioned near the core of the IPEN reactor (IEA-R1, 4MW, pool type) - see figure 1. The thermal neutron flux at the irradiation position [1.18(7) x $10^{13}$ n/cm$^2$s] was monitored by means of the gold foils activation technique (Geraldo et al. 1992, and Maidana et al. 1994). Contributions from epithermal neutrons [3.52(22) x $10^{12}$

n/cm$^2$s] were checked too, via irradiation of additional gold foils wrapped with cadmium foils (1 mm thick).

Irradiation time (8 minutes for all samples) was chosen from simulations, to allow control on possible radiation damage in the Makrofol foils. These were etched by a solution of KOH, and the tracks from the neutron induced fission of uranium were counted in a projection optical microscope. The comparison of these results with those from the standard solutions of uranyl nitrate allowed the determination of the uranium content of the biological samples.

## 3. Results and Discussion

We would like to emphasize that in this experiment the animals were submitted to a long-lasting daily diet with uranium, initiating immediately after weaning and lasting till the maturity. Therefore, contrary to the experiments where animals are submitted to single doses (as e.g. in La Touche et al. 1987), two animals by group is adequate since the measured quantities, uranium content in the organs, correspond to the uranium absorption rates integrated in a long period of time. Thus, possible metabolic fluctuations are averaged out in time, while in single-dose experiments the average is achieved by using a larger number of animals. This can be assessed by a mere visual inspection of typical results on transfer coefficients, plotted as a function of time (see e.g. figure 3 in Assimakopoulos et al. 1993), where after a prolonged feeding period the amount of transferred radioactive material saturates.

The transfer coefficient, as defined by eq.1, is

$$f = \frac{C}{A},$$

where, now, we put $C = \frac{k}{p}$; $k$ is the amount of uranium we measured for each organ, and $p$ is its weight. $A$ is the average amount of uranium daily intaken by the animals in the last 15 days of the experiment. All parameters and results for the group of animals fed with 100 ppm of uranium are in Table 1, while in figure 2 the transfer coefficients are plotted as a function of the uranium concentration (in ppm) present in the animals diet.

The results from the 0.5 ppm-U group were discarded because they are not conclusive, in the sense that the amounts of uranium transferred to the organs ($k$) are very small, giving rise to a poor counting statistics (large uncertainties). Nevertheless it is possible to say that the amounts of transferred uranium, observed for this group of animals (0.5 ppm-U), are as small as those observed in the control group (zero ppm-U).

The U-intake parameter $A$, ranging from 2 to 100 ppm-U/day, corresponds to ~ 0.1 to 5.2 mg-U per animal per day, or, ~ 0.5 to 26 mg-U per kilogram of animal body weight per day.

Other results and observations, related to clinical evaluation and urine/feces examination, are presented below with the discussion.

3.1 Overall and common characteristics

One distinct and common feature of the transfer coefficients $f$, in the full 2-100 ppm-U range, is their concavous shape with a minimum around 20 ppm for all organs (less apparent only for the intestine - see figure 2). When observed individually, the data sets between 2 and 100 ppm-U exhibit, for all organs, a smooth trend within the experimental uncertainties; some fluctuations are visible at the low-ppm region only for liver and kidneys. This smooth trend could be indicating that possible metabolic fluctuations were averaged out, as discussed above, because statistical fluctuations associated with the measurement itself should be small (the fission track technique is quite precise).

These somewhat unexpected findings could indicate that metabolic aspects do not play a major role, since the transfer coefficients for all organs show the same dependence on the amount of ingested uranium. From a microscopic point of view, our results also suggest that structurally different cells, from different tissues, would absorb uranium by the same mechanism.

It is clear from figure 2 that the absorption of uranium, as a function of intake ($A$), proceeds through two different regimes, taking place in the ranges: 2-20 ppm-U ($f$ decreasing) and 20-100 ppm-U ($f$ increasing). These two cases are now discussed separately.

3.2 Group of animals that received 2 to 20 ppm of U and showed $f$ decreasing

This behavior of $f$ could be an indication for an inverted intake/uptake relationship.

In fact, an inverse relationship between the amount of ingested low-levels of uranium, and the uptake factor, has been proposed elsewhere (Legget and Harrison 1995 and Karpas et al. 1998). Thus, if there is indeed an inverse relation between uranium intake (represented by $A$ in our case - equation 1) and uptake (from intestine into the blood stream, and from there to the organs), this could indicate that uranium does fulfill some role in the body biochemistry, or that its behavior is typical of an essential element, or even that it mimics some essential element such as calcium. In this scenario, the amount of uranium content per kilogram of organ, $C = C(A)$, should be a nearly constant function of $A$ (the intake parameter); therefore, the ratio $C/A$ (which represents $f$ and is nearly proportional to the uptake factor) would be a decreasing function of $A$, as observed in the present work. A few representative examples are shown in Figure 3. We note that in the 2-20 ppm-U range, the slopes of $C = C(A)$ for e.g. skin and heart are very small comparatively to the slope of the dose (intake), while for $A > 20$ ppm-U the slopes of $C = C(A)$ are similar to that of the intake. The only exception is verified for the intestine - this is a salient issue discussed below.

Therefore, our findings are compatible with some sort of "uranium essentiality" up to an intake of ~20 ppm-U ( ~5 mg-U per kilogram of body weight per day). Above $A$ = 20 ppm-U a dramatic increase of the $C = C(A)$ slopes is observed (discussed in the next section).

3.3 Group of animals that received 20 to 100 ppm of U and showed $f$ increasing

The sudden change of regime observed at the "turning point" $A \cong 20$ ppm-U, for all organs other than intestine, indicates that the cause is extra-organ and, much more important, that this "cause" is common to all organs (they all have the same "turning point"). The most plausible explanation for this intriguing behavior of $f$, for $A > 20$ ppm-U, surprisingly came from urine analysis results. It was detected occult blood in the urine of the animals pertaining to the groups that received 20, 50 and 100 ppm of uranium in the food, all along the last one-third period of the experiment. This could be an indication that kidney malfunction are taking place (other details in section 3.5).

