



Repeated KI prophylaxis in case of prolonged exposure to iodine radioisotopes: pharmacokinetic studies in adult rats

G. Phan, R. Chioukh, D. Suhard, A. Legrand, C. Moulin, T. Sontag, F. Rebière, C. Bouvier-Capely, M. Agarande, V. Renaud-Salis, et al.

► To cite this version:

G. Phan, R. Chioukh, D. Suhard, A. Legrand, C. Moulin, et al.. Repeated KI prophylaxis in case of prolonged exposure to iodine radioisotopes: pharmacokinetic studies in adult rats. *Pharmaceutical Research*, 2019, 35 (12), pp.227. 10.1007/s11095-018-2515-1 . hal-02881796

HAL Id: hal-02881796

<https://hal.science/hal-02881796>

Submitted on 8 Jul 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 Repeated KI prophylaxis in case of prolonged exposure to iodine radioisotopes:
2 pharmacokinetic studies in adult rats

3 Guillaume Phan¹, Rym Chioukh¹, David Suhard¹, Alexandre Legrand¹, Charlotte Moulin¹, Thibaud
4 Sontag¹, François Rebière¹, Céline Bouvier-Capely¹, Michelle Agarande¹, Valérie Renaud-Salis¹, Jean-
5 René Jourdain¹

6 Corresponding author: Guillaume Phan, email guillaume.phan@irsn.fr

7 ¹ Institute for Radiation Protection and Nuclear Safety, Health Division, 31 avenue de la Division
8 Leclerc, F-92260 Fontenay-aux-Roses, France

9

10

11

12

13

14

15

16

17

18

19

20

21 Proposed running title: KI pharmacokinetics in the rats

22 Abstract

23 **Purpose** To propose a new and effective dose regimen for stable potassium iodide (KI) repeated
24 prophylaxis in case of prolonged exposure to radioactive iodine.

25 **Methods** The pharmacokinetics of iodine was determined in rats by compartmental analyses after
26 intravenous and oral administrations of the optimal dose of 1 mg/kg KI, which was previously selected
27 in a dose-effect study. The thyroid protection against iodine-125 incorporation was followed during
28 24h after a single oral dosing of KI. A repeated KI prophylaxis was modeled using initial estimates of
29 iodine pharmacokinetic parameters.

30 **Results** A dose regimen consisting in administrations of 1 mg/kg daily for eight days was selected and
31 studied. Plasma iodine concentrations predicted by simulation were verified by experimental data and
32 varied after the third dose of KI between 174 and 1190 µg/l. The inhibition study of iodine-125
33 binding in the thyroid as a function of the time showed that the protection effect of KI could be
34 correlated to stable iodine plasma concentrations. Hence, a theoretical decrease in iodine-125 thyroid
35 uptake from 63% to 88% could be achieved in a 24h-interval between two KI doses.

36 **Conclusion** Given the satisfactory levels of thyroid protection, this dose regimen could be envisaged
37 in order to extent KI indications for repeated prophylaxis.

38 Keywords

39 Potassium iodide prophylaxis; pharmacokinetics; dose regimen; pharmacokinetic-pharmacodynamic
40 relationship; rats

45 Introduction

46 Exposure of populations to radioactive iodine released from reactor during nuclear accidents at a
47 nuclear power plant may be responsible in the absence of appropriate protective measures for the
48 occurrence of thyroid cancer, particularly after irradiation in childhood ~~in infants and children~~ (1, 2).
49 The health consequences can nevertheless be limited by the implementation of protective measures,
50 such as the sheltering of populations, their evacuation, the implementation of food restrictions and
51 finally, the ingestion of stable iodine tablets. A single dose of 130 mg of potassium iodide (KI) in
52 adults provides adequate protection for the thyroid for 24 hours. The ingestion of stable iodine should
53 ideally occur two hours before exposure to the radioactive plume or failing this, at the latest within 2
54 to 8 hours after exposure (3). The aim of this preventive measure is to saturate the thyroid gland with
55 non-radioactive iodine and thus prevent the binding of radioactive isotopes of iodine. However, the
56 recent Fukushima disaster has raised questions about the conditions for implementing stable iodine
57 prophylaxis. Indeed, this accident has shown that a single intake of potassium iodide tablets cannot
58 satisfactorily protect populations exposed to repeated releases of radioactive iodine (4). Thus, if the
59 current doctrine envisages the possibility of a second dose, especially in case of impossibility of rapid
60 evacuation of populations, it gives to this day no indication as to the conditions for implementing
61 repeated doses of stable iodine. As mentioned in the iodine thyroid blocking guidelines of the World
62 Health Organization, which have been recently updated, further research is needed to reinforce the
63 evidence of efficacy of stable iodine prophylaxis, namely on the dosage, the time of administration
64 and optimal dosing regimen for multiple administrations of stable iodine in case of repeated or
65 prolonged releases of radioactive isotopes of iodine, as well as the adverse health effects of stable
66 iodine administration (5). A few clinical studies have been published focusing on repeated prophylaxis
67 by stable iodine in children (6) or in adult volunteers (7-9). However, the number of iodine doses
68 tested was limited and the design of the dosage regimen was not explicitly supported by the
69 pharmacokinetics of stable iodine. Besides, a correlation between plasma or serum stable iodine
70 concentrations and a blockade of radio-isotopes of iodine uptake in the thyroid has already been
71 suggested in previous studies but available data are sparse and to our knowledge, this type of

