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Original article

Pharmacokinetics of cadmium following intravenous and oral administration to non-lactating ewes

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Summary — In a preliminary study, ewes received daily oral cadmium chloride administrations and cadmium concentration was measured in blood and tissues. A pharmacokinetic analysis of cadmium disposition was then carried out in ewes administered cadmium chloride iv and, 21 months later, orally in the same ewes. Pharmacokinetic parameters were analysed using a 3-compartment open model. The systemic availability was 0.15–0.5%, the half-life of elimination was 100–150 d, the blood clearance was 0.12–0.16 l.kg⁻¹.d⁻¹ and the steady-state volume of distribution was 17–35 l/kg. Following iv administration cadmium was found in tissues about 2 years later.

cadmium / ewe / kinetics / bioavailability

Résumé — Pharmacocinétique du cadmium par voie intraveineuse et orale chez la brebis non lactante. Lors d'une première étude, du chlorure de cadmium a été administré à doses répétées par voie orale à des brebis et les concentrations sanguines et tissulaires en cadmium ont été mesurées. Puis l'étude de la pharmacocinétique du cadmium a été réalisée après injections intraveineuses de chlorure de cadmium à des brebis, suivies, 21 mois plus tard, d'administrations répétées de chlorure de cadmium par voie orale. Les paramètres pharmacocinétiques ont été calculés selon un modèle tricompartmental ouvert, en considérant simultanément l'ensemble des données. La biodisponibilité du cadmium est de l'ordre de 0,15 à 0,5%, le temps de demi-vie d'élimination de 100 à 150 j, la clairance sanguine de 0,12 à 0,16 l.kg⁻¹.d⁻¹ et le volume de distribution à l'équilibre de 17 à 35 l/kg. Les concentrations en cadmium mesurées dans les tissus montrent qu'une partie du cadmium administré par voie intraveineuse reste stockée dans les organes après un délai de 2 ans.

cadmium / brebis / cinétique / biodisponibilité

* Correspondence and reprints

INTRODUCTION

Cadmium is a widely distributed heavy metal in industrialized countries and is known for its cumulative properties in continental ecological cycling (Nriagu, 1980; Sharma, 1980). In animals, cadmium accumulates mostly in the liver and the kidney. In experimental animals, cadmium can cause a nephrotoxicosis in the same way as in human beings (Powell *et al*, 1964; Murakami *et al*, 1983; Nordberg, 1984). The purpose of studying cadmium pharmacokinetics in the ewe is to provide basic information on the systemic availability and persistence of this heavy metal in ovine tissues. This could lead to new methods to modulate this accumulation, thus reducing animal contributions of cadmium to the consumer diet, as Miller previously proposed (Miller *et al*, 1969). In a previous experiment, we documented the linearity of cadmium kinetics after *iv* administrations in ewes (Han *et al*, 1994). The purpose of the present experiments was to study the disposition of cadmium after multiple oral administrations of cadmium chloride in the same ewes.

MATERIALS AND METHODS

Animals

Seven Lacaune-Prealps crossbreed ewes of about 2 years of age at the beginning of the experiment were used. They came from the Brouessy farm (INRA, France). Throughout study, the mean weight was 56 kg and no diseases were detected.

The animals were kept in the sheepfold of the École nationale vétérinaire d'Alfort, France. They received 1 kg of granulated feed and 0.3 kg of hay daily in the morning. The granulated feed was composed of oats (47%), dehydrated lucern (30%), chopped straw (20%) and a mineral additive (3%). Water was given *ad libitum*. Cadmium, calcium, zinc, iron, magnesium, copper and selenium levels were measured in the drinking water,

hay and granulated feed. In the granulated feed, protein, phosphorus, manganese, lead and vitamin D levels were also determined.

Experimental design

In the first experiment, 3 ewes (No 0562, 0880, 9315) received daily oral cadmium chloride administrations at a dosage of 2 mg.kg⁻¹.d⁻¹ for 16 d and 0.3 mg.kg⁻¹.d⁻¹ for an additional 16 d at which time they were slaughtered.