As pointed out elsewhere (La Touche et al. 1987), the kidneys seem to operate as a transient collecting point for uranium, removing it from the circulation rather than storing it. Thus, the increasing character of $f$, from 20 to 100 ppm-U, may possibly reflect a gradually increasing inability of the kidneys to remove uranium from the blood. Since there is a well known correlation between the contents of radioactive materials in the blood and in the organs, it is very likely that our observations for $A > 20$ ppm-U, as expressed by the $f$-curves (Figure 2) or, more dramatically, by the functions $C = C(A)$ in Figure 3, are directly related to the enhancement of the uranium concentration in the blood. Therefore, toxicology related malfunction of the kidneys, is an important point to be considered in the evaluation of radiobiological harms caused by prolonged ingestion of uranium. However, kidney malfunction is not the only mechanism by which enhancement of uranium in the blood occurs, as addressed next.

The absorption of uranium in rats, following single oral gavage with uranyl nitrate, was investigated by La Touche et al. (1987) at gavage levels ranging from 0.003 to 45 mg-U per kilogram of body weight. Uranium tissue burdens were determined at 0.25 to 240 h following gavage. In order to allow a quantitative comparison with our results, we converted those from La Touche et al. (1987), for intestine, to units of transfer coefficients, namely, $d.kg^{-1}$. However, since the intake took place from a single oral gavage, these are differential quantities (represented here by $f_N$ and shown in Figure 4) corresponding to a single day feeding of an adult male Wistar rat. On the other hand, the transfer coefficients we measured could be interpreted as an integral of $f_N$ in a prolonged (60 days) feeding period, but by considering only the residual loss component of $f_N$ which, e.g., for the large intestine, is verified for $t \geq 50$ h ( $t$ is the post-gavage time).

In our plot of La Touche et al. (1987) results we added the data of both small and large intestines. We note that the residual loss component for the dosage of 3 mg-U/kg (curve-1 in figure 4), is substantially higher than that for 30 mg-U/kg (curve-2 in figure 4). The piling up effect of several $f_N$ residual loss components, corresponding to several days intake of these dosages, should provide integral transfer coefficients similar to those we measured, although some saturation could spoil the linearity of this adding effect. As illustrated in figure 4, our results of intestine, for ~3 and 30 mg-U/kg intake (shaded bands), are in qualitative agreement with those from La Touche et al. 1987 (that is, $f(1) > f(2)$ ). By taking the average of $f_N$ between 60 and 100h, $\langle f_N \rangle$, we found out that

$$f(1) \approx 40.\langle f_N(1) \rangle, \text{ and} \qquad (2)$$

$$f(2) \approx 30.\langle f_N(2) \rangle, \qquad (3)$$

which is quite compatible with the "piling up effect" mentioned above (it is important to remember that this experiment took 60 days, and started immediately after weaning).

According to La Touche et al. (1987) and also supported by our findings, the fact that $f_N(1) > f_N(2)$ many hours after gavage, which is also supported by our findings, could be an indication that GI absorption is more efficient at higher U-concentrations. As a consequence, uranium burden in blood should be higher, which also contributes to the increase of $f$ in all organs (from 20 to 100 ppm-U) as observed in the present work.

3.4 Tissues peculiarities

From the data set displayed in figure 2, it becomes clear that the most evident differences among the majority of the tissues are related to the magnitudes of their transfer coefficients.

As discussed above for the 20-100 ppm-U region, the increasing character of $f$ is determined by the equally increasing uranium content in the blood. Therefore, it could be argued if the different $f$ magnitudes would possibly be correlated to the variations of the blood flux in the tissues. We show in table 2, in this regard, some data on the percentage of the cardiac output in rats (Petty 1982), as well as these same data normalized to the masses of the tissues, that is, percentage of the cardiac output per gram of tissue, $C_N$ (expressed as $\%g^{-1}$).

We present in figure 5 a scatter plot of $f$ (for 100 ppm-U) with its corresponding normalized cardiac output ($C_N$); the straight line was obtained from a linear regression. The correlation coefficient ($R$) is equal to 0.984, and the confidence coefficient ($P$) is < 0.0001. Such a strong correlation between $f$ and $C_N$ is, however, questionable. In fact, a mere visual inspection of figure 5 reveals that the correlation is solely driven by the point associated with the kidneys. By performing the linear regression without the point for kidneys we obtained $R = 0.255$ and $P = 0.626$, that is, no correlation is verified (figure 6). Also shown in figure 6 are the points for the intake of 50 ppm-U. The two sets of points, for 100 and 50 ppm-U, differ from each other only by their magnitudes, while all the structures are at the same positions. Therefore, it is very likely that these structures do not represent statistical fluctuations. A stringent test supporting such a possibility is provided by the scatter plot shown in figure 7, where a correlation between $f$ (100 ppm) and $f$ (50 ppm) is verified. In fact, from the linear fit we got $R = 0.966$ and $P = 3.93 \times 10^{-4}$ for this log-log plot, but the fitted line is nearly diagonal; therefore, a linear correlation is reasonably achieved.

The data displayed in figure 6 are quite revealing, in the sense that they indicate the existence of accentuated peculiarities among the tissues, as regarding the amount of transferred uranium (that is, the uranium biokinetics). We note, for example, that $f$ (liver) > $f$ (heart), but $C_N$ (liver) < $C_N$ (heart), indicating that the balance between deposited uranium and removed uranium, by the blood, is higher for the liver comparatively with the heart. Some results quite recently reported by Karpas et al. (1998), indicate that uranium absorbed through the intestine interchanges with uranium retained in the organs.

The whole picture seems to be now quite clear, namely: while the increasing uranium burden in the blood explains the increasing character of $f$ (from 20 to 100 ppm-U), for all tissues other than intestine, the peculiarities of the uranium biokinetics, from tissue to tissue, determine the different magnitudes of $f$. There are, however, second order mechanisms by which uranium distribution could be facilitated, as e.g. the capillary permeability. It is a well-known fact that the kidneys and the liver present the highest capillary permeability (Guyton and Hall 1996). In this case, large-size molecules could be transferred from the blood to the kidneys and liver much more easily, as compared with the other tissues. If uranium is transported by the blood attached to some protein, it would be expected to obtain higher transfer coefficients for the kidneys and the liver compared to the other tissues. Incidentally, our results show that $f$ for the kidneys (liver) is two (one) orders of magnitude higher than an average of $f$ (taken over all the other tissues). We believe it is worthwhile pursuing, in further investigations, this and other issues addressed in this work, on the grounds of the arguments outlined above.