correlation has never been fully characterized experimentally or by pharmacokinetic-pharmacodynamic (PKPD) modeling. In early studies in healthy volunteers, the minimal serum iodide concentration inducing a thyroid iodine-131 uptake of less than 1.3% was determined around 100 µg/l (10). In another study, a thyroid iodine-123 uptake of less than 2% in euthyroid volunteers has been associated with serum iodine concentrations of at least 220 µg/l (9). Hence, in the frame of the research program PRIODAC co-funded by the French National Research Agency, we undertook to revise and complete the data on stable KI prophylaxis by conducting pharmacological and toxicological studies in the rats. An optimal single dose of 1 mg/kg KI has first been determined from experiment in adult rats and was selected on the basis of the level of thyroid protection against iodine-125 incorporation as well as on the thyroid distribution and urinary elimination of stable iodine (11). The purposes of the present work were to study the pharmacokinetics of KI after administration of the specific dose of 1 mg/kg KI to rats and to assess the duration of the thyroid protective effect of this dose in order to propose an optimal dose regimen for repeated KI prophylaxis.

Materials and Methods

Animals

Male Wistar rats (strain code: 003, 8-9 weeks age and weighing 280-360 g) were used in this study. The animals were purchased from Charles River Laboratories (Saint Germain sur l'Arbresle, France) and handled in compliance with the French Legislation (articles R214-87 to R214-137 of French Rural Code) and the European Directive (2010/63/EU) regarding the care and use of laboratory animals. Experimental protocols were reviewed and approved by the IRSN Ethics Committee. Six rats were used per sampling time after the oral administration of KI and five rats per sampling time after the intravenous injection of KI. They had free access to water and food before and throughout the experimental period. The rats are fed with AO4C pellets (Scientific Animal Food and Engineering, Augy, France) daily during acclimation periods and experiments. The controlled iodine content of the diet meets rodent food requirements (0.3 mg/kg pellets). After exposure, the animals were anesthetized by isoflurane inhalation prior to being euthanized by intracardiac puncture.

99 *Chemicals*

100 Stable potassium iodide (I-127) solutions at different concentrations in sterile water pH 7.4 were
101 prepared and provided by the French Central Armed Forces Pharmacy (Orléans, France). Radioactive
102 potassium iodide I-125 solution at a concentration of 3700 MBq/ml and with a specific activity of
103 643.8 MBq/pg was purchased from Biotrend (Köln, Germany).

104 *Experiment protocols*

105 *Experiment 1: Pharmacokinetics of stable iodine after a single intravenous administration of KI*

106 Rats were injected once in the lateral tail vein with either physiological saline or 1 mg/kg of KI
107 (volume = 0.2 ml of a KI solution at a concentration of 1.75 g/l). The rats were then placed
108 individually in metabolic cages and euthanized by intracardiac puncture at the corresponding time for
109 each rat prior to harvesting the blood and the thyroid (5 rats per time point). The sampling times were:
110 0, 0.167, 0.333, 0.667, 1, 2, 4, 6, 8 and 24 h post KI administration. Urine was collected from 24-h
111 time-point animals.

112 *Experiment 2: Pharmacokinetics of stable iodine after a single oral administration of KI*

113 Rats were administered once orally by esophageal gavage with either physiological saline or 1 mg/kg
114 of KI (volume = 1 ml of a KI solution at a concentration of 0.35 g/l) using a disposable plastic cannula
115 (Instech laboratories, Plymouth Meeting, USA). The rats were then placed individually in metabolic
116 cages and euthanized by intracardiac puncture at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 24 and
117 48 h post KI administration to harvest the blood and the thyroid (6 rats per time point). Urine was
118 collected from 24-h and 48-h time-point animals.

119 *Experiment 3: Effect of a single oral administration of stable KI on the 24h-thyroid uptake of iodine I-*
120 *125*

121 Rats were administered once orally by esophageal gavage with either physiological saline or 1 mg/kg
122 of KI (volume = 1 ml of a KI solution at a concentration of 0.35 g/l) one hour prior to being injected in

the lateral tail vein with 1.11 MBq/kg of I-125 (volume = 1 ml/kg). The rats were then placed individually in metabolic cages and euthanized by intracardiac puncture at 1, 2, 4, 12, 16, 20, and 24 h post KI administration to harvest the blood and the thyroid (6 rats per time point).

Experiment 4: Simulation and experimental verification of repeated daily oral administrations of stable KI

The simulation of different KI dose regimen was performed using Phoenix WinNonlin software version 6.3 (Certara, Princeton, USA) and the final parameter estimates obtained from the selected pharmacokinetic model. In order to verify the plasma iodine concentrations at different times during a repeated administration of KI, groups of rats were administered orally by esophageal gavage with either physiological saline or 1 mg/kg of KI (volume = 1 ml of a KI solution at a concentration of 0.35 g/l) once a day for up to eight days. The rats were then placed individually in metabolic cages and euthanized by intracardiac puncture at 6h after three KI administrations (day 3), at 24 h after four KI administrations (day 5), at 24 h after eight KI administrations (day 9) and 48 h after eight KI administrations (day 10) to harvest the blood and the thyroid (4 rats per time point).