In the second study, another 3 ewes (No 9090, 9091, 9501) received 3 *iv* administrations of cadmium at 3 different dosages (0.033, 0.1, 0.33 mg/kg). The order of the 3 administrations was assigned to each ewe according to a 3 x 3 latin square design and a washout period of 21 d was respected between each administration. At 641 d after the first *iv* administration, the same ewes received daily oral cadmium chloride: 2 mg.kg⁻¹.d⁻¹ for 21 d and 1 mg.kg⁻¹.d⁻¹ for 19 d.

Subsequently, the same ewes received cadmium acetate orally for 31 d at a dosage of 1 mg.kg⁻¹.d⁻¹, at which time they were slaughtered. Cadmium blood concentrations measured after acetate cadmium administrations were not used for pharmacokinetic analysis, but increased cadmium concentrations in tissues. One animal (No 9055) was not exposed to cadmium and was used as a control.

Administration of cadmium

For oral administration, cadmium was enclosed in a gelatin capsule and placed over the base of the tongue. The capsule was immediately swallowed.

In the second experiment, the ewes received *iv* administrations of cadmium solutions prepared with cadmium chloride (CdCl₂, Merck, Nogent-sur-Marne, France). The concentrations selected for the injection of 2–3 ml of solution were 0.66, 2 and 6.6 mg/ml for the dosages of 0.033, 0.1 and 0.33 mg/kg, respectively. To avoid hemolysis, the osmolarity of the solutions was made similar to that of serum by adding sodium chloride. The solutions were sterilized in autoclaves for 20 min. The *iv* injections were performed in the left jugular vein *via* a catheter (Intraflon 2/Vygon).

Sampling

Blood samples (2 ml) were collected from the right jugular vein into special heparinized tubes under vacuum (Ref 367735 Vacutainer tubes, Beckton Dickinson, Maylan, France, known not to interfere with the analysis of trace elements, metals or metalloids).

In the first experiment, blood was collected twice a day: in the morning before cadmium administration and 6 h after cadmium administration. On d 15 and 30, blood was collected at 0, 30, 45, 60, 75, 90, 105, 120, 150, 180, 240 and 360 min after cadmium administration.

In the second study, after each iv administration, the blood collections extended over a 21-d period. Samples were taken at 24, 23.5, 23, 22, 21, 20, 18 and 16 h and 5 min before the first cadmium administration. After iv administrations samples were collected at 2, 5, 8, 10, 20, 30 and 60 min and 2, 3, 4, 6, 8 and 10 h and at 1, 2, 3, 5, 7, 10, 15 and 20 d. Three additional samples were taken at d 187, 208 and 237 after the first iv administration of cadmium. During the period of oral administration, blood samples were taken 3 times per week from day 636 (4 d before the first oral cadmium chloride administration on d 641), the morning before cadmium administration and every morning before cadmium administration from d 671 to 680.

The blood was stored at 4°C until analysis. Ewes were slaughtered 1 d after the last oral cadmium administration and liver, kidney, muscle, abomasum and small intestine samples were collected and frozen at -20°C until analysed for their cadmium content.

Cadmium measurement

Blood cadmium concentrations were determined by electrothermal atomic absorption spectrophotometry with a spectrophotometer 1100B Perkin Elmer AGA 700 (Hoenig and De Kersabiec, 1990), using a technique of direct measurement after dilution of samples 1:10 in 0.05 N nitric acid in the presence of triton, according to the technique recommended by Lauwerys *et al* (1990) (decomposition temperature: 550°C; atomization temperature: 1 450°C). The linearity of the calibration curve extended to 40 µg/l blood. The limit of detection was estimated to be 0.3 µg/l, the limit

of quantification was estimated to be 0.8 µg/l, and the intraday coefficient of variation was 25% at 0.8 µg/l, 15% at 1 µg/l, 8% at 2 µg/l and 4% at 5 µg/l.