Finally, we did not find in literature data about uranium transfer coefficients for rat tissues, measured with the same experimental conditions as in the present work. Comparison with data obtained with other species could be useless, given the great biological variability, but order of magnitude cross-check could make sense. Thus, we mention in passing the case of $^{238}U$ and $^{210}Po$ transfer from chicken's diet to its meat in the low concentration range, namely (Izak-Biran et al. 1989)

$f(^{238}U) \approx 1.2$ dkg $^{-1}$, and

$f(^{210}Po) = (2.4 \pm 1.6)$ dkg $^{-1}$.

For rat skin at the low ppm-U region we got $f \approx 2.2$ dkg $^{-1}$.

3.5 Toxicology related observations

The urine of the rats, from the groups fed with 50 and 100 ppm-U concentrations in the last 15 days of the experiment, was darker than that from the animals of the other groups. However, the laboratorial examination revealed that pH, protein concentrations, cetonic bodies, nitrite, bilirubin and urobilinogen, in all animals, ranged within the normal parameters for rats, in all the animals. On the other hand, the animals from the two groups of higher doses exhibited more aggressiveness.

The urine of the animals, from the groups fed with 20, 50 and 100 ppm-U in the last one-third period of the experiment, showed blood: 50 red blood cells per ml, approximately. This blood seems to reflect, probably, a renal tubular lesion, which caused exposition of the tubular lumen to peritubular capillaries allowing, thus, some blood to come into the renal tubule and then to the urine.

We did not observe any severe toxicity effect, which manifests itself, primarily, by reduction of animals weight. In fact, the gain of weight in all animals, in the whole period of the experiment, was compatible with the normal development of Wistar rats.

The peculiarities of this experiment, as e.g. the prolonged duration, prevents its direct comparison with most of the results found in the literature. Notwithstanding, there

is a number of results on acute renal failure (ARF) induced by uranyl nitrate, at dosages of 10mg per kg of body weight; this is, approximately, the daily intake of the animals from the 50 ppm-U group of the present experiment. For example, Haley (1982) reported sequential changes in renal morphology, occurring for 5 subsequent days after a subcutaneous injection of uranyl nitrate (10mg/kg body wt), both in saline-and water-drinking rats (Sprague-Dawley, males). It was revealed, by scanning electron microscopy, abnormalities in glomerular epithelial cells similar to those seen in humans with chronic renal disease.

Although, in our case, uranyl nitrate was administered mixed with the food, which could result in a relatively slow development of tubular necrosis, we stress the fact that the animals starting the experiment were very young. We refer the reader, in this regard, to the work of Pelayo et al.(1983), where it was investigated the acute renal toxicity of uranyl nitrate in canine puppies (10 mg/kg body wt). Morphologic alterations, consistent with the nephrotoxic effects of the heavy metal (uranium), were observed in the proximal tubules of the most differentiated nephrons.

Although the present study does not permit one to characterize the degree of ARF, one could certainly speculate that the correlation between the increasing character of $f$, and the observation of blood in urine for intake $\geq$ 20 ppm-U (see discussion above), is a convincing indication of kidney malfunction.

## 4. Conclusions

We believe it is worthwhile presenting a survey of all the most relevant information, arguments, etc., contained in this paper, but assembling them in the following categories: plain facts (from this work and from literature), inferred conclusions and presumptions.

### 4.1 Plain facts

#### 4.1.a From this work

(1a) remarkable characteristics of the data points (figure 2): smooth sequence and small fluctuations only at the very low ppm-region. Two orders of magnitude differences from kidneys to testicles.

(2a) the $f$-curves for ALL ORGANS exhibit concavous shapes, with minima at 20 ppm-U (except for intestine). There are, therefore, two distinct components: from 2 to 20 ppm-U ($f$-comp.1) and from 20 to 100 ppm-U ($f$-comp.2).

(3a) the uranium concentration functions $C = C(A)$, figure 3, have small slopes from 2 to 20 ppm-U, and they increase steeply from 20 to 100 ppm-U (except for intestine).

(4a) $f$ (intestine) is an ever decreasing function in the entire ppm range.

(5a) it was found blood in the urine of the animals from the groups of 20, 50 and 100 ppm-U ($f$-comp.2 range).

4.1.b From literature

(1b) kidneys remove uranium from the blood. Thus, kidney malfunction results in the enhancement of uranium concentration in the blood.

(2b) blood flux intensities change appreciably from organ to organ (table 2).

(3b) cappilaries in kidneys and liver are much more permeable.

(4b) $f$ (low-U) > $f$ (high-U) for intestine, indicating that GI absorption is more efficient at higher uranium intake concentrations.

(5b) a possible signature for the "essentiality" of uranium is the inverted intake/uptake relationship : $f$ decreasing, or, $C = C(A)$ constant or nearly constant.

(6b) uranium is transported to, or removed from, the tissues through the blood.

4.2 Inferred conclusions

(1) uranium is essential, and/or it mimics some essential element (as calcium) : inferred from 3a, 5b and 2a ($f$-comp.1).

(2) $f$-comp.2 : would reflect the gradual enhancement of the uranium concentration in the blood stream, caused by an equally increasing inability of the kidneys to remove uranium : inferred from 2a, 5a, 1b and 6b.

(3) the uranium content of organs results from a "piling up effect" of residual uranium, following many daily intakes, as verified for intestine : inferred from comparison with literature (figure 4) and calculation (expressions 2 and 3).

(4) magnitudes of $f$ are not correlated with blood flux intensity : inferred from table 2 and figure 6.

4.3 Presumptions

(1) metabolical and physiological aspects of the organs seem to play no major role in the uranium transfer process, as a function of the intake ($f$-curves with the same shape).

(2) the biokinetics of uranium strongly varies from organ to organ, which explains the equally strong variation of $f$ from organ to organ.

(3) the higher magnitudes of $f$ in the kidneys and in the liver, plus the greater capillary permeability of these tissues, would indicate that uranium is transported by the blood attached to a large-size molecule (maybe some protein).