Iodine analysis in biological samples

After euthanasia of the animals, the thyroid is dissected, rinsed, dried on gauze and weighed. The blood and the urines are centrifuged using an Eppendorf centrifuge 5810R (4000 rpm, for 20 min at 4 °C). The samples of blood plasma, urines and thyroids are stored at -20 °C prior to analysis. The total radioactivity of iodine-125 contained in the thyroids is determined by gamma counting (gamma multidetector RIASTAR A5410, Packard). The analysis of stable iodine in blood plasma and thyroids was adapted from a method previously developed for the quantification of iodine in the urines by inductively coupled plasma mass spectrometry (12). After slow thawing of samples at laboratory temperature (+ 21 °C), the blood plasma and the urines are diluted respectively 1/100th and 1/10 000th with 2% ammonia solution (solution made from the Suprapur® 25% ammonia solution, Merck) and then stabilized with a sodium thiosulfate solution at 184 mg/l in 2% ammonia. The total iodine content is determined by direct measurement of three aliquots of each sample by inductively coupled plasma

mass spectrometry (ICP-MS, X Series II and iCAP™ Q, Thermo Electron, Courtaboeuf, France) using the standard addition method. The internal calibration range consists of a standard solution of stable iodide at 1000 mg/l (Iodides AVS Titrimorm IC Standard, Prolabo). Tellurium Te-125, used as the second internal standard, is added to the samples at a concentration of 1.25 mg/l from a standard 1000 mg/l solution (Tellurium ICP standard Certipur, Merck). The internal calibration range is constituted in each sample by the following concentrations: 0, 2, 4, 6, 8, 10 and 12 µg/l of stable iodide. The same method for determination of stable iodine by ICP-MS is applied to the thyroids after preliminary mineralization of the samples in a microwave oven (Ethos TC, Milestone, Italy) in 50 ml of ammonia 4M for 30 minutes at 200 °C. A volume of 1 ml of the mineralized solution is then diluted to 1/125th in 2% ammonia for iodine analysis by ICP-MS. The results of measurements of radioactive iodine I-125 expressed in number of counts per minute and per gram of tissue (cpm/g) are converted into kilo Bequerels per gram of tissue (kBq/g) and then as a percentage of injected activity. The results of stable iodine measurements by ICP-MS in blood plasma, urine and thyroid samples expressed in counts per second (cps) are converted to µg/l (or ng/ml) of sample after correlation with calibration curves.

Statistical and pharmacokinetic analyses

All data are expressed as the mean ± standard deviation of a minimum of six independent experiments. The comparisons of the results were performed using Student *t*-test and *p* values of less than 0.05 were considered significant. The concentration-time kinetic profiles for stable iodine and the theoretical model describing the pharmacokinetic/pharmacodynamic correlation are obtained by compartmental pharmacokinetic analysis and linear regression from the data using Phoenix WinNonlin version 6.3 (Certara, Princeton, USA). The naïve pool approach, in which all data were treated as they were obtained from the same animal, was used to develop the pharmacokinetic and pharmacokinetic-pharmacodynamic models. The plasma data after intravenous and oral dosing were analysed separately using the classic modeling ~~engine-tool~~ of the software in order to compare the different patterns and to select the most ~~relevant-relevant~~ pharmacokinetic model. Then the data were fitted simultaneously using the population mode of the software in order to derive common parameters and increase accuracy and precision of the parameter estimates (13, 14). The pharmacokinetic-pharmacodynamic

models were also obtained after simultaneous fit of pharmacologic effects observed in the thyroid and stable iodine plasma data. The selection of the most accurate mathematical models is based on the comparison of the calculated statistical parameters of each model such as the Akaike information criterion (AIC) or the Bayesian criterion of Schwarz (SBC): $AIC=2k-\text{Log}(L)$ and $SBC=-2\text{Log}(L)+k\text{Log}(n)$ (k is the number of estimated parameters of the model; L is the maximum value of the model likelihood function and n is the number of observations). The most accurate mathematical model is the one with the best visual agreement between data and predictions and the lowest AIC and SBC values (15-17).

Results

Pharmacokinetics of stable iodine after a single intravenous administration of KI (Experiment 1)

The mean stable iodine plasma concentrations at different sampling times post KI intravenous injection are presented in the table I and the figure 1. ~~According to the pharmacokinetic modeling, the most accurate model from a statistical point of view that best fitted the plasma data was the one-compartment model with first order rate distribution and elimination processes. Indeed, the statistical parameters of this model (AIC=134.92; SBC=135.53) were better than the two-compartment's associated parameters (AIC=138.64; SBC=139.85).~~ The one compartmental model was selected, as it was associated with lower AIC and SBC values (AIC=134.92; SBC=135.53) compared with the two compartment model (AIC=138.64; SBC=139.85), still providing an adequate description of the data, as shown in figure 1 where observations and model predictions appear superimposed. The predicted plasma iodine levels were generated with the selected model and represented by the curve in the figure 1. After intravenous injection of 1 mg/kg KI, the iodine plasma concentration extrapolated to time zero was about 1275 µg/l and the concentrations decreased with a half-life of about 5.45 hours (Table III).