Tissue samples were dry-ashed at 450°C to obtain white ashes. After destruction, the samples were dissolved in 5 ml (5 N) nitric acid and diluted with distilled water to final volume of 50 or 100 ml. The cadmium concentration was determined by electrothermal atomic absorption spectrophotometry (decomposition temperature: 300°C; atomization temperature: 1 400°C). After appropriate dilution, concentrations were read using a calibration curve. Method accuracy was controlled with certified material (bovine liver 1577b of NIST (US Department of Commerce, National Institute of Standards and Technology, Gaithersburg MD, USA), pig kidney 0675 of BCR (Commission of the European Communities, Community Bureau of Reference, Brussels, Belgium). Detection limit was 4 µg/kg dry matter, quantification limit was 15 µg/kg dry matter and the intraday coefficient of variation was 4% at 100 µg/kg dry matter and 2% at 200 µg/kg dry matter.

Pharmacokinetic analyses

Pharmacokinetic analyses were computed using a program of nonlinear regression adapted from Multi (Yamaoka *et al*, 1981). The general poly-exponential equation was fitted to the iv data:

$$C(t) = \sum_{i=1}^n Y_i \exp(-\lambda_i t) \quad [1]$$

In this equation (corresponding to a iv single administration), C is the cadmium concentration at time t , Y_i is the coefficient of the i th exponential term. Initial estimates were obtained using linear regression methods on the data following the third iv dose. These estimates were refined by nonlinear regression. The number of exponents (2 or 3) needed for each data set was determined by application of Akaike's information criterion (Yamaoka *et al*, 1978).

Cadmium blood concentrations corresponding to the multiple cadmium chloride oral and iv administrations were calculated in each ewe using the principle of superposition.

The values of the basic kinetic parameters were determined from the data of the second experiment. The volume of the central compartment (V_c) was obtained using the equation:

$$V_c = \frac{\text{Dose}}{\sum_{i=1}^n Y_i} \quad [2]$$

The steady-state volume of distribution (V_{ss}) was obtained using the equation:

$$V_{ss} = V_c \left(1 + \frac{k_{12}}{k_{21}} + \frac{k_{13}}{k_{31}} \right) \quad [3]$$

where k_{12} , k_{21} , k_{13} , k_{31} represent the first-order distribution rate constants between compartment 1 and compartments 2 and 3 respectively.

The mean residence-time after iv administration (MRT_{iv}) was calculated using the equation:

$$MRT = \frac{\sum_{i=1}^n \frac{Y_i}{\lambda_i^2}}{\sum_{i=1}^n \frac{Y_i}{\lambda_i}} \quad [4]$$

The blood clearance (Cl) was calculated from the equation:

$$Cl = \frac{\text{Dose}}{AUC_{iv}} \quad [5]$$

In equation [5], AUC_{iv} is the area under the blood concentration *versus* time curve after iv administration calculated by integrating equation [1].

The systemic availability (F) and the rate constant of absorption (K_a) were obtained by the method of semisimultaneous administrations (Wijnand, 1992). Estimates of F and K_a were found by fitting a tricompartmental multiple dosage model function to the data.

RESULTS

Diet composition

Diet composition and total mineral intake are shown in table I. Cadmium intake was less than $2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ and calcium and magnesium intakes were 15 and 2 g/d, respectively, throughout the experiment.

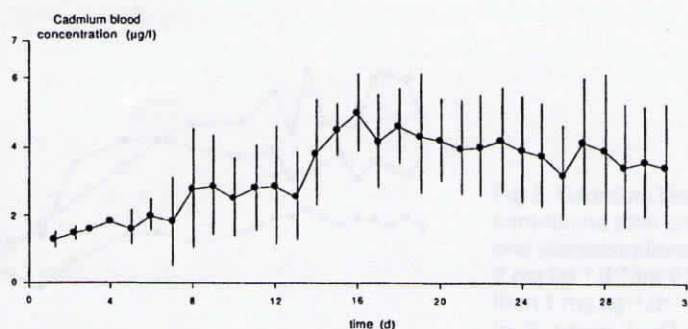
First study

Control blood cadmium concentrations were less than the limit of quantification of the

Table I. Average composition of the diet and total mineral intake per day during the study.

