Chemosphere 171 (2017) 564–570

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Toxicokinetics of chlordecone in goats: Implications for risk management in French West Indies

Agnès Fournier [a, *], Cyril Feidt [a], Marie-Laure Lastel [a], Harry Archimede [b], Jean-Pierre Thome [c], Maurice Mahieu [b], Guido Rychen [a]

[a] Université de Lorraine, INRA, USC 340, UR AFPA, 2 avenue de la Forêt de Haye, TSA 40602, 54518, Vandœuvre-lès-Nancy Cedex, France
[b] INRA, URZ, UR 143, Domaine Duclos, F-97170, Petit-Bourg, Guadeloupe, France
[c] Université de Liège, LEAE-CART, Allée du 6 Août, 11, 4000, Liège, Belgium

HIGHLIGHTS

- Chlordecone is almost completely absorbed after oral administration.
- The half-life of chlordecone is 20 days in dry goat.
- A strategy of decontamination is possible due to the short half-life.

ARTICLE INFO

Article history:
Received 24 June 2016
Received in revised form
8 December 2016
Accepted 11 December 2016
Available online 13 December 2016

Handling Editor: A. Gies

Keywords:
Goat
CLD
Half-life
Serum
Absorption

ABSTRACT

The former use of chlordecone (CLD) in the French West Indies has resulted in long-term pollution of soils. CLD is known to be potentially transferred towards animal products of animals reared outdoors, mainly through accidental soil ingestion. Several studies indicate that soil bound CLD is bioavailable when administered to farm animals. Currently there is a need to quantify the level of CLD absorption and its toxicokinetic characteristics in the ruminant and particularly in the goat. These are considered as important farm species in the French West Indies. The objective of this study was to evaluate the absorption rate and the half-life of CLD in the non-lactating goat. The goats were administered either intravenously (i.v., n = 6) or orally (p.o., n = 6) one dose (1 mg kg^{-1} body weight) of CLD. Blood samples were collected at defined times up to 160 days post-dosing. CLD was analyzed in serum by high-resolution gas chromatography. A comparison of the area under the serum concentration-time curves (AUC) showed that the i.v. route is equivalent to the oral route. Thus, CLD is considered almost completely absorbed after p.o. administration, as shown by the mean absolute bioavailability. The comparison between the pharmacokinetic profiles of CLD following oral and intravenous dose showed a difference during the first 14 days and a similar kinetic after this period. The half-life of CLD in serum was close to 20 days. These results highlight a possible strategy of decontamination due to the short half-life of CLD, obtained in dry goats that did not excrete fat matter.

1. Introduction

Chlordecone (CLD) was extensively used in the French West Indies to control the banana black weevil (*Cosmopolites sordidus*), officially from 1972 to 1993 (Le Déaut and Procaccia, 2009). The use of this pesticide was banned in 1990 (Arrêté du 3 juillet 1990) and used by exemption until 1993 in the French West Indies. This organochlorine insecticide is lipophilic, persistent with a log Kow of 4.5 or 5.4 according to Howard et al. (1991) or Hansch et al. (1995). It is qualified as carcinogenic in mice and rats (IARC, 1979) and suspected to increase the risk of prostate cancer in human (Multigner et al., 2010) and to impair cognitive and motor development of infants after an exposure during pregnancy or via breast feeding (Dallaire et al., 2012; Boucher et al., 2013; Costet et al., 2015). CLD was included as a Persistent Organic Pollutant

* Corresponding author.
E-mail address: agnes.fournier@univ-lorraine.fr (A. Fournier).

http://dx.doi.org/10.1016/j.chemosphere.2016.12.054
0045-6535/

(POP) under the Stockholm Convention in 2009. CLD is persistent in the soil and as a result more than 8% of agricultural soils in Martinique and Guadeloupe are considered as highly contaminated with concentrations above 1 mg kg^{-1} of dry matter (DM) (Le Déaut and Procaccia, 2009). These high concentrations of CLD in soil can result in a contamination of farm animals and especially of ruminants. Indeed in Guadeloupe, ruminants are usually tethered, at roadsides, at beaches, in meadows or on old banana areas. Such practices are used by 60% of goat breeders (Alexandre et al., 2008; Gunia et al., 2010) and 90% of cattle breeders (Naves, 2003; Galan et al., 2008). In this case, ruminants are exposed to CLD present in the grazed soil of old banana plantations. Accordingly in 2011 and 2012, one third of cattle slaughtered in a Guadeloupe slaughterhouse (le Moule) and originated from polluted areas was found to be contaminated on the basis of peri-renal fat analysis. Nearly 10% of carcasses exceeded the Maximum Residue Limit (MRL) of 100 μg CLD kg^{-1} fat matter fixed by the European Union (Commission regulation) (Personal communication, French ministry of agriculture, Direction Générale de l'Alimentation (DGAL)). In Guadeloupe, such contamination is of concern for cattle but also for goats reared for their meat. Additionally this goat production sector is not fully organized and still mainly informal, with small familial units of production (Alexandre et al., 2008) and then remain uncontrolled for sanitary or contamination concerns.

To evaluate the risk of exposure of the local population through the consumption of the contaminated food, while protecting the local livestock, it is necessary to better understand the different steps of CLD transfer in the animal. Some information is already available in the literature, particularly on the level of soil ingestion in ruminants reared outdoor (Jurjanz et al., 2012) and on the bioavailability of the soil bound CLD in exposed farm animals after exposure to contaminated soil. Indeed, Jurjanz et al. (2014) demonstrated that CLD was not retained by soils of French West Indies (andosol or nitisol) and was efficiently extracted by the digestive tract of lambs showing that ingestion of contaminated soil is a real potential source of exposure for the ruminants. Nevertheless, to evaluate the risk of transfer of CLD in tissues of ruminant, there is a real need to quantify the absorption rate of CLD and its elimination by ruminants, particularly the goat, because it is considered as an important farm species in the French West Indies. These different parameters (absorption, bioavailability, metabolism and elimination rate) are key elements that determine the accumulation potential of the molecule in animal products. One study concerning CLD in the ruminant (Smith and Arant, 1967) provides information on the transfer of the CLD in the milk of dairy cows, but no studies were found describing the absorption and the elimination from the blood. These toxicokinetic parameters have already been studied in rodents (Egle et al., 1978; Richter et al., 1979; Wang et al., 1981), piglets (Soine et al., 1983) or human (Adir et al., 1978; Cohn et al., 1978), but since the digestive function of ruminant (a polygastric animal) is much more developed than that of monogastric animal, additional studies need to be carry out in these animals.