The distribution of iodine in the thyroid was quite variable as a function of the time after KI intravenous injection (Table I). The thyroid iodine content fluctuated from 596 ± 334 µg/g to 1141 ± 475 µg/g in control rats and from 602 ± 241 µg/g to 1039 ± 329 µg/g in treated rats. Although

a 19% increase in the thyroid iodine content of the treated rats could be observed at 24h, this difference was not statistically significant.

The total excreted amount of iodine recovered in the urines 24h post KI dosing was about $246 \pm 58 \mu\text{g}$ whilst the control rats excreted about $19 \pm 5 \mu\text{g}$ (Table I). This amount of iodine excreted in treated rats accounted for about 84% of the injected dose of $269 \mu\text{g}$ iodine from $350 \mu\text{g}$ KI.

Pharmacokinetics of stable iodine after a single oral administration of KI (Experiment 2)

The mean stable iodine plasma concentrations at different sampling times post KI oral gavage are presented in the table II and the figure 2. ~~The pharmacokinetic modeling showed that these data were best fitted by a one-compartment model with first order rate distribution and elimination processes since the related statistic parameters (AIC=151.42; SBC=153.34) were better than those of other models tested such as the two-compartment model (AIC=152.42; SBC=155.61). The subsequent predicted plasma values were generated with the selected model and represented by the curve in the figure 2 and the main pharmacokinetic parameters were calculated and presented in the table III.~~ The one compartmental model was also selected, as it was associated with lower AIC and SBC values (AIC=151.42; SBC=153.34) compared with the two compartment model (AIC=152.42; SBC=155.61), still providing an adequate description of the data, as shown in figure 2 where observations and model predictions appear superimposed. According to this model, iodine is absorbed rapidly and reaches a peak plasma level of about $993 \mu\text{g/l}$, approximately 38 minutes after oral administration. In addition, the plasma concentration of iodine 24 hours after dosing (predicted value of $158 \mu\text{g/l}$ and measured value of $175 \pm 102 \mu\text{g/l}$) remains approximately two times higher than the iodine concentration in the control rats ($69 \pm 8 \mu\text{g/l}$). The concentrations then decreased with a half-life of about 8.8 hours to the value of the control rats after 33 hours. ~~The first order rate constants which were derived after simultaneous fitting of intravenous and oral data by a population approach are presented~~ Parameter estimates resulting from the simultaneous analysis of the intravenous and oral data are listed in the table III.

The content of stable iodine in the thyroid fluctuated from $692 \pm 267 \mu\text{g/g}$ to $1024 \pm 284 \mu\text{g/g}$ in control rats and from $814 \pm 298 \mu\text{g/g}$ to $989 \pm 124 \mu\text{g/g}$ in treated rats, irrespective of the sampling time. As after intravenous injection of KI, this parameter did not significantly differ as a function of the time post KI dosing compared with control rats, although it tended to increase by 10% at 24h and by 15% at 48h in treated rats (Table II).

The cumulated stable iodine excretion in the urines was about $173 \pm 42 \mu\text{g}$ after 24h and an additional amount of about $29 \pm 6 \mu\text{g}$ was excreted during the next following 24h (Table II). Considering a total administered dose of about $269 \mu\text{g}$ iodine, 24h-excretion of about $14 \mu\text{g}$ iodine in control rats, and iodine oral bioavailability of 90% (Table III), then the total 24h- and 48h-excretion of iodine in treated rats represented respectively, 65% and 71% of the administered dose.

Effect of a single oral administration of stable KI on the 24h-thyroid uptake of iodine I-125: Pharmacokinetic-pharmacodynamic correlation (Experiment 3)

The measurements of thyroid I-125 activity as a function of time after oral administration of 1 mg/kg KI are shown in Table IV and the Figure 3. The theoretical stable iodine plasma concentrations corresponding to the same observation times and which were obtained in the pharmacokinetic studies are reported in the same table as well as in Figure 3 for comparison purpose. These results showed that the efficacy of a single dose of KI in terms of avoided iodine I-125 activity in the thyroid compared with the control rats, was comprised between 87% (at 2 hours) and 61% (at 24 hours). A decrease in iodine-125 avoided activities in the thyroid (expressed as a percentage of thyroid uptake in control rats) and in stable iodine plasma concentrations can be observed as a function of time from 1 hour after KI administration. This observation supports the hypothesis of a correlation between the efficacy of stable iodine and its concentration in plasma. In addition, a decrease in iodine-125 uptake in the thyroid of the treated rats (expressed as a percentage of the initial injected activity) is observed as a function of increasing stable iodine plasma concentrations.

This decrease in the uptake of iodine-125 can be modeled under the Phoenix software by an inhibition type pharmacological function (EI) after simultaneous fitting of stable iodine plasma data and the observed effects (Figure 4).

Hence, the modeling results showed that the uptake of iodine I-125(EI) can be decreased by stable iodine plasma concentration as in equation 1:

$$EI = E_0 I_0 \times (1 - C / (IC_{50} + C))$$

(Equation 1)

Where

C : stable iodine plasma concentration

IC_{50} : half-effect concentration, $IC_{50} = 174.49 \mu\text{g/l}$

$E_0 I_0$: initial extrapolated iodine-125 uptake, $E_0 I_0 = 1.7749\%$

Conversely, the thyroid protection efficacy (expressed in terms of avoided iodine-125 uptake compared with control rats) as function of stable iodine plasma concentrations can be modeled by a classical sigmoid dose-response function E_{max} (E) (Figure 5).