Parameter	Hay	Granulated food	Water	Total intake
Protein (g/kg)		118		
Phosphorus (g/kg)		4.9		
Calcium (g/kg)	6.9	12.9	0.1	15.1 g
Magnesium (g/kg)	1.1	1.6	0.0052	1.9 g
Iron (mg/kg)	156	236	0.016	283 mg
Copper (mg/kg)	3.8	6.8	0.011	8.0 mg
Manganese (mg/kg)		39		
Zinc (mg/kg)	18	51	0.098	56.5 mg
Selenium (mg/kg)	0.015	0.18	NQ	0.18 mg
Lead (mg/kg)		0.35		
Cadmium (mg/kg)	0.1	0.055	0.0084	0.0976 mg
Vitamin D (UI/kg)		700		

Fig 1. Mean cadmium blood concentrations in 3 ewes after oral cadmium administrations of first $2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for 16 d and then $0.3 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for 16 d.



analytical technique ($0.8 \mu\text{g/l}$). The mean blood concentration–time profile of cadmium after oral administration of 2 mg/kg cadmium for 16 d followed by 0.3 mg/kg for 16 d to 3 ewes is shown in figure 1. Cadmium blood concentrations increased progressively during the first 16 d of treatment to reach a concentration of $5 \pm 1 \mu\text{g/l}$ and then decreased very slowly during the 16 following days.

Second study

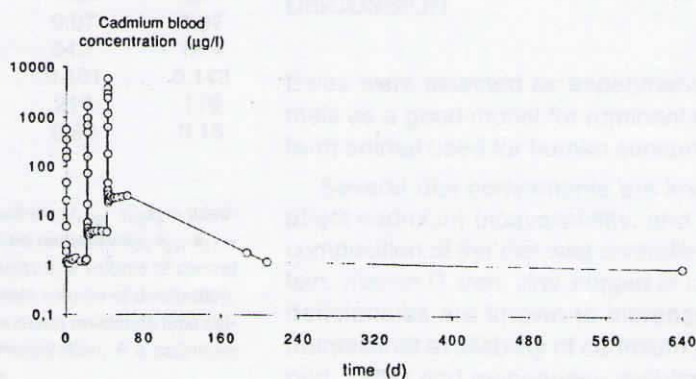
The blood cadmium concentrations in the control ewe were below the limit of quantification during the entire study.

The mean values of blood concentrations before cadmium iv administrations were also below the limit of quantification.

These concentrations rose immediately after iv cadmium administration up to a maximum of 450 to $5800 \mu\text{g/l}$ depending on the dose (fig 2). The blood concentrations then decreased very rapidly for 4–6 h and more slowly thereafter. The blood concentration–time profile after the repeated oral administrations of cadmium chloride is shown in figure 3 for each ewe. Blood cadmium concentrations rose during the first 21 d of administration to a plateau concentration during the following 19 d from $4.1 \pm 0.3 \mu\text{g/l}$ to $7.8 \pm 0.8 \mu\text{g/l}$ depending on the ewe).

According to Akaike's information criterion, the disposition of cadmium in all ewes was better fitted by a triexponential equation corresponding to a 3-compartment open model. The individual pharmacokinetic parameters are listed in table II. The cadmium chloride systemic availability ranged

Fig 2. Cadmium blood concentrations after cadmium iv administrations of 0.033 , 0.1 , 0.33 mg/kg at d 21, 42 and 63, respectively in ewe 9090.



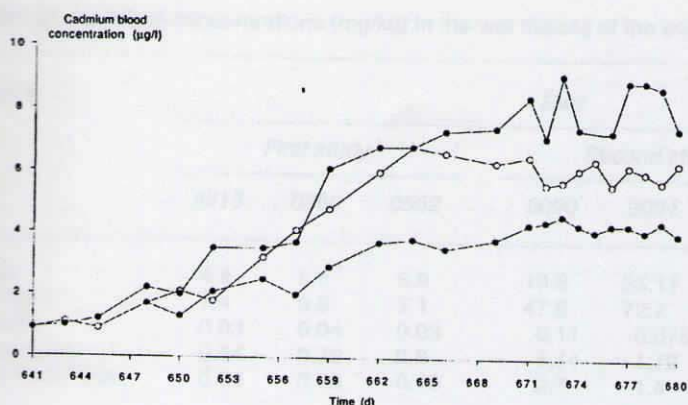


Fig 3. Cadmium blood concentrations after cadmium oral administrations of first $2 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for 21 d and then $1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ for 19 d in 3 ewes (—○— ewe 9090, —●— ewe 9091, —■— ewe 9501).

from 0.15 to 0.5%. The half-life of elimination was 101–151.5 d, the mean residence time following iv administration was 119–216 d and blood clearance was $0.122\text{--}0.161 \text{ l}\cdot\text{d}^{-1}\cdot\text{kg}^{-1}$.