## 5. Final remarks

It is clear, on one hand, that short-term investigations involving a small number of animals could yield misleading estimates of e.g. mean GI absorption, material concentrations in organs, etc., due to sizable inter-and intra-animal variability in intake, uptake, excretion and interchange between blood and systemic deposits in bone and other tissues.

The present work, on the other hand, refers to a long-term observation, where the measured quantities (transfer coefficients) resulted from time integrated effects (see figure 4 and expressions 2 and 3). Very important, in this regard, is the fact that we used animals just after weaning. In this case, it is very likely that the young animals were often in positive uranium balance (between uptake and excretion) due to a buildup of uranium in the growing skeleton. Moreover, the GI tract of newborn animals is orders of magnitude more permeable to a number of radionuclides, including U, than is that of the adult (see Sullivan and Gorham 1982).

As pointed out elsewhere (La Touche et al. 1987), the results of rat studies may be used to infer human absorption of uranium. Additionaly, the conditions of our experiment simulate a real human life scenario, associated with prolonged intake of uranium contained in food.

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Table 1

Results for the group of animals fed with 100 ppm of U in the food.

| organ | $p$ (kg) | $k$ (g) | $A$ (g d$^{-1}$) | $f$ (d kg$^{-1}$) |
|---|---|---|---|---|
| kidney | $1.63(5).10^{-3}$ | $16\ (6).10^{-4}$ | $5.19(8).10^{-3}$ | 188(73) |
| liver | $21.79(5).10^{-3}$ | $35.8(41).10^{-4}$ | $5.19(8).10^{-3}$ | 31.6(47) |
| intestine | $20.12(5).10^{-3}$ | $3.3(6).10^{-4}$ | $5.19(8).10^{-3}$ | 3.2(6) |
| heart | $1.76(5).10^{-3}$ | $1.5(3).10^{-4}$ | $5.19(8).10^{-3}$ | 16(4) |
| skin | $31.04(5).10^{-3}$ | $2.6(8).10^{-4}$ | $5.19(8).10^{-3}$ | 1.6(5) |
| testicle | $8.33(5).10^{-3}$ | $0.42(11).10^{-4}$ | $5.19(8).10^{-3}$ | 0.93(25) |
| brain | $1.37(5).10^{-3}$ | $0.22(3).10^{-4}$ | $5.19(8).10^{-3}$ | 3.2(5) |

Table 2

Percentage of the cardiac output to some organs of rats according to Petty (1982).

| organ | % | $C_N$(% g$^{-1}$)* |
|---|---|---|
| kidneys | 15 ± 3.9 | 9.2 ± 2.4 |
| liver | 12 ± 2.8 | 0.55 ± 0.13 |
| skin | 10 ± 1.2 | 0.32 ± 0.04 |
| intestine (average**) | 3 ± 0.5 | 0.15 ± 0.03 |
| heart | 2 ± 0.5 | 1.14 ± 0.28 |
| brain | 1.7 (sic) | 1.24 |
| testicles | 0.78 (sic) | 0.094 |

* percentage of the cardiac output per gram of organ.
** average of large and small intestines.

## FIGURE CAPTIONS

Fig.1 - Core configuration of the IAE-R1 reactor and position of sample irradiation.

Fig.2 - Transfer coefficients (this work) of rat tissues, as a function of the uranium concentration (in ppm) in the animals food. The lines (dashed and solid) are only to guide the eyes.

Fig.3 - Concentration of uranium in rat organs, $C$ ($\mu$g/g), as a function of the uranium intake, $A$, expressed as ppm in the animals food. The dashed lines are only to guide the eyes. All of these lines reach the points at $A$ = 100ppm-U, not shown in this graphic.

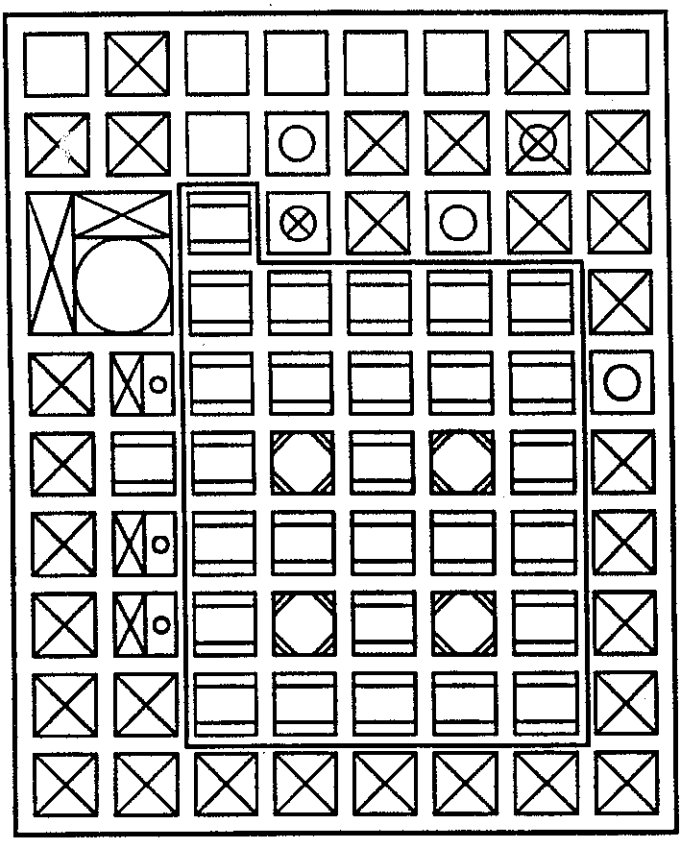
Fig.4 - Transfer coefficients of rat intestines, as a function of post-gavage time (data points connected by curves 1 and 2); adapted from La Touche et al. 1987 (details in the text - p.7). Shaded bands : this work.

The curve 2 reaches the data point $f_N$ = 0.026 (d.kg $^{-1}$) at $t$ = 96 h, not shown in this graphic but indicated by an arrow.

Fig.5 - Scatter plot of transfer coefficients ( $f$ ) for some tissues, including the kidneys, against the normalized percentage of cardiac output received by each tissue (% per g). The straight solid line was obtained by linear regression ( $R$ = 0.984 and $P$ < 0.0001 ). Intake $A$ = 100 ppm-U.