This effect (E) can be related to plasma stable iodine as in equation 2:

$$E = E_{\text{max}} \times C / (EC_{50} + C)$$

(Equation 2)

Where

C : stable iodine plasma concentration

E_{max} : maximum effect, $E_{\text{max}} = 94.19\%$

EC_{50} : half effect concentration, $EC_{50} = 87.26 \mu\text{g/l}$

According to these models, the theoretical initial uptake is about 1.77% of the injected activity, corresponding to the absolute uptake of iodine 125 by the thyroid in the absence of stable iodine circulating in the plasma (Figure 4). In addition, the theoretical maximum inhibition of iodine-125 uptake (associated with a minimum uptake of 0.25%) at infinite concentrations of stable iodine would

be more than 94% (Figure 5). This kinetic modeling of the protective effect of stable KI can be exploited to verify the efficacy of the selected dose of 1 mg/kg KI by correlating stable iodine plasma concentrations to a predicted effect. Thus, a minimum plasma concentration of 174 $\mu\text{g/l}$ of stable iodine would be associated with an uptake of 0.89% of the injected activity (Figure 4), which would represent a 63% decrease in the uptake of iodine-125 compared with control rats (Figure 5). Similarly, a maximum plasma concentration of 1190 $\mu\text{g/l}$ of stable iodine would be associated with an uptake of 0.23% of the injected activity and a theoretical reduction of 88% of the uptake in control rats. Finally, an efficacy of 75% reduction in the uptake of iodine-125 can be associated with an interpolated concentration value of approximately 340 $\mu\text{g/l}$ (Figure 5). In terms of kinetics, the predicted stable plasma iodine concentrations were higher than 500 $\mu\text{g/l}$ for about 10 hours after KI dosing. Therefore, repeated KI prophylaxis with daily dose of 1 mg/kg would theoretically be more than 75% effective for 10 hours (75% to 88%) and comprised between 63% and 75% from 10 hours to 24 hours post dosing.

Simulation and experimental verification of repeated daily oral administrations of stable KI (Experiment 4)

Based on the results of the kinetic study of stable KI protective effect for 24h (experiment 3), a dose of 1 mg/kg KI once daily could be pertinent and simple enough to ensure a good compliance in case of prolonged KI prophylaxis. Hence this dose regimen was simulated with the pharmacokinetic software and tested in rats in order to check the concordance between the measured iodine plasma concentrations during or at the end of repeated prophylaxis and the values predicted by modeling. The simulation of iodine plasma concentrations during a daily repeated oral administration of 1 mg/kg KI was performed using the final estimates of iodine first order rate constants such as the volume of distribution (~~0.8040~~0.8038 l.kg^{-1}), the absorption rate (5.71 h^{-1}) and the elimination rate (0.0864 h^{-1}) which were determined by non-compartmental analysis of plasma data after single oral administrations of KI (experiment 2). The plasma concentration measurements at different sampling times during repeated prophylaxis were interpreted using the mathematical model obtained in the 24h-kinetic study

of the protective effect of 1 mg/kg KI (experiment 3). The simulation of iodine plasma concentrations during a repeated KI prophylaxis and the plasma samples measurements are presented in Table V and Figure 6.

According to this simulation, the steady-state has been achieved after the third dose of KI and plasma iodine concentrations varies between a maximum concentration of approximately 1190 $\mu\text{g/l}$ and a minimal concentration of approximately 174 $\mu\text{g/l}$ (before a subsequent KI administration) (Figure 6). Hence, this dose regimen makes it possible to maintain concentrations at least two times higher than the concentration of the control rats (about 77 $\mu\text{g/l}$) throughout the duration of the treatment.

The values of the average iodine plasma concentrations measured in the control rats were uniform regardless of the sampling time (Table V, Figure 6). With the exception of the measurements in the rats at day 9 (ie 24 hours after the 8th dose of KI) which was higher than the expected theoretical value, the mean values of the concentrations measured at the other times in the treated rats (day 3 + 6h, day 5 and day 10) were consistent and of the same order of magnitude as the predicted values. These results validated the selected dose regimen model.

Discussion

For many years, the absence of analytical methods for the direct determination of iodide anion or stable iodine in blood and organs represented an obstacle to research on the pharmacodynamics and pharmacokinetics of iodine (18). Hence, the development of biokinetic or pharmacokinetic models for iodine was mainly based on studies using radioisotopes of iodine which are toxic elements (3, 19, 20) and on computational modeling (21, 22). Former alternative methods for the quantification of stable iodine in organs and blood were either indirect and dependent on the measurement of iodine in other biological matrixes such as the urines (23, 24), or were based on the Sandell-Kolthoff colorimetric reaction after digestion methods of the samples which could lead to a loss of iodine (25, 26). Recently, more sensitive methods for direct determination of iodine based on ion chromatography (18, 27-29) or capillary electrophoresis coupled to mass spectrometry were developed (30), but very few studies have

been performed with ICP-MS mass spectrometry for the direct measurement of iodine in serum (30, 31). If we refer to the available biokinetic models, free iodine once absorbed into the blood, is distributed evenly between the extracellular and intracellular medium of red blood cells (32). In addition, whole blood would be a biological matrix with high organic matter content that would be less favorable for the accuracy and sensitivity of ICP-MS measurements. These are the reasons why iodine was dosed only in plasma after centrifugation of blood in our studies.