Table II. Pharmacokinetic parameters describing cadmium disposition in 3 ewes after oral and iv administration of cadmium.

Parameter	Ewe		
	9090	9091	9501
$t_{1/2\pi}$ (min)	5	4	6
$t_{1/2\alpha}$ (min)	21	20	1 036
$t_{1/2\beta}$ (d)	126.5	151.5	101
k_{21} (d^{-1})	68	73	15
k_{31} (d^{-1})	0.32	0.32	0.035
$t_{1/2k_a}$ (min)	255	149	35.7
V_c (l/kg)	0.05	0.07	0.07
V_{ss} (l/kg)	21.9	34.7	16.9
Cl ($\text{l}\cdot\text{d}^{-1}\cdot\text{kg}^{-1}$)	0.122	0.161	0.143
MRT_{iv} (d)	179	216	119
F (%)	0.25	0.50	0.15

$t_{1/2\pi}$ and $t_{1/2\alpha}$ = distribution half-life; $t_{1/2\beta}$, $t_{1/2k_a}$ = elimination and absorption half-lives respectively; k_{21} , k_{31} = first-order-distribution constants; V_c = volume of central compartment; V_{ss} = steady-state volume of distribution; Cl = blood clearance; MRT_{iv} = mean residence time calculated after a single iv administration; F = cadmium chloride systemic availability.

Cadmium concentration in the tissues

Cadmium concentrations in the control ewe tissues were low (table III). The highest concentrations were found in the liver and kidneys of treated ewes: 5.9 ± 1.3 and $21.9 \pm 1.8 \text{ mg/kg}$ in the livers of the first and second experiment ewes, respectively; $6.5 \pm 4 \text{ mg/kg}$ and $56.7 \pm 13.9 \text{ mg/kg}$ in the kidneys of the first and second study ewes, respectively. The small intestine and abomasum cadmium concentrations were higher in treated than in control ewes. The cadmium muscle concentrations were low in all ewes, close to the control ewe values in the first experiment ($0.03\text{--}0.04 \text{ mg/kg}$), and slightly higher in the second experiment ($0.07\text{--}0.11 \text{ mg/kg}$).

DISCUSSION

Ewes were selected as experimental animals as a good model for ruminants and a farm animal used for human consumption.

Several diet components are known to affect cadmium bioavailability, and so the composition of the diet was controlled. Protein, vitamin D, iron, zinc, copper or calcium deficiencies are known to increase gastrointestinal availability of cadmium (Hietaanen, 1981) and manganese supplementa-

Table III. Cadmium concentrations (mg/kg) in the wet tissues of the ewes.

Tissue	Ewe						Control 9055
	First study			Second study			
	9315	0880	0562	9090	9091	9501	
Liver	4.4	6.5	6.9	19.8	23.11	22.7	0.08
Kidney	7.4	9.9	2.1	47.8	72.7	49.6	0.38
Muscle	0.03	0.04	0.03	0.11	0.075	0.09	0.03
Abomasum	0.64	0.76	0.6	4.14	1.79	0.68	0.021
Small intestine	0.80	0.73	0.49	2.7	1.4	1.2	0.025

First study: after cadmium oral administrations of 2 mg.kg⁻¹.d⁻¹ for 16 d and then 0.3 mg.kg⁻¹.d⁻¹ for an additional 16 d. Second study: after cadmium iv administration of 0.033, 0.1, 0.33 mg/kg 21 months before and cadmium oral administration of 2 mg.kg⁻¹.d⁻¹ for 21 d and then 1 mg.kg⁻¹.d⁻¹ for 50 d.

tion to decrease cadmium availability (Sarhan, 1986). The diet provided a good balance of magnesium, selenium, zinc, iron, copper, vitamin D and proteins and was calcium-supplemented (15 g/d/ewe instead of 5 g/d/ewe). Such high calcium supplementation might have decreased cadmium gastrointestinal availability.