Fig.6 - Scatter plot of transfer coefficients ($f$) for some tissues, excluding the kidneys, against the normalized percentage of cardiac output received by each tissue (% per g). The straight line was fitted to the points for $A$ = 100 ppm-U ( $R$ = 0.255 and $P$ = 0.626 ). The letters drawn close to the points represent the initials of the organs (see organs listing in Tables 1 or 2). The lines connecting the points are only to guide the eyes.

Fig.7 - Scatter plot for $f$ (50 ppm-U) against $f$ (100 ppm-U). The straight line was obtained by linear fit ($R$ = 0.966 and $P$ = 3.93 x $10^{-4}$).



FUEL ELEMENT

CONTROL ELEMENT

GRAPHITE REFLECTOR

PLUG

IRRADIATION ELEMENT

NEUTRON SOURCE

IRRADIATION POSITION

Fig. 1

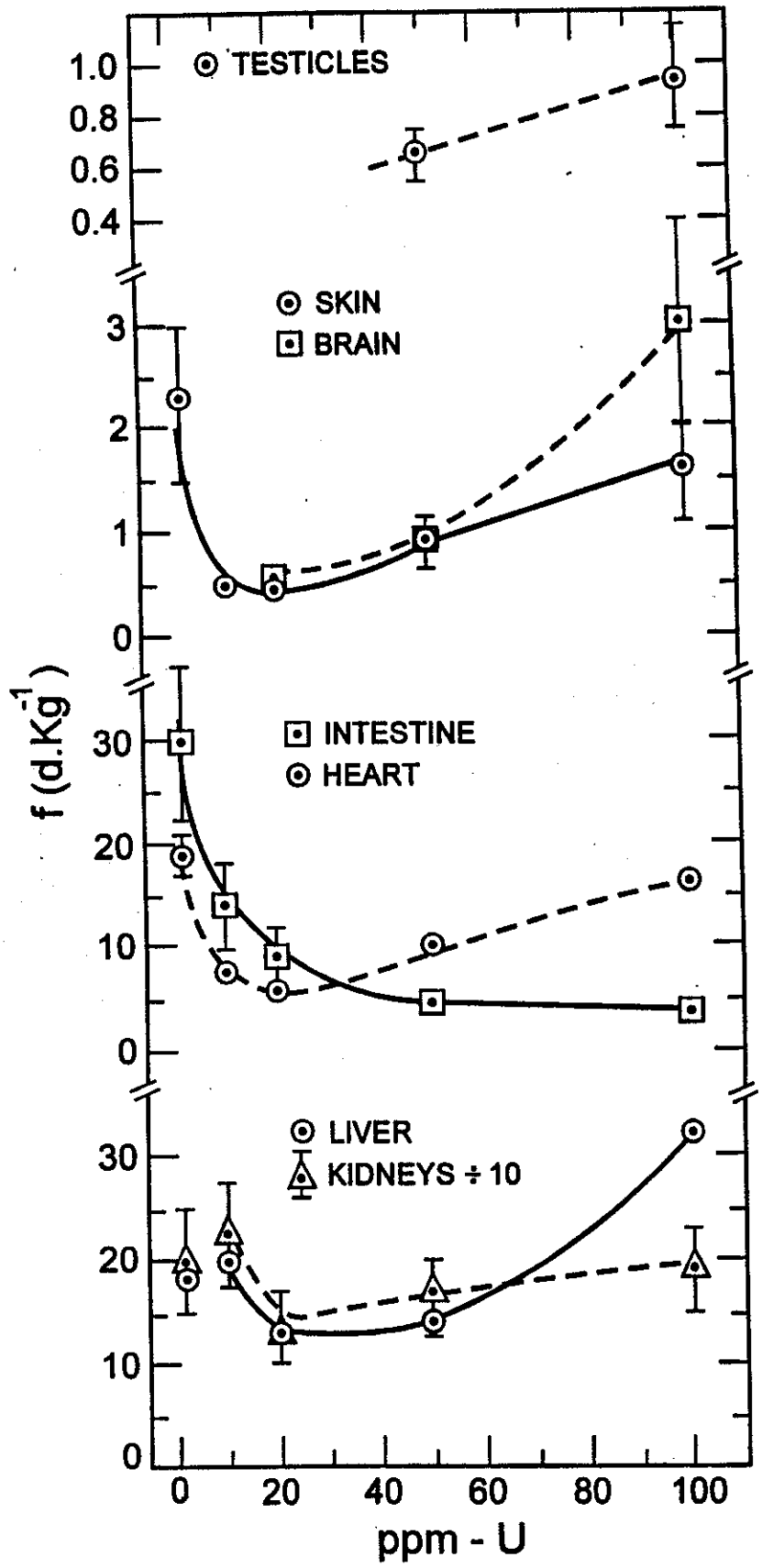
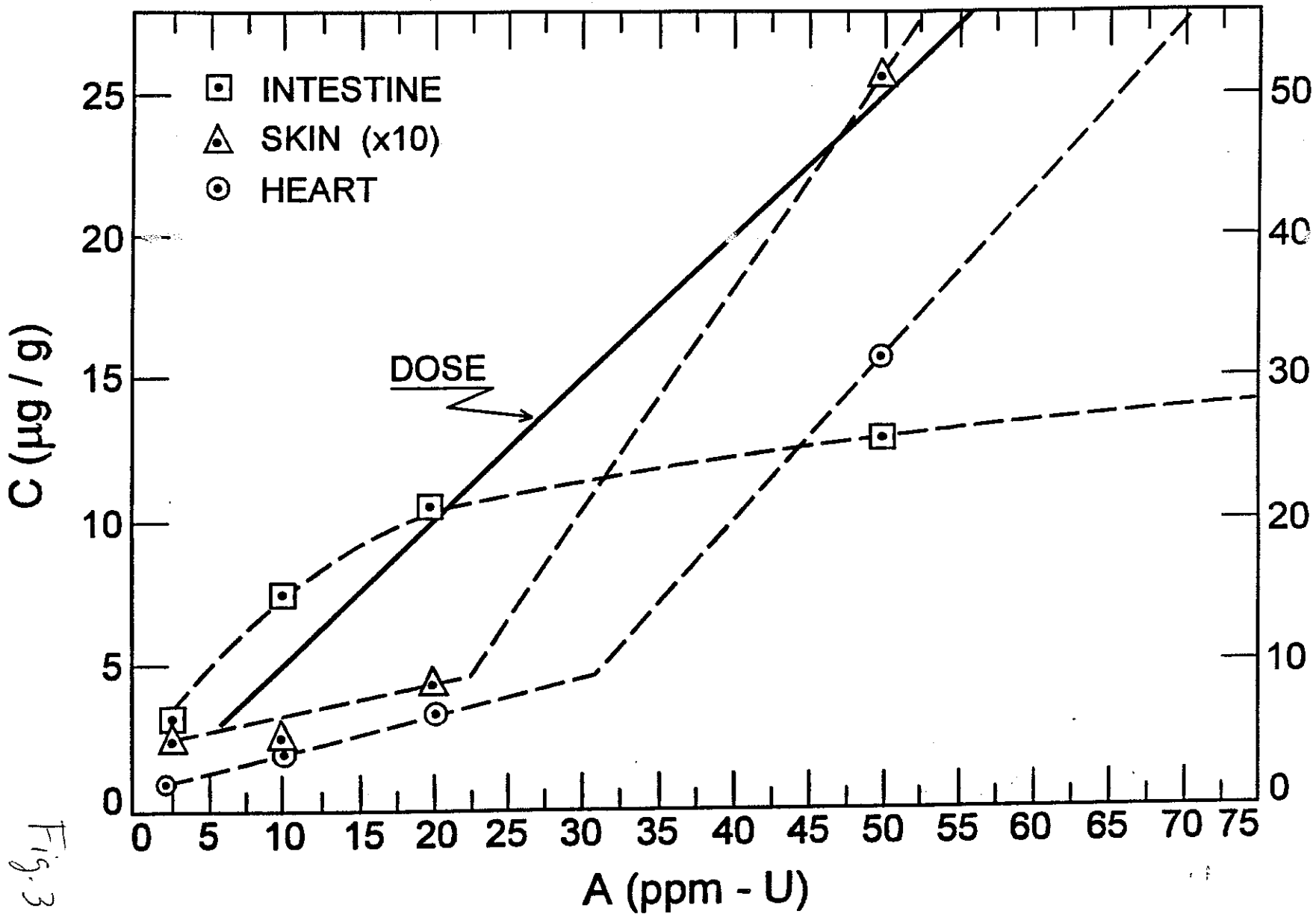