The aim of this study was to determine the toxicokinetic parameter assessing the internal exposure to CLD in goats. Adult female non lactating goats were exposed to a dose of CLD either by oral or intravenous administration. CLD concentrations in serum were monitored to obtain the pharmacokinetic parameters (particularly absorption and elimination rate) of CLD in goats. Knowing this information is essential for the development of a risk management tool like a mathematical model transfer (for example like developed for other POP in laying hens, Fournier et al., 2015), which intends to represent the CLD transfer from the soil to the ruminants tissues.

2. Material and methods

2.1. Goats and management

The animal protocol was in accordance with the general directive N°2010/63/UE on animal care. Twelve Creole multiparous goats (*Capra hircus*, 33.5 ± 5.3 kg body weight (BW)) from the herd of the INRA experimental station of le Moule (Guadeloupe) were placed in individual barns. The selected adult goats were non-lactating and non-pregnant, in order to have animals with a comparable and stable physiological status. Prior to the experiment, goats were allowed an 8-day adaptation period, during which the daily feed ration was established to meet requirements for maintenance of goats (INRA, 2007). Each day the goats received a ration of commercial feed and meadow hay, water and salt *ad libitum* with individual BW recorded weekly. No signs of physical stress or adverse effect on the body weight, physiological status and behavior were observed after intravenous (i.v.) or *per os* (p.o.) administration of CLD at 1 mg kg^{-1} BW, but two goats died at 25 and 45 days respectively, without any link with CLD exposure (i.v. administration group).

2.2. Experimental procedure

The experiment consisted of a single exposure of goats to the CLD (1 mg kg^{-1} BW) (Kepone 99.9%, Sigma Aldrich) administered by i.v. ($n = 6$) or p.o. ($n = 6$) at time $t = 0$ and blood collected at set intervals for 24 weeks after the dosing. This high dose of CLD was chosen to be able to follow the decrease of the CLD concentrations.

CLD was dissolved in cremophor (polyethoxylated castor oil) and administrated by i.v. injection in the jugular vein or mixed with commercial feed and given p.o. in a dough ball. At 0, 3, 6, 15, 30, 45 min 1, 2, 4, 8, 12 h, 1, 3, 7, 14, 21, 28, 50, 70, 101, 128, 163 days for the i.v. treatment and at 0, 2, 4, 6, 8, 12, 24, 36, 48, 60 h, 3, 4, 5, 7, 11, 14, 21, 28, 50, 70, 101, 128, 163 days for the p.o. treatment, after CLD administration, blood samples (2 × 10 ml) were taken using an intravenous external catheter (BD Insyte-WTM, 16GA 1.77 IN, 1.7 × 45 mm, 205 ml min^{-1}, ref 381357) for the first hours and then by venepucture (BD vacutainer®, ref 368815), allowed to clot for 2 h and stored during 24 h at 4 °C before centrifugation at 1500*g* for 10 min to get serum samples which were stored at −20 °C until analysis.

2.3. CLD analysis

Quantification of CLD in serum was performed by the Center for Analytical and Research Technology at Liege University (CART, Belgium). CLD was analyzed in serum according to the methods previously described by Debier et al. (2003) and Multigner et al. (2010) with slight modifications. Briefly, serum samples (2 ml) were thawed and weighed. Proteins were denatured by adding 100 μl triethylamine and 5 ml formic acid (Sigma-Aldrich chemie Gmbh, Steinheim, Germany). The 5b-monohydrochlordecone is a good candidate as a surrogate internal standard according to its behavior similar to that of CLD during the several steps of the analysis. However, it is well known that there could be traces of 5b-monohydrochlordecone in soils (Cabidoche et al., 2009; Orndorff and Colwell, 1980) and that cattle, ewe and goat could ingest this compound with CLD if they ingest contaminated soils during grazing. However, according to the results obtained in previous studies for CLD analysis in goat, lamb and ewe serum (Jurjanz et al., 2014; Lastel et al., 2016; Lerch et al., 2016) which had the opportunity to ingest CLD and eventually 5b-monohydro-CLD during their grazing in meadows which were "naturally" contaminated by CLD in Guadeloupe and Martinique there was no evidence that

there was 5b-monohydrochlordecone in the serum of these animals. A peak, in ^{63}Ni ECD analysis, which has a retention time similar to the 5b monohydrochlordecone, can be observed only when there was very high concentrations of CLD (about 200 ng g^{-1} serum). In this case, the ratio between 5b-mono-hydro-CLD and CLD concentrations was 0.032%. Then, such a supposed "5b-monohydrochlordecone" concentration is below the LOQ (i.e. 0.06 ng g^{-1} serum). Moreover, for lower concentration in CLD (<10 ng g^{-1} serum), the "5b-monohydrochlordecone" signal is in the background noise.