The ewes came from a noncontaminated area and had received feedstuff with a low cadmium content (2 µg.kg⁻¹.d⁻¹) compared to the oral cadmium dosage (0.3–2 mg.kg⁻¹.d⁻¹). Control cadmium blood concentrations were low, likely much lower than our quantification level. Indeed, during the first experiment, repeated oral doses of 0.3 mg.kg⁻¹.d⁻¹ were not enough to maintain a blood concentration of 5 µg/l, which was obtained by daily administrations of cadmium at 2 mg/kg. In control conditions, the cadmium intake was only 2 µg.kg⁻¹.d⁻¹, *ie* 150 times lower. Assuming that cadmium kinetics are linear, the control blood concentrations may have been 30–40 ng/l, *ie* 25 times lower than our level of quantification.

The cadmium oral dosages (0.3–2 mg.kg⁻¹.d⁻¹) were equivalent to a concen-

tration of approximately 20–120 mg/kg cadmium in granulated feed. Although the cadmium dosages used provided a higher cadmium content than the usual levels in the diet of sheep, cadmium in leaves of plants grown on soil supplemented with 40 mg cadmium/kg ranged from 18.5 to 264.7 mg/kg (Van Bruwaene *et al*, 1984). In some industrial and mining areas, growing plants contained from 5 to 80 mg cadmium/kg on dry weight, and winter forage hay contained up to 15 mg/kg (Leita *et al*, 1991). Therefore, our dosages and repeated oral administrations simulated cadmium exposure to sheep in contaminated areas.

Cadmium is slowly eliminated (Miller, 1973; Van Bruwaene *et al* 1982; Robards and Worsfold, 1991), which means that the sampling periods and wash-out intervals are too long to determine all the kinetic parameters by classical methods. The semisimultaneous or sequential method (Wijnand, 1992) assume cadmium linearity and allow the estimation of all the kinetic parameters, even *F*, in less time than the classical methods.

In the present experiment, the gastrointestinal availability of CdCl₂ was found to

be low (0.15–0.5%). In dogs, a pharmacokinetic method gave a percentage of daily absorbed dose of 0.15–0.6% (Matsuno *et al*, 1991). Other approaches gave similar results with total body cadmium retention of 0.3–0.4% in goats (Miller *et al*, 1969), 0.09% in steers (Johnson *et al*, 1981), and 0.035–0.75% in dairy cows (Neathery *et al*, 1974; Van Bruwaene *et al*, 1982). The percentage of the cadmium dose absorbed in the *in situ* rat intestine loop was 0.09–1.8% (Goon and Klaassen, 1989). The pharmacokinetic approach is easier to carry out and gives similar results to the approaches requiring animal slaughter.

The half-life of cadmium absorption was 36–255 min. Although rather fast, this result agrees with another study, where an intestinal loop was infused *in situ* with CdCl₂ in rats and 30 min after incubation, cadmium was detected in liver (Ohta and Cherian, 1991).

In this experiment, the volume of the central compartment was approximately 0.06 l/kg, close to the 0.05 l/kg obtained in the rat (Frazier, 1980). According to Nordberg and Nordberg (1987) and our previous experiments (Han *et al*, 1994), cadmium in blood cells accumulates at much higher concentrations than in plasma. The central compartment, may therefore represent the blood cells, because the total blood volume in sheep is 0.066 l/kg (Swenson, 1977).