The ICP-MS method adapted in the present work for the quantification of iodine in blood plasma samples proved to be sensitive enough since the results were coherent with data obtained with other methods. Indeed, average iodine plasma concentrations in male control rats varied between 76 µg/l (Table I) and 103 µg/l (Table II) in the present work. The iodine plasma concentration reported in a recent study was slightly lower around 51.1±10.4 µg/l in pregnant rats (31), however those values are comparable and in the same order of magnitude. Similar conclusions could be drawn about measurements of iodine content in thyroids and iodine concentration in the urines. The total iodine content in the thyroids weighing in average 20 µg in the adult rats was comparable with values comprised between 10 and 15 µg iodine which were previously published (20, 33). Contrary to our previous dose-effect study, the total iodine content in the thyroid sampled at 24h post KI administration in the control rats and the treated rats did not differ significantly in the present work probably because the experimental conditions were not exactly the same (different animal batches and KI solutions), and certainly also because of interindividual variability attested by high standard deviations in the measures. Nonetheless, the increase trend in iodine content in the thyroids of KI treated rats supports the assumption of a possible saturation of thyroid in iodine for KI doses very closed to 1 mg/kg (11). In addition, the total iodine excretions in the 24h-urines in the male rats of about 14 µg/24h to 19 µg/24h were slightly higher than values around 4 µg/24h which were measured in other studies in female rats (31). The discrepancy could be explained by the different physiology of the female rats before pregnancy compared with male rats, as well as by the different iodine content in the diets which were used in the studies.

In the present study, the early plasma iodine measurement around 800 µg/l after intravenous dosing may suggest a short infusion instead of a bolus dose although the injection was performed in less than five seconds and no retention at the injection site was observed. As an explanation, it was assumed that the maximal plasma concentration was not yet reached in all animals euthanized soon after the intravenous bolus. As far as the pharmacokinetics of iodine was concerned, it is interesting to note that the elimination half-life value determined in the rats after KI oral administration of about 8.75 ± 1 h was comparable with the data in the literature: an 8.27 h iodine plasma elimination half-life was determined in a study in which iodine was determined in rat serum samples by ion chromatography (28).

The bioavailability value of 90% determined in the present study was consistent with available data in the literature indicating a bioavailability of iodides higher than 90% and up to 99% depending on the diet (32). The pharmacokinetic modeling of iodine after intravenous or oral administration were both consistent, as attested by the statistics. More complicated biokinetic or pharmacokinetic models with larger number of compartments have been published so far in order to describe the metabolism of dietary iodine or to estimate radiation dose induced by radioiodine incorporation in the thyroid (19, 29, 32, 34, 35). Besides, a limited number of biokinetic models have been dedicated to stable iodine as a thyroid blocking agent (21, 22, 36). Anyhow, the kinetic models and the analysis of plasma data in the present work were sufficient for the determination of the main pharmacokinetic parameters (volume of distribution, absorption constant and elimination constant) which were useful to model and to study iodine plasma concentrations as a function of the time during a repeated KI prophylaxis.

In the frame of the present research program, it was decided to study a repeated KI prophylaxis for eight days, in order to propose a countermeasure adapted to scenarios of repeated releases of radioactive iodine over more than a week, like the events that occurred after the Fukushima accident in Japan in 2011. This was also in agreement with other authors who recommended that the maximal duration of a repeated prophylaxis in case of impossibility to evacuate the population would be eight days (37).

In terms of thyroid protection, it has been reported in the literature that the percentage of avoided dose to the thyroid is comprised between 50% and 75% if the exposure occurs 48 hours after single oral administration of 100 mg to 200 mg of stable iodide (1.8 to 3.7 mg/kg KI) (3). Such levels of thyroid protection could serve as target values of minimal efficacy and were selected for the assessment of KI dose regimen in our study. According to the pharmacokinetic-pharmacodynamic relationship determined in this study, the minimal iodine plasma concentration which would be necessary to block at least 75% of the radioiodine thyroid uptake in the rats was around 340 µg/l. Interestingly, this iodine plasma level is consistent and of the same order of magnitude as values published in a previous work. Indeed, a decrease in the thyroid iodide uptake has been observed for plasma iodine concentrations higher than 500 µg/l in rats treated with different doses of sodium iodide (38). This iodine effect-concentration modeling resulting from the combination of the results of pharmacokinetic studies (experiment 1) and the protection kinetic study (experiment 3) presents the advantage of demonstrating the existence of a correlation between the effect of oral KI administration and the stable iodine plasma concentrations and thus allowed to verify the efficacy of the repeated KI prophylaxis. Besides, the proposed dose regimen remains interesting from a predictive point of view since it exhibits satisfactory levels of protection of the thyroid by stable iodine throughout the repeated treatment. The other reason for selecting an optimal KI dose which is lower than the dose currently used in single administrations was to prevent side effects potentially induced by repeated administrations of excessive iodine doses (37). Therefore, this dose regimen was also evaluated from a toxicological point of view in another study and proved to be safe since the secretion of thyroid hormones and the main biochemical parameters were unaffected in adult rats by daily administrations of 1 mg/kg KI over a period of 8 days (39). Finally, this dose regimen was studied in an animal model kept under sufficient dietary iodine intake. Further refinements and dose adjustments could be implemented to the repeated prophylaxis model by taking into account the dietary iodine; as it was suggested that the level of thyroid protection by KI could be different when the dietary levels of iodine was sufficient or deficient (for instance 250 µg/day and 50 µg/day in humans, respectively) (5, 40).