Then, 50 µl of 5b-monohydrochlordecone (100 pg $µl^{-1}$ in acetone; Dr. Ehrenstorfer®, Augsburg, Germany) were added as a surrogate internal standard. The mixture was subjected to solid-phase extraction in 6 ml (1 g) Supelco Supelclean™ Envi-C18 SPE Tubes (Supelco, Bellefonte, PA, USA). Samples were added and the column was rinsed with 2 ml of distilled water and dried for 20 min under a 200 mbar vacuum. CLD was eluted by means of 5 ml diethylether/n-hexane (15/85, v/v) which were collected in another tube. The solvent was evaporated under a gentle stream of nitrogen to a final volume of 50 µl. Then 3 ml of n-hexane were added to extract corresponding to elution. These samples were subjected to acidic purification by using 98% w/v sulfuric acid according to the method described by Debier et al. (2003). The organic layer contained CLD and 5-b-monohydrochlordecone. 5 µl of nonane were added to this organic layer that was then evaporated, leaving only the nonane fraction. Then, 45 µl of n-hexane and 50 µl of an hexanic solution of PCB209 (100 µg ml^{-1}) used as a volume internal standard were added to the extracts. The purified extracts were analyzed for CLD by high-resolution gas chromatography (HRGC) using a Thermo Quest Trace 2000 gas chromatograph equipped with a^{63}Ni ECD detector (Thermo Quest, Milan, Italy) and an autosampler for liquids (Thermo Quest AS 2000). The analytical and quantification parameters were described elsewhere for CLD analysis (Multigner et al., 2010). For each series of ten experimental samples, there were a procedural blank, a matrix blank and a quality control (QC) sample. The matrix blank was goat serum (Sigma Aldrich chemie Gmbh, Steinheim, Germany) and the QC was goat serum spiked with CLD (Dr. Ehrenstorfer®, Augsburg, Germany) at a nominal concentration of 2.5 µg kg^{-1} wet weight. The CLD concentrations in each sample and in the QC were corrected for initial sample weight, and for the percentage recovery of the surrogate 5b-monohydrochlordecone as an estimation of CLD recovery. Recovery rates were always between 60 and 140% according to the requirement of SANCO (2014). The CLD limit of detection (LOD) was 0.02 µg kg^{-1} wet weight, and the limit of quantification (LOQ) was 0.06 µg kg^{-1} wet weight.

2.4. Calculations and statistical analysis

CLD concentration vs. time curves in goats was individually analyzed using the PROC NLIN procedure of the Statistical Analysis Systems software package (SAS, version 9.3, SAS Institute, Cary, NC). Following the results of the i.v. administration, the pharmacokinetic model applied to the data was a one-compartmental open model in all the animals (Eq. (1)). Effectively, CLD seems to be rapidly distributed in the organism due to the association of CLD with high-density lipoproteins and with specific liver proteins (Soine at al., 1984a,b). This short phase of distribution can be hardly distinguished and the instability of the concentrations data observed for the first sampling times did not allow to obtain this distribution slope. Eq. (1):

$$C(t) = Ae^{-kt} \quad (1)$$

where C(t) (ng g^{-1}) represents CLD serum concentration at time t, A ((ng g^{-1}) is the concentration extrapolated to time 0 and k (d^{-1}) is the elimination slope and represents the elimination constant. The toxicokinetic parameters of CLD in the non-lactating goats were calculated using this model. Area under the serum curve from zero to infinity ($AUC_{0\rightarrow\infty}$) was calculated by the linear trapezoidal method with extrapolation to infinity. The extrapolated area was estimated by Eq. (2):

$$AUC_{last\rightarrow\infty} = C_{last}/k \quad (2)$$

In which C_{last} is the last measured concentration.

Serum CLD elimination half-life was calculated by Eq. (3):

$$T1/2 = Ln(2)/k \quad (3)$$

Total body clearance (Cl_{tot}) was determined by Eq. (4):

$$Cl_{tot} = Dose/AUC_{0\rightarrow\infty} \quad (4)$$

The apparent volume of the distribution (V_z) was calculated by Eq. (5):

$$V_z = Cl_{tot}/k \quad (5)$$

CLD serum concentration curves after p.o. administration were analyzed following the same procedure as used for i.v. analysis.

Absolute bioavailability (F) of the CLD allows to quantify the absorption. This parameter F was calculated as the ratio of the areas under the curve (AUC) obtained for each mode of administration, Eq. (6):

$$F = AUC_{p.o.}/AUC_{i.v.} \times 100 \quad (6)$$

Statistical analyses were performed by means of the SAS software package. In order to compare the pharmacokinetics parameters obtained after an i.v. or a p.o. administration of CLD, non parametric tests were chosen in reason of the distribution of the values. The data were analyzed as independent measures using the NPAR1WAY procedure with the WILCOXON option. The goat was considered as the experimental unit. A unilateral test is chosen to compare the AUC and a bilateral test is used to compare the other parameters. Differences were considered significant for P-values < 0.05.

3. Results and discussion

3.1. CLD kinetic pattern after i.v. and p.o. administration

The elimination kinetic of CLD in the goat serum following i.v. or p.o. administration is shown in Fig. 1. During the first day following i.v. administration of CLD, serum concentrations declined rapidly as expected due to the distribution and dilution of the molecule in the organism (2517 ± 589 ng g^{-1} (mean ± SD) at t = 3 min and 851 ± 163 ng g^{-1} at t = 1 h). After oral administration, the amount of CLD in serum gradually increases over time to reach maximum concentration (509 ± 66 ng g^{-1} (mean ± SD)) at the fourth day (T_{max}). This gradual absorption phase corresponds to the digestive transit time in ruminants and particularly time the fiber fodder may remain in the rumen (rumination phase) of the goat. After the 4th day, serum concentrations of CLD are of the same order of magnitude for a same time between goats treated intravenously or orally (Fig. 1).

The time to reach the maximum concentration here corresponds to relatively slow absorption in comparison with a study in mice (T_{max} = 2 d) (Wang et al., 1981). The CLD concentrations obtained with the p.o. treatment remained stable after that for a 10 d period (5–15 d) (Fig. 2). The observed plateau in the present study was also observed in ewes (Lerch et al., 2016). This plateau could

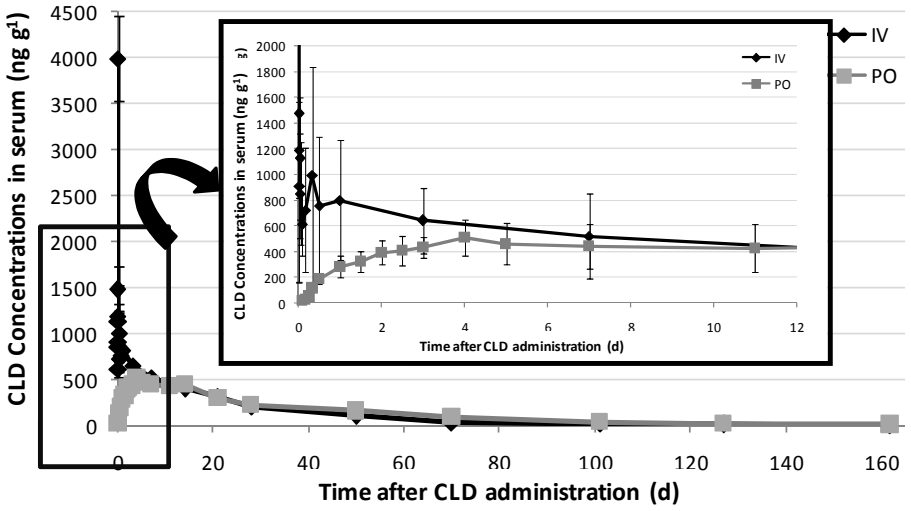

Fig. 1. Serum chlordecone (CLD) concentration (ng/g) vs. time in adult female goats (n = 6) after a single intravenous (IV) or oral administration (PO) of CLD at 1 mg kg PV: observed kinetics from t = 0 to t = 163 d.