The steady-state volume of distribution of cadmium was large (17–35 l/kg), reflecting the slow return from the deep compartments to blood because cadmium is concentrated in certain tissues of these ewes. As previously described (Neathery *et al*, 1974), the highest concentrations of cadmium are found in the kidneys and liver; cadmium levels are far lower in the other tissues. In goats, 0.17 and 0.08% of the cadmium total dose given orally is retained, respectively, in the liver and the kidneys (Miller *et al*, 1969). Our preliminary study results are very similar (about 0.19% of the

total dose in the liver and 0.08% in the kidneys). About 75–85% of the body cadmium is usually found in the liver and the kidneys of ruminants (Miller *et al*, 1969; Johnson *et al*, 1981). Because the liver and kidneys weighed 700 and 270 g respectively, and 80% of the body cadmium is usually found in liver and kidneys, about 6 (ewe 9315) to 9 (ewe 0880) mg cadmium was retained in the whole body of the first study ewes. The percentage of cadmium retained probably reached 0.3–0.4% of the dose. These results are similar to the cadmium availabilities calculated with a pharmacokinetic method in the second study (0.15–0.5%). The cadmium amount absorbed in the second experiment by the ewes, calculated from the oral dose administered and the availability estimated for each ewe, ranged from 11 to 28 mg. The cadmium amount actually retained in the body of these ewes was higher (26.8–35.8 mg). This suggests that a large fraction of the iv dose given 2 years before was still stored in the tissues. The liver and the kidneys can store large amounts of cadmium for a very long time.

Table IV. Exposure time (d) necessary to reach cadmium blood concentration of 0.8 µg/l estimated with the kinetic parameters issued from the second study.

Oral dosage (mg.kg ⁻¹ .d ⁻¹)	Ewe		
	9090	9091	9501
0.03	Never	420	Never
0.1	85	62	180
0.2	36	27	40
0.3	22	16	12
1	4	2	< 1
2	< 1	< 1	< 1

Never: the oral dosage is too low to reach cadmium blood concentration of 0.8 µg/l.

Cadmium clearance was low ($0.12-0.16 \text{ l.kg}^{-1}.\text{d}^{-1}$) and reached approximately $0.13-0.17\%$ of the cardiac output. This low blood clearance reflects the inability to eliminate cadmium accumulated in blood cells since only the low concentrations of cadmium in plasma are available for elimination.

The mean residence time following iv administration was 119–216 d. The half-life of elimination was 100–150 d. This long elimination half-life is a result of the large volume of distribution and slow elimination of cadmium. In dogs, the half-life of elimination based on a two-compartment open model was 100–700 d (Matsuno *et al*, 1991). Nevertheless, our elimination half-life is rapid compared to biological half-lives of 30 years in human (Kjellström cited in Robards and Worsfold, 1991) or compared to the half-life in renal tissue of 10–33 years (Tsuschiya and Kjellström cited in Task Group, 1973; Bernard cited in Robards and Worsfold, 1991). Our parameter, calculated from blood concentration data, reflects the overall elimination process and does not reflect the half-life of a given tissue such as the kidney. Blood half-life values may reflect more recent exposures than kidney values (Task Group, 1973).

According to our kinetic parameters, cadmium blood concentrations in ewes exposed to a mean pollution consumption of $0.3 \text{ mg.kg}^{-1}.\text{d}^{-1}$ would increase for 1.5–2 years (5 times the half-life of elimination), then reach a plateau concentration of $6.2 \pm 2.9 \mu\text{g/l}$. The blood concentration would be quantifiable after $17 \pm 5 \text{ d}$ of exposure. When the exposure to cadmium pollution stops, blood concentrations would remain quantifiable for $360 \pm 180 \text{ d}$ and detectable for $540 \pm 215 \text{ d}$. The exposure time necessary to reach quantifiable concentrations in blood for different pollution levels are shown in table IV. Blood values may reflect long exposure to low pollution levels ($0.2 \text{ mg.kg}^{-1}.\text{d}^{-1}$ for more than a month) or high pollution levels. With our analytical method,

blood concentrations could not detect pollution levels exposure below $30 \mu\text{g.kg}^{-1}.\text{d}^{-1}$.

Our experiment is the first to calculate pharmacokinetic parameters for cadmium after oral administration to non-lactating ewes. We found low cadmium availability, a large volume of distribution and accumulation of cadmium in certain tissues (liver and kidney) which explains the low elimination rate. Future studies could result in methods to decrease cadmium availability and tissue accumulation to reduce the contribution of cadmium in animal tissues to the consumer diet.

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