TESTICLES
SKIN
BRAIN
INTESTINE
HEART
LIVER
KIDNEYS ÷ 10
f (d.Kg-1)
ppm - U
1.0
0.8
0.6
0.4
3
2
1
0
30
20
10
0
30
20
10
0
0
20
40
60
80
100

Fig. 2


INTESTINE
SKIN (x10)
HEART
DOSE
C (µg / g)
A (ppm - U)
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5
10
15
20
25
30
35
40
45
50
55
60
65
70
75

Fig. 3

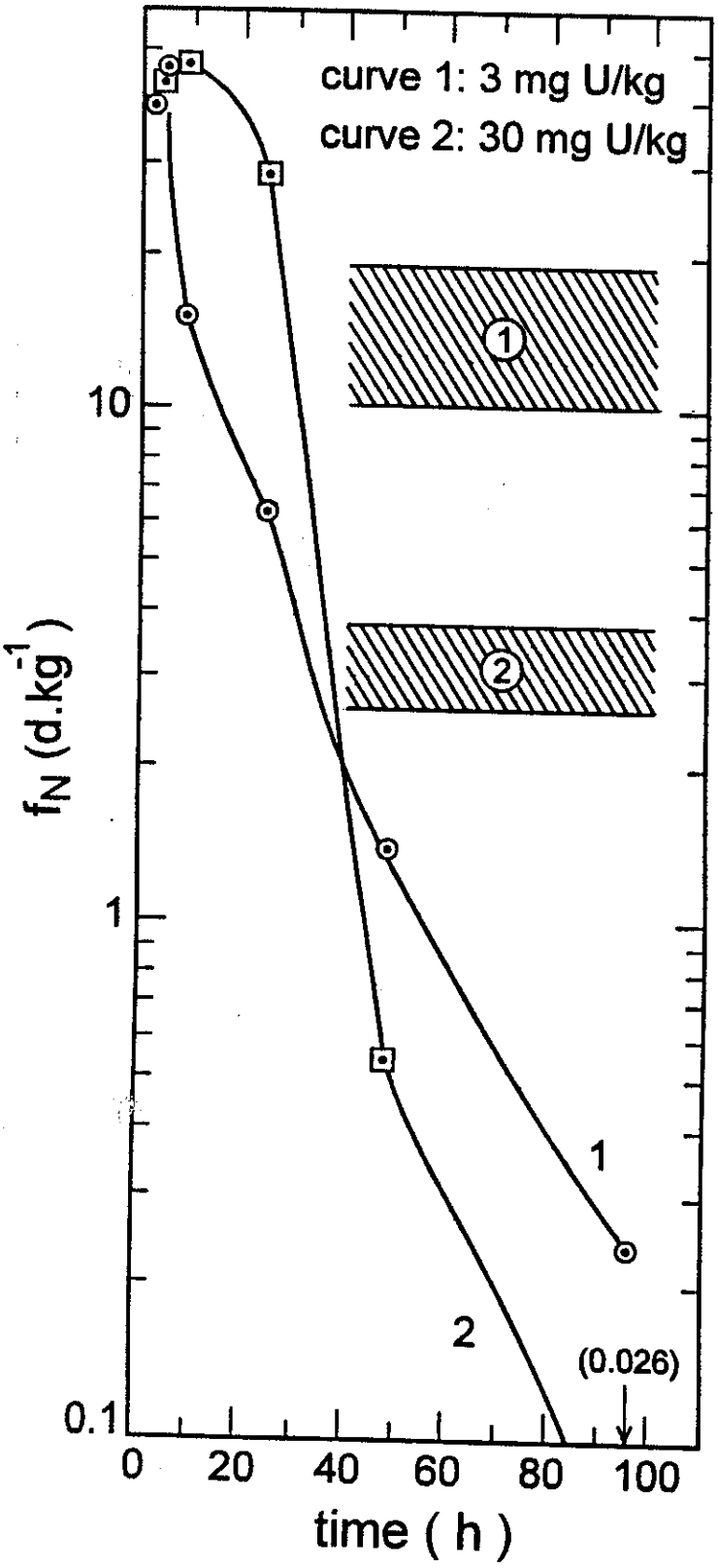
curve 1: 3 mg U/kg
curve 2: 30 mg U/kg
1
2
10
1
0.1
$f_N$ (d.kg$^{-1}$)
1
2
(0.026)
0
20
40
60
80
100
time ( h )