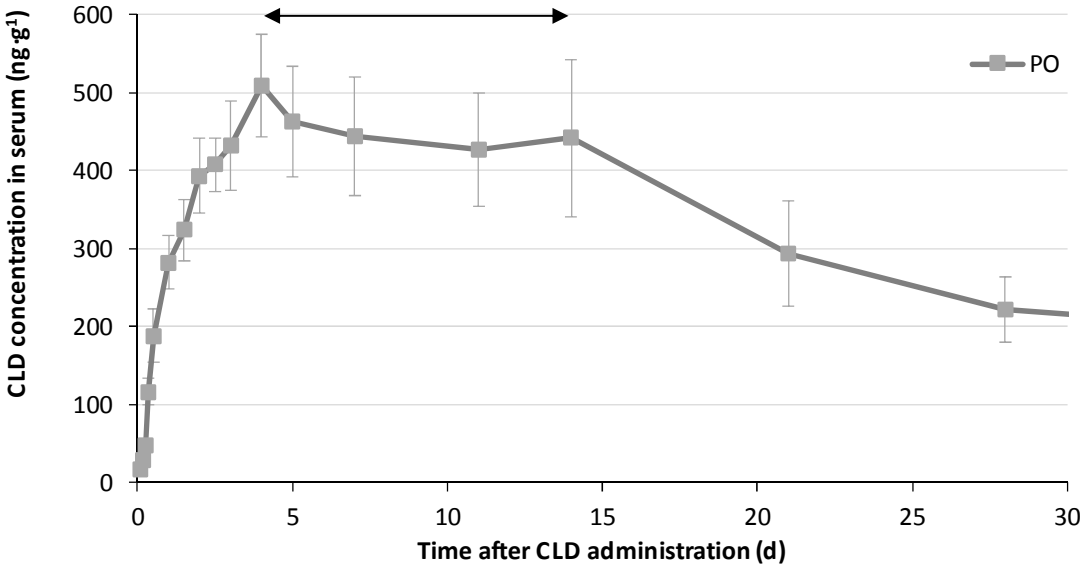

Fig. 2. A plateau of serum chlordecone (CLD) concentrations observed after the oral administration of CLD from t = 4 d to t = 15 d.

correspond to a progressive release of CLD contained in the rumen, following interactions of adsorption between the dose contained in the cremophor of the dough ball and the ruminal content. In addition, it is known that the forage quality influences its transit time and its digestibility in ruminants. The digestibility is typically much lower in the forage from the tropics in comparison to temperate ones (Assoumaya et al., 2007). In general, the larger the ingested particles, the longer the emptying time will be. Thus, assuming the cremophor is adsorbed on particles of different sizes; the absorption of CLD present on the large particles will be longer and may happen several days after the medium rumination time estimated at 3 d. The specific role of rumen as feed and pollutants reservoir (specifically if pollutants are linked with ruminal materials) has already been discussed in studies of perfluorooctane sulfonate (PFOS) in sheep and in cows (Kowalczyk et al., 2012, 2013). In addition, Fisher et al. (1986) showed in fish that almost twice as much CLD remained in the food 24 h after the exposure when the food was more coarsely ground, than when it was finely ground. These two elements could be at the origin of the plateau.

After this plateau (T = 15 d), which corresponds to the steady-state between the input (absorption) and the output (elimination), CLD concentrations in serum decreased progressively. This was also observed in serum of i.v. group. The similarity of the terminal slope for i.v. and p.o. suggests that this slope corresponds really to the elimination, and that a flip-flop kinetic could be rule out.

Finally, the observed kinetic has an atypic pattern (a plateau of 15 d which is absent in a typic pattern) but it was already found for CLD and PFOS in others little ruminants.

3.2. Absolute bioavailability and absorption

The AUCs, determined by non-compartmental methods, are not significantly different (P > 0.1) between the two treatments (Table 1). The value of the absolute bioavailability F is defined by Eq. (6), is 120± 17%. This F value is not significantly different from 100%,

Table 1
Values for chlordecone (CLD) toxicokinetic parameters and variables (mean ± SD) following intravenous and oral administration of 1 mg CLD·kg^{-1} to six adult female goats per treatment.

Parameters	IV (mean ± SD)	PO (mean ± SD)	P
k (day^{-1})	0.043 ± 0.004	0.032 ± 0.003	0.12
A (ng g^{-1})	675 ± 170	660 ± 96.4	0.81
$AUC_{0\rightarrow\infty}$ (ng day g^{-1})	16,376 ± 3935	19,767 ± 3164	0.13
% AUC extrapolated	10.16 ± 6.45	1.86 ± 0.79	NA
$T_{1/2}$ (day)	16.9 ± 1.54	23.2 ± 2.54	0.12
V_z (g)	57,451 ± 18,330	55,133 ± 7036	0.94
Cl (g day^{-1})	2401 ± 428	1676 ± 189	0.32
F (%)	NA	121 ± 17	NA

NA: not applicable, k: elimination slope, A: concentration extrapolated to time 0, $AUC_{0\rightarrow\infty}$: area under the curve from time zero to infinity, %AUC extrapoled: percentage of $AUC_{0\rightarrow\infty}$ which is extrapoled, $T_{1/2:\ \text{half-life,}}$ Vz: apparent volume of distribution, Cl: clearance, F: bioavailable fraction.

meaning the rate of absorption of CLD can be equated to 100% of the ingested dose. The CLD bioavailability for this study corresponds to almost complete absorption as observed in rats (90%) (Egle et al., 1978). CLD data in other non ruminant species suggested already a high absorption rate of the same order of magnitude (Egle et al., 1978; Boylan et al., 1978; Kavlock et al., 1980) and in consequence any real effect of intestinal and hepatic first pass.