413 Conclusion

1
2
3 414 The pharmacokinetic parameters of iodine after oral and intravenous administration of the optimal
4
5 415 dose of 1 mg/kg KI have been determined in order to model a dose regimen consisting of repeated
6
7 416 daily administrations of this dose over 8 days. The results of thyroid protection kinetic studies and
8
9 417 plasma kinetics of stable iodine during a repeated prophylaxis showed that this dose regimen would
10
11 418 provide over 75% thyroid protection for ~~10-14~~ hours after the first KI administration and more than
12
13 419 60% protection prior the subsequent KI dosing. Ultimately, application of uncertainty factors may be
14
15 420 necessary in order to transpose the KI doses and the results obtained experimentally in the rats to
16
17 421 humans. The rationale for selecting and using smaller KI doses than the currently recommended single
18
19 422 dose in adults in case of repeated KI prophylaxis was to maintain efficient protection of the thyroid
20
21 423 whilst minimizing the risks of adverse effects. Hence, further pharmacological and toxicological
22
23 424 studies of repeated administrations of KI should be performed not only in adults, but also in animal
24
25 425 models representing more sensitive individuals such as the children or the pregnant women before
26
27 426 considering the extension of the indications of KI as potential treatment in case of prolonged exposure
28
29 427 to radioisotopes of iodine.
30
31
32
33

428 Acknowledgments

34
35
36
37
38 429 The authors are thankful to the Central Army Pharmacy for providing solutions of KI, Dr Delphine
39
40 430 Denais-Lalieu (DVM), Mélanie Berchet, Amandine Sache, Romain Granger and Frédéric Voyer from
41
42 431 the animal experiment support group of IRSN for animal care.
43
44

432 Declaration of conflicting interests

45
46
47
48
49 433 The authors declared no potential conflicts of interest with respect to research, authorship and
50
51 434 publication of this article.
52
53

435 Funding

54
55
56
57 436 These studies were supported by the research program in Nuclear Safety and Radiation Protection of
58
59 437 the French National Research Agency (ANR) (contract number ANR-11-RSNR-0019).
60
61
62
63
64
65