Fig. 4

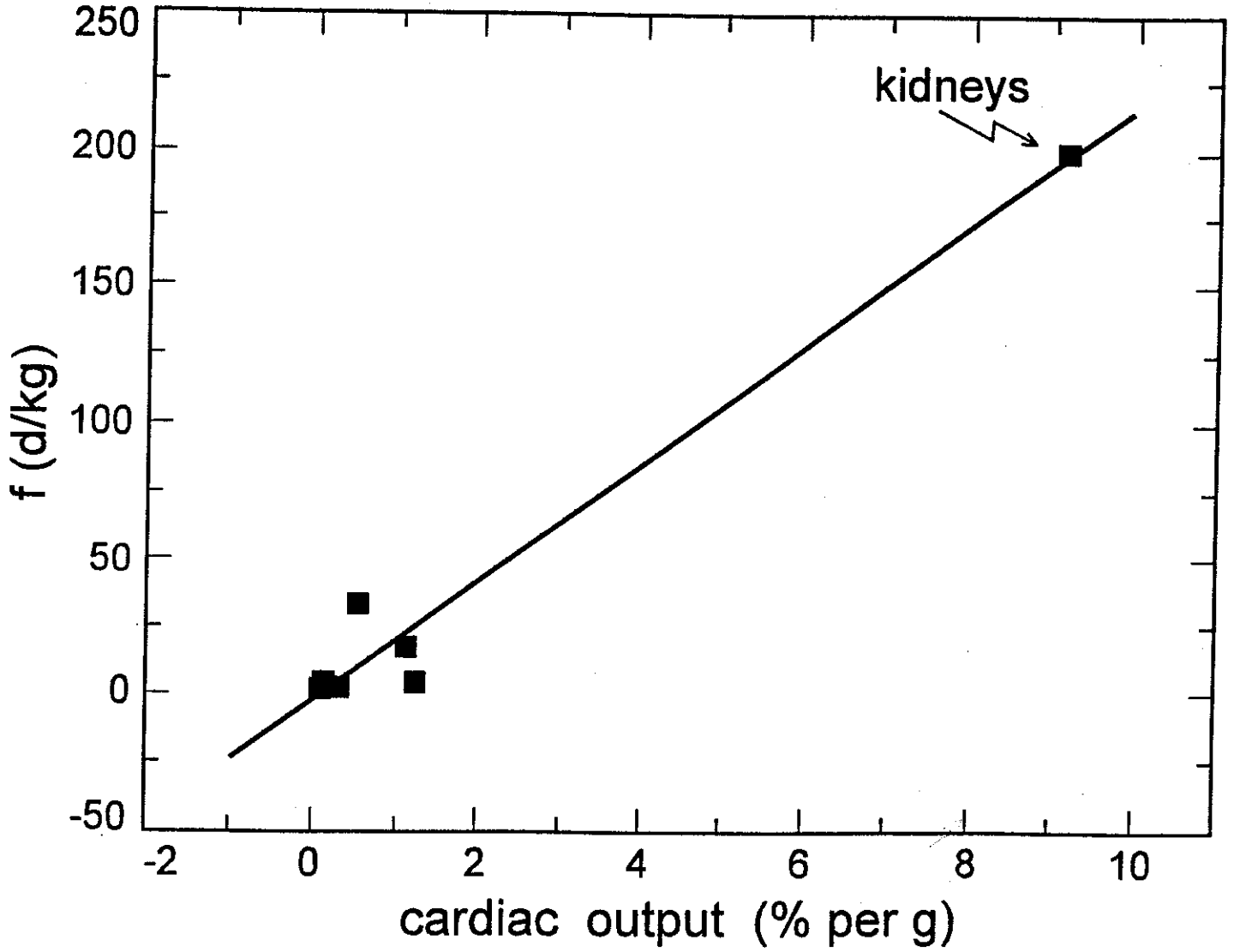
250
200
150
100
50
0
-50
f (d/kg)
kidneys
-2
0
2
4
6
8
10
cardiac output (% per g)