These results are consistent with the absorption models developed in ruminants for organochlorinated and brominated compounds. Different authors (McLachlan, 1994; Sweetman et al., 1999; Kierkegaard et al., 2009) report that the absorption rate is a function of the lipophilicity of the molecule: the absorption is highest when a log Kow is between 5 and 6. However, when log Kow >6.5: the absorption rate decreases. This shows when log Kow is close to 5, the absorption rate of CLD should be close to 100% according to the model, and this calculation is indeed consistent with the results obtained in this study.

3.3. Elimination of CLD

The half-life of CLD elimination from the serum was estimated to 16.9 ± 1.5 days and 23.2 ± 2.5 days after an i.v. and a p.o. administration of CLD respectively. The difference between these values is not significant ($P > 0.1$). These half-lives observed for the CLD in serum are of the same order of magnitude as those observed in serum of growing piglets (12–22 days, Soine et al., 1983), in serum of growing juvenile goats (15 days, Lastel et al., 2016); in the muscle of Creole ducks (20 days, Jondreville et al., 2014a) or the muscle of beef (43 days, Mahieu et al., 2015) or in cow milk (20 days, Smith and Arant, 1967). The half-life of CLD can be modulated via the clearance of the molecule, that is a function of the metabolic capacity of the animal to metabolize the parent molecule and to eliminate it latter. Indeed, the CLD can be converted to various metabolites, particularly to chlordecol (CLD-OH) through the intervention of an enzyme: the aldoketo-reductase (Fariss et al., 1980). But this enzyme is not present in all species, or its level of activity is species dependant, as highlighted for example in Houston et al. (1981), with a higher activity in gerbil than in rat or guinea pig. The real decontamination of the animal (elimination of the parent molecule and its metabolites) is obtained only if these metabolites are rapidly excreted. This complete elimination could be checked in a furthered study, with kinetics establishment of CLD and metabolites in urine and in faeces. Effectively these biological matrices are known to contain CLD and/or metabolites in different species (pig or gerbil) (Soine et al., 1983; Houston et al., 1981).The half-life of CLD is also dependent on the physiological status of the animal. An increase of the elimination of the molecule via lactation in mammals or via eggs laying in birds ($T_{1/2} = 5$ days in laying hen with a high laying rate versus $T_{1/2} = 20$ days in duck with a lower laying rate, Jondreville et al., 2014b, a; $T_{1/2} = 20$ days in dairy cow milk (Smith and Arant, 1967) versus $T_{1/2} = 43$ days in growing meat cattle (Mahieu et al., 2015)) can decrease this duration.

In addition to the animal parameters (metabolic capacity and physiological status) affecting the half-life of CLD, the molecule characteristics influence the intensity of the metabolism. CLD is an organochlorinated ketone, which exhibits this type of behavior. CLD can be regarded as an “intermediate” compound regarding its persistence in goats. Indeed, toxicokinetic studies in goats showed shorter half-lives for other molecules such as zearalenone (ketone, $T_{1/2}$ in plasma = 28 h, Dong et al., 2010) or endosulfan (chlorinated, $T_{1/2}$ in milk = 8.7 days, Nag et al., 2007), while other environmental chlorinated pollutants are more persistent (NDL-PCBs: $T_{1/2}$ in milk = 51 days; PCDD/Fs: $T_{1/2}$ in milk = 59 days; Fournier et al., 2013).

In conclusion, CLD has a relatively short half-life in comparison with other organic pollutants.

3.4. Implications of these results in terms of risk management

According to the initial contamination level of the animal, it is therefore possible to envisage a strategy of animal depuration in the field that allows the production of animal products containing CLD below the MRL. The implementation strategy for such an approach might include a blood or serum sample being taken to provide the initial level of contamination in the animal. To assess the CLD level in the tissues it would be necessary to evaluate the statistical relationship between CLD concentrations in serum and tissues. Marchand et al. (2010) established already such relationship for PCBs between bovine tissues to predict contamination levels in muscle and liver destined to human consumption. Effectively if these relationships are known, it should be possible to predict a suitable lag time prior to slaughtering to obtain CLD concentrations in tissues below the MRL.

Effectively, today in slaughterhouses, the usual strategy to control the level of CLD in the carcass while avoiding decreasing its economic value, consists of a sampling of the perirenal fat. If the concentration of CLD in the perirenal fat is above the MRL (100 μg kg^{-1}) the carcass is destroyed, with negative economic consequences for the farmer. To avoid this situation, the *in vivo* monitoring presented at the beginning of this part could be a solution, with a serum sampling to check if the CLD level of the animal tissues is in accordance with the regulatory threshold (before the slaughtering).

In the literature, no significant differences have been observed between half-life of CLD in several tissues, during the depuration period in laying hens (Jondreville et al., 2014b). At steady-state, the level in different tissues is correlated and these authors obtained in the laying hens tissue/serum ratio of 7.7, 1.55 and 0.57 for liver, abdominal fat and muscle respectively.

These coefficients are unknown for goat, but the following relationship can be established (Eq. (7)):

$$C_{\text{perirenal fat}} = \alpha\, C_{\text{serum}} \tag{7}$$

with $C_{\text{perirenal fat,}}$ the concentration of CLD in the perirenal fat, C_{serum}, the concentration of CLD in serum and α, the coefficient of correlation between the concentration in serum and the concentration in perirenal fat.

In case of monitoring, C_{serum} at the monitoring sampling time is $C_{\text{serum}}(i)$. The time t_d necessary to decrease the level in perirenal fat from $\alpha\, C_{\text{serum}}(i)$ to the MRL is given by the following relationship (Eq. (8)):

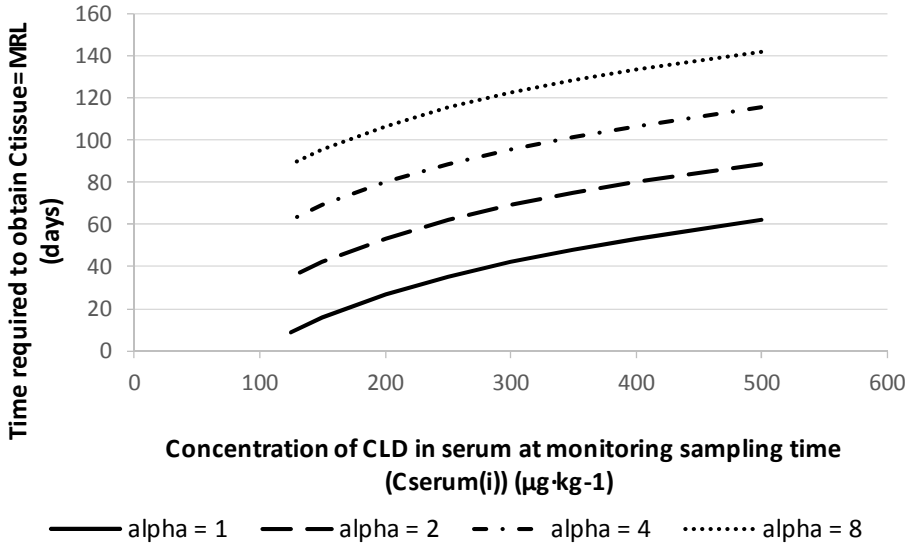

Fig. 3. Simulation of the time required to obtain a concentration of CLD inferior or equal to the Maximum Residue Limit (100 µg kg^{-1}) in function of the correlation coefficient between the concentration of CLD in the tissue and the concentration of CLD in the serum.

$$t_d = -(1/k) \times \ln(MRL/\alpha\, C_{serum}(i)) \quad (8)$$

If α is known, it is easy to obtain a graph t_d in function of $C_{serum}(i)$ and to assess the time t_d, with a value of k at 95% confidence interval, $k_{95\%}$ = (k_{mean} − 2 standard deviation (SD)) to obtain the lowest k value and in consequence the highest half-life value. In this study, $k_{95\%}$ = 0.026 day^{-1}. Simulations can be realized for different values of α. The choice of the values for these simulations is based on the values of coefficient correlation in the laying hens (Jondreville et al., 2014b) to obtain a plausible scale of values. Fig. 3 illustrates that for the same concentration in serum, the time required to obtain level of CLD below the regulatory threshold is different according to the correlation coefficient between the concentration in serum and the concentration in tissue. This coefficient varies with the type of the physiological tissue. For example, if the concentration in serum is 300 µg kg^{-1}, and α = 0.5, 2 and 8 for muscle, adipose tissue and liver respectively, the time required to obtain levels of CLD below the regulatory threshold is: 16, 70 and 123 days for muscle, adipose tissue and liver respectively. From these abacuses, the sanitary authority has an indication to decide of the time required to be sure that C_{tissue} < MRL.

A final point that is important to note is that the data obtained in this study could be used to calibrate a future CLD transfer model in goats. The same work has to be conducted with ovine species, since this ruminant is also consumed in Martinique and other parts of the French West Indies. The results of such further research could be used to compare the results between the different ruminants.

4. Conclusion

This toxicokinetic study of CLD in 12 non-lactating adult goats shows high absorption and a serum half-life of approximately 20 d. This duration is compatible with a decontamination of animals in the field meaning a depuration strategy seems conceivable *in situ*. This study provides applied tools that could be used by the animal producers in the French West Indies to ensure safe production systems and reduce the risk of adverse human health effects from CLD in soil. Further studies would help to assess the correlation between serum and different tissues to manage the depuration of contaminated animals *in situ*, or to assess the effectiveness of other risk management options e.g. soil ingestion, sequestration, clearance.

Acknowledgements

The experimentation was partially funded by Plan National Chlordécone 2 (CHLORDEPAN project). The authors thank Claude Barbier, Laurent Béramice (INRA, PTEA) and Pamela Hartmeyer, Christine Grandclaudon, Hervé Toussaint and Matthieu Delannoy (URAFPA) for technical support. They are also grateful to Jean-Paul Payan (INRS) for his advice on toxicokinetics and thank warmly Darren J. Beriro from British Geological Survey for English proofreading and advice.

References

Adir, J., Caplan, Y.H., Thompson, C., 1978. Kepone serum half-life in humans. Life Sci. 22, 699–702.

Alexandre, G., Asselin de Beauville, S., Shitalou, E., Zebus, M.-F., 2008. An overview of the goat meat sector in Guadeloupe: conditions of production, consumer preferences, cultural functions and economic implications. Livest. Res. Rural Dev. 20 (1), 9. Article n° 14.

Arrêté du 3 juillet, 1990. Concerning the Conditions of Issue and Use, in Agriculture, of Poisonous and Hazardous Substances (relatif aux conditions de délivrance et d'emploi, en agriculture, de substances vénéneuses et dangereuses). JORF n°197 du 26 août 1990 page 10406, NOR: ECOC9000070A. https://www.legifrance.gouv.fr/jo_pdf.do?id=JORFTEXT000000708664 (Accessed 6 September 2016) (In French).

Assoumaya, C., Sauvant, D., Archimède, H., 2007. Comparative study of intake and digestion of tropical and temperate forages (Etude comparative de l'ingestion et de la digestion des fourrages tropicaux et tempérés). INRA Prod. Anim. 20 (5), 383–392 (In French).

Boucher, O., Simard, M., Muckle, G., Rouget, F., Kadhel, P., Bataille, H., Chajès, V., Dallaire, R., Monfort, C., Thomé, J.P., Multigner, L., Cordier, S., 2013. Exposure to an organochlorine pesticide (chlordecone) and development of 18-month-old infants. Neurotoxicology 35, 162–168.

Boylan, J.J., Egle, J.L., Guzelian, P.S., 1978. Cholestyramine: use as a new therapeutic approach for chlordecone (kepone) poisoning. Science (New York, N.Y.) 199 (4331), 893–895.