Fig 5

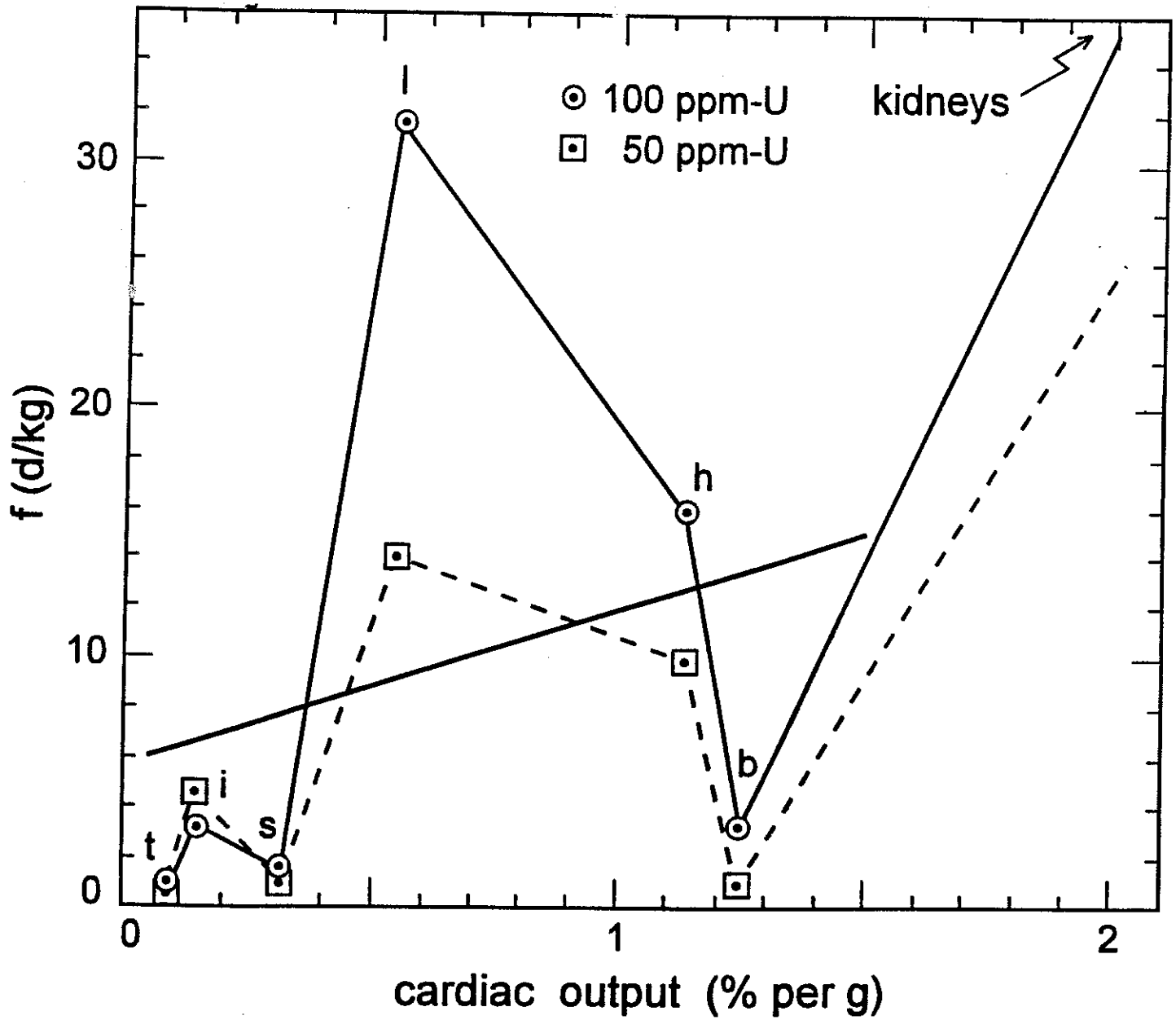
100 ppm-U
50 ppm-U
kidneys
l
h
b
i
s
t
f (d/kg)
cardiac output (% per g)
0
10
20
30
0
1
2

Fig. 6

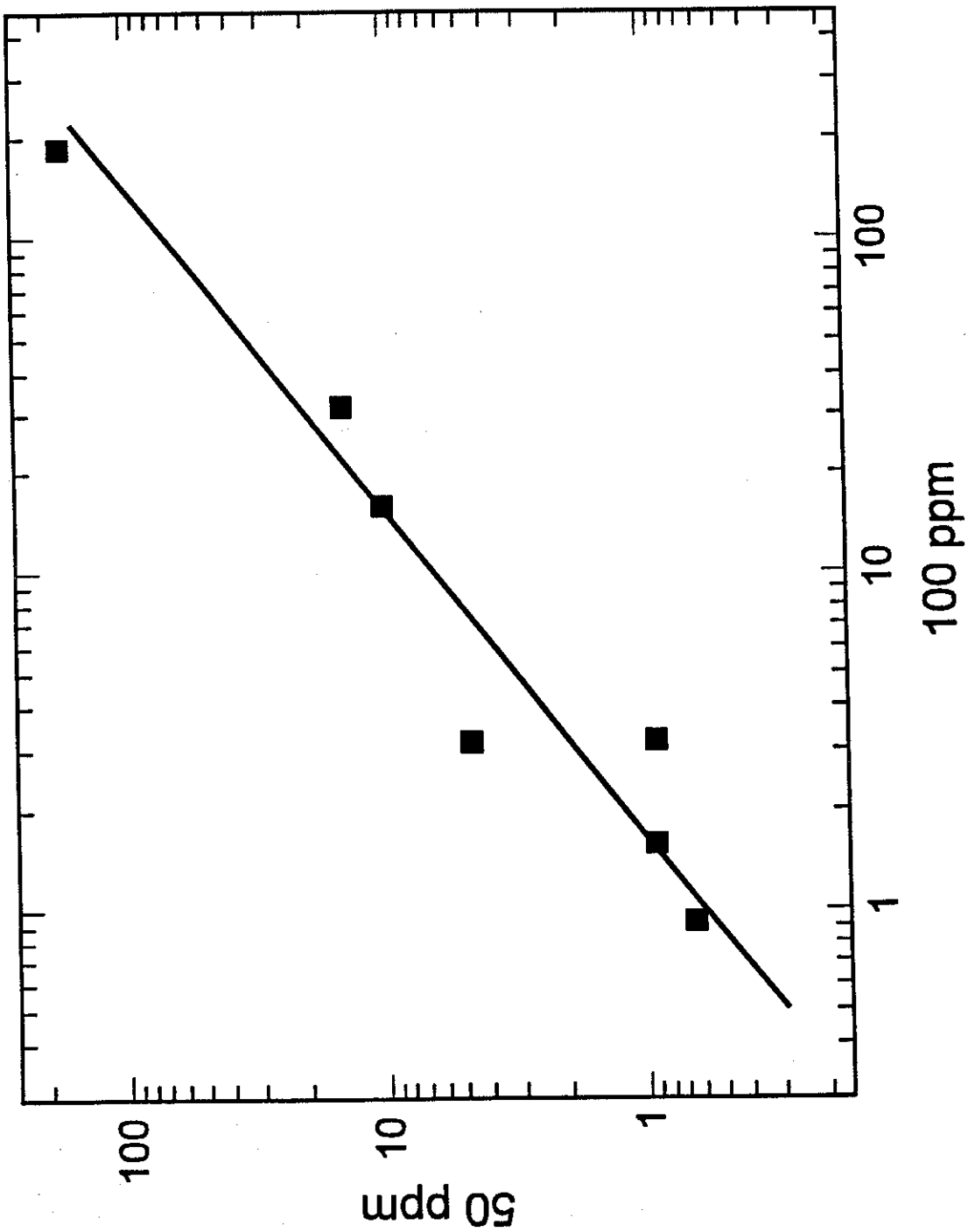


Fig. 7