Cabidoche, Y., Achard, R., Cattan, P., Clermont-Dauphin, C., Massat, F., Sansoulet, J., 2009. Long-term pollution by chlordecone of tropical volcanic soils in the French West Indies: a simple leaching model accounts for current residue. Environ. Pollut. 157 (5), 1697–1705.

Cohn, W.J., Boylan, J.J., Blanke, R.V., Fariss, M.W., Howell, J.R., Guzelian, P.S., 1978. Treatment of chlordecone (Kepone) toxicity with cholestyramine: results of a controlled clinical trial. New. Engl. J. Med. 298 (5), 243–248.

Costet, N., Pelé, F., Comets, E., Rouget, F., Monfort, C., Bodeau-Livinec, F., Linganiza, E.-M., Bataille, H., Kadhel, P., Multigner, L., Cordier, S., 2015. Perinatal

exposure to chlordecone and infant growth. Environ. Res. 142, 123–134.
Dallaire, R., Muckle, G., Rouget, F., Kadhel, P., Bataille, H., Guldner, L., Seurin, S., Chejès, V., Monfort, C., Boucher, O., Thomé, J.P., Jacobson, S.W., Multigner, L., Cordier, S., 2012. Cognitive, visual, and motor development of 7-month-old Guadeloupean infants exposed to chlordecone. Environ. Res. 118, 79–85.
Debier, C., Pomeroy, P.P., Dupont, C., Joiris, C., Comblin, V., Le Boulenge, E., Larondelle, Y., Thome, J.P., 2003. Quantitative dynamics of PCB transfer from mother to pup during lactation in UK grey seals *Halichoerus grypus*. Mar. Ecol. 537 Prog. Ser. 247, 237–248.
Dong, M., He, X.J., Tulayakul, P., Li, J.Y., Dong, K.S., Manabe, N., Nakayama, H., Kumagai, S., 2010. The toxic effects and fate of intravenously administered zearalenone in goats. Toxicon 55, 523–530.
Egle, J.L., Fernandez, S.B., Guzelian, P.S., Borzelleca, J.F., 1978. Distribution and excretion of chlordecone (Kepone) in the rat. Drug Metab. Dispos. 6, 91–95.
Fariss, M.W., Blanke, A.V., Saady, J.J., Guzelian, P., 1980. Demonstration of major metabolic pathways for chlordecone (Kepone) in humans. Drug Metab. Dispos. 8 (6), 434–438.
Fisher, D.J., Clark, J.R., Roberts Jr., M.H., Connolly, J.P., Mueller, L.H., 1986. Bioaccumulation of kepone by spot (*Leiostomus xanthurus*): importance of dietary accumulation and ingestion rate. Aquat. Toxicol. 9, 161–178.
Fournier, A., Rychen, G., Marchand, P., Toussaint, H., Le Bizec, B., Feidt, C., 2013. Polychlorinated biphenyl (PCB) decontamination kinetics in lactating goats (*Capra hircus*) following a contaminated corn silage exposure. J. Agric. food Chem. 61, 7156–7164.
Fournier, A., Martin, O., Travel, A., Puillet, L., Feidt, C., Jondreville, C., 2015. Modelling the PCBs transfer into hen eggs: influence of the physiological characteristics of the animal. Environ. Toxicol. Chem. 34 (1), 173–183.
Galan, F., Julien, L., Duflot, B., 2008. Panorama of Animal Pathways and Typology of Operating Systems with Livestock from Guadeloupe (Panorama des filières animales et typologie des sytèmes d'exploitation avec élevage de guadeloupe), pp. 1–63. Programme" Réseaux De Références" POSEI France. http://www.odeadom.fr/wp-content/uploads/2012/11/Panorama_filieres_animales_typologie_systemes_exploitation_elevage_Guadeloupe_2008.pdf (Accessed 6 September 2016) (In French).
Gunia, M., Mandonnet, N., Arquet, R., de la Chevrotière, C., Naves, M., Mahieu, M., Alexandre, G., 2010. Production systems of Creole goat and their implications for a breeding programme. Animal 4 (12), 2099–2105.
Howard, P.H., Boethling, R.S., Jarvis, W.F., Meylan, W.M., Michalenko, E.M., 1991. Handbook of Environmental Degradation Rates. Lewis Publishers, Chelsea, MI. http://esc.syrres.com/interkow/webprop.exe.
Hansch, C., Leo, A., Hoekman, D., 1995. Exploring QSAR: Hydrophobic, Electronic, and Steric Constants. American Chemical Society, Washington, p. 65. US ATSDR 1995.
Houston, T.E., Mutter, L.C., Blanke, R.V., Guzelian, P.S., 1981. Chlordecone alcohol formation in the Mongolian gerbil (Meriones unguiculatus): a model for human metabolism of chlordecone (Kepone). Fundam. Appl. Toxicol. 1 (3), 293–298.
IARC, 1979. Chlordecone. In: Some Halogenated Hydrocarbons. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 20. International Agency for Research on Cancer, Lyon, France, pp. 67–81.
INRA, 2007. Feeding of Bovines, Ovines and Caprines (Alimentation des bovins, ovins et caprins). Tables Inra 2007. Edition Quae, pp. 1–307 (In French).
Jondreville, C., Lavigne, A., Jurjanz, S., Dalibard, C., Liabeuf, J., Clostre, F., Lesueur-Jannoyer, M., 2014a. Contamination of free-range ducks by chlordecone in Martinique (French West Indies): A field study. Sci. Total Environ. 493, 336–341.
Jondreville, C., Fournier, A., Mahieu, M., Feidt, C., Archimède, H., Rychen, G., 2014b. Kinetic study of chlordecone orally given to laying hens (*Gallus domesticus*). Chemosphere 114, 275–281.
Jurjanz, S., Feidt, C., Pérez-Prieto, L., Ribeiro Filho, H., Rychen, G., Delagarde, R., 2012. Soil intake of lactating dairy cows in intensive strip grazing systems. Animal 6 (8), 1350–1359.
Jurjanz, S., Jondreville, C., Mahieu, M., Fournier, A., Archimède, H., Rychen, G., Feidt, C., 2014. Relative bioavailability of soil-bound chlordecone in growing lambs. Environ. Geochem. Health 36, 911–917.
Kavlock, R.J., Chernoff, N., Rogers, E., Whitehouse, D., 1980. Comparative tissue distribution of mirex and chlordecone in fetal and neonatal rats. Pestic. Biochem. Physiol. 14 (3), 227–235.
Kierkegaard, A., De Wit, C.A., Asplund, L., McLachlan, M.S., Thomas, G.O., Sweetman, A.J., Jones, K.C., 2009. A mass balance of tri-hexabrominated diphenyl ethers in lactating cows. Environ. Sci. Technol. 43, 2602–2607.
Kowalczyk, J., Ehlers, S., Fürst, P., Schafft, H., Lahrssen-Wiederholt, M., 2012. Transfer of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) from contaminated feed into milk and meat of sheep: pilot study. Arch. Environ. Contam. Toxicol. 63, 288–298.
Kowalczyk, J., Ehlers, S., Oberhausen, A., Tischer, M., Fürst, P., Schafft, H., Lahrssen-Wiederholt, M., 2013. Absorption, distribution, and milk secretion of the perfluoroalkyl acids PFBS, PFHxS, PFOS, and PFOA by dairy cows fed naturally contaminated feed. J. Agric. Food Chem. 61, 2903–2912.
Lastel, M.L., Lerch, S., Fournier, A., Jurjanz, S., Mahieu, M., Archimède, H., Feidt, C., Rychen, G., 2016. Chlordecone disappearance in tissues of growing goats after a one month decontamination period – Effect of body fatness on Chlordecone retention. Environ. Sci. Pollut. Res. 23, 3176–3183.
Le Déaut, Y., Procaccia, C., 2009. Report on the Impacts of the Use of Chlordecone and Pesticides in the West Indies: Assessment and Future Prospects (Rapport sur les impacts de l'utilisation de la chlordécone et des pesticides aux Antilles: bilan et perspectives d'évolution). OPECST, Paris. Assem. Natl. no 1778, p. 223. http://www.senat.fr/rap/r08-487/r08-4871.pdf (Accessed 6 September 2016) (In French).
Lerch, S., Guidou, C., Thomé, J.P., Jurjanz, S., 2016. Non-dioxin-like polychlorinated biphenyls (PCBs) and chlordecone release from adipose tissue to blood in response to body fat mobilization in ewe (*Ovis aries*). J. Agric. Food Chem. 64 (5), 1212–1220.
Mahieu, M., Fournier, A., Lastel, M.L., Feidt, C., Rychen, G., Archimède, H., 2015. Chlordecone and animal breeding, individual variability of the excretion capacity of ruminants and consequences on their contamination. In: Schoelcher, Martinique, Devault, D., Macarie, H., Feliot-Rippeault, M., Couderchet, M. (Eds.), Protection des cultures et santé environnementale, héritage et conception nouvelles, Actes du 44ème congrès du groupe français des pesticides, 26-29 mai 2014. Editions du GFP, France, pp. 156–163 (in press) (In French).
Marchand, P., Cariou, R., Vénisseau, A., Brosseaud, A., Antignac, J.P., Le Bizec, B., 2010. Predicting PCFF/F and dioxin-like PCB contamination levels in bovine edible tissues from *in vivo* sampling. Chemosphere 80, 634–640.
McLachlan, M.S., 1994. Model of fate of hydrophobic contaminants in cows. Environ. Sci. Technol. 28, 2407–2414.
Multigner, L., Ndong, J.R., Giusti, A., Romana, M., Delacroix-Maillard, H., Cordier, S., Jegou, B., Thomé, J.P., Blanchet, P., 2010. Chlordecone exposure and risk of prostate cancer. J. Clin. Oncol. 28, 3457–3462.
Nag, S.K., Mahanta, S.K., Raikwar, M.K., Bhadoria, B.K., 2007. Residues in milk and production performance of goats following the intake of a pesticide (endosulfan). Small Rumin. Res. 67, 235–242.
Naves, M., 2003. Characterization and Management of a Local Cattle Population in the Tropical Area: the Creole Cattle of Guadeloupe (Caractérisation et gestion d'une population bovine locale de la zone tropicale : le bovin créole de Guadeloupe). Thèse de l'Institut National Agronomique, Paris, p. 283 (In French).
Orndorff, S.A., Colwell, R.R., 1980. Microbial transformation of Kepone. Appl. Environ. Microbiol. 398–406.
Richter, E., Lay, J.P., Klein, W., Korte, F., 1979. Paraffin-stimulated excretion of 2, 4, 6, 2′, 4′-pentachlorobi [14 C] phenyl by rats. Toxicol. Appl. Pharmacol. 50 (1), 17–23.
SANCO, 2014. Guidance Document on Analytical Quality Control and Validation Procedures for Pesticide Residues Analysis in Food and Feed. SANCO/12571/2013 Supersedes SANCO/12495/2011, p. 48. http://www.eurl-pesticides.eu/library/docs/allcrl/AqcGuidance_Sanco_2013_12571.pdf (Accessed 6 September 2016).
Smith, J.C., Arant, F.S., 1967. Residues of kepone in milk from cows receiving treated Feed. J. Econ. Entomol. 60 (4), 925–927.
Soine, P.J., Blanke, R.V., Schwartz, C.C., 1983. Chlordecone metabolism in the pig. Toxicol. Lett. 17 (1–2), 35–41.
Soine, P.J., Blanke, R.V., Chinchilli, V.M., Schwartz, C.C., 1984a. High-density lipoproteins decrease the biliary concentration of chlordecone in isolated perfused pig liver. J. Toxicol. Environ. Health 14, 319–335.
Soine, P.J., Blanke, R.V., Schwartz, C.C., 1984b. Isolation of chlordecone binding proteins from pig liver cytosol. J. Toxicol. Environ. Health 14, 305–317.
Sweetman, A.J., Thomas, G.O., Jones, K.J., 1999. Modelling the fate and behaviour of lipophilic organic contaminants in lactating dairy cows. Environ. Pollut. 104, 261–270.
Wang, T.P.H., Ho, I.K., Mehendale, H.M., 1981. Correlation between neurotoxicity and chlordecone (kepone) levels in brain and plasma in the mouse. Neurotoxicology 2, 373–381.