438 References

- 1
2
3 439 1. M.C. Mahoney, S. Lawvere, K.L. Falkner, Y.I. Averkin, V.A. Ostapenko, A.M. Michalek, K.B.
4 440 Moysich, and P.L. McCarthy. Thyroid cancer incidence trends in Belarus: examining the
5 441 impact of Chernobyl. *International Journal of Epidemiology*. 33:1025-1033 (2004).
- 6 442 2. V.V. Shakhtarin, A.F. Tsyb, V.F. Stepanenko, M.Y. Orlov, K.J. Kopecky, and S. Davis. Iodine
7 443 deficiency, radiation dose, and the risk of thyroid cancer among children and adolescents
8 444 in the Bryansk region of Russia following the Chernobyl power station accident.
9 445 *International Journal of Epidemiology*. 32:584-591 (2003).
- 10 446 3. P. Verger, A. Aurengo, B. Geoffroy, and B. Le Guen. Iodine kinetics and effectiveness of
11 447 stable iodine prophylaxis after intake of radioactive iodine: A review. *Thyroid*. 11:353-360
12 448 (2001).
- 13 449 4. C. Reinersand R. Schneider. Potassium iodide (KI) to block the thyroid from exposure to I-
14 450 131: Current questions and answers to be discussed. *Radiation and Environmental*
15 451 *Biophysics*. 52:189-193 (2013).
- 16 452 5. World Health Organization. Iodine thyroid blocking: guidelines for use in planning for and
17 453 responding to radiological and nuclear emergencies, Geneva, 2017, p. 46.
- 18 454 6. K.M. Saxena, E.M. Chapman, and C.V. Pryles. Minimal dosage of iodide required to
19 455 suppress uptake of iodine-131 by normal thyroid. *Science*. 138:431-433 (1962).
- 20 456 7. R.G. Cuddihy. Thyroidal iodine-131 uptake, turnover and blocking in adults and
21 457 adolescents. *Health Physics*. 12:1021-1025 (1966).
- 22 458 8. Y. Kunii, T. Uruno, K. Mukasa, K. Sekiya, K. Iwaku, A. Suzuki, K. Sugino, J. Yoshimura Noh,
23 459 and K. Ito. Inhibitory effect of low-dose inorganic iodine on thyroidal radioactive iodine
24 460 uptake in healthy Japanese adults. *Endocrine Journal*. 63:21-27 (2016).
- 25 461 9. E. Sternthal, L. Lipworth, and B. Stanley. Suppression of thyroid radioiodine uptake by
26 462 various doses of stable iodide. *New England Journal of Medicine*. 303:1083-1088 (1980).
- 27 463 10. M. Blumand M. Eisenbud. Reduction of thyroid irradiation from 131-I by potassium iodide.
28 464 *Journal of the American Medical Association*. 200:1036-1040 (1967).
- 29 465 11. G. Phan, F. Rebiere, D. Suhard, A. Legrand, F. Carpentier, T. Sontag, M. Souidi, J.R. Jourdain,
30 466 M. Agarande, and V. Renaud-Salis. Optimal KI Prophylactic Dose Determination for Thyroid
31 467 Radiation Protection After a Single Administration in Adult Rats. Dose-response : a
32 468 publication of International Hormesis Society. 15:1-8 (2017).
- 33 469 12. G. Landon, C. Bouvier-Capely, A. Legrand, T. Sontag, G. Finance, M. Saint-Hilaire, F. Rebière,
34 470 X. Millot, V. Renaud-Salis, and M. Agarande. Validation and comparison of two calibration
35 471 methods for themeasurement of stable iodine in the urinary matrix by ICP-MS: standard
36 472 addition vs external calibration. *American Journal of Analytical Chemistry*. 8:245-263
37 473 (2017).
- 38 474 13. J. Gabrielsson, B. Meibohm, and D. Weiner. Pattern Recognition in Pharmacokinetic Data
39 475 Analysis. *AAPS Journal*. 18:47-63 (2016).
- 40 476 14. J. Gabrielsson and D. Weiner. Pharmacokinetics and pharmacodynamic data analysis:
41 477 concepts and applications, Swedish Academy of Pharmaceutical Sciences, Stockholm, 2016.
- 42 478 15. H. Akaike. A New Look at the Statistical Model Identification. *IEEE Transactions on*
43 479 *Automatic Control*. 19:716-723 (1974).
- 44 480 16. J. Gabrielssonand D. Weiner. Akaike and Schwarz criteria. Pharmacokinetics and
45 481 pharmacodynamic data analysis: concepts and applications, Swedish Academy of
46 482 Pharmaceutical Sciences, Stockholm, 2016, p. 389.
- 47 483 17. G. Schwarz. Estimating the Dimension of a Model. *Ann Statist*. 6:461-464 (1978).
- 48 484 18. H.G. Abrahamyanand A.S. Hovhannisyan. Comparative pharmacokinetics of iodide anion at
49 485 administration of iodine preparations. *New Armenian Medical Journal*. 5:26-32 (2011).
- 50 486 19. V. Berkovski. New iodine models family for simulation of short-term biokinetics processes,
51 487 pregnancy and lactation. *Food and Nutrition Bulletin*. 23:87-94 (2002).

- 488 20. E.D. McLanahan, M.E. Andersen, and J.W. Fisher. A biologically based dose-response model
1 489 for dietary iodide and the hypothalamic-pituitary-thyroid axis in the adult Rat: Evaluation
2 490 of iodide deficiency. *Toxicological Sciences*. 102:241-253 (2008).
- 3 491 21. M. Jang, H.K. Kim, C.W. Choi, and C.S. Kang. Age-dependent potassium iodide effect on the
4 492 thyroid irradiation by ¹³¹I and ¹³³I in the nuclear emergency. *Radiation Protection*
5 493 *Dosimetry*. 130:499-502 (2008).
- 6 494 22. M. Jang, H.K. Kim, C.W. Choi, and C.S. Kang. Thyroid dose estimation with potassium iodide
7 495 (KI) administration in a nuclear emergency. *Radiation Protection Dosimetry*. 132:303-307
8 496 (2008).
- 9 497 23. D.A. Koutras, A.D. Pharmakiotis, N. Koliopoulos, J. Tsoukalos, A. Souvatzoglou, and J.
10 498 Sfontouris. The plasma inorganic iodine and the pituitary-thyroid axis in pregnancy. *J*
11 499 *Endocrinol Invest*. 1:227-231 (1978).
- 12 500 24. S. Nagataki, K. Shizume, and K. Nakao. Effect of iodide on thyroidal iodine turnover in
13 501 hyperthyroid subjects. *Journal of Clinical Endocrinology and Metabolism*. 30:469-478
14 502 (1970).
- 15 503 25. C.S. Liberman, S.C. Pino, S.L. Fang, L.E. Braverman, and C.H. Emerson. Circulating Iodide
16 504 Concentrations during and after Pregnancy¹. *The Journal of Clinical Endocrinology &*
17 505 *Metabolism*. 83:3545-3549 (1998).
- 18 506 26. T. Paul, B. Meyers, R.J. Witorsch, S. Pino, S. Chipkin, S.H. Ingbar, and L.E. Braverman. The
19 507 effect of small increases in dietary iodine on thyroid function in euthyroid subjects.
20 508 *Metabolism*. 37:121-124 (1988).
- 21 509 27. G.E. Abraham. Serum inorganic iodide levels following ingestion of a tablet form of Lugol
22 510 solution: evidence for an enterohepatic circulation of iodine. *The Original Internist*. 11:29-
23 511 34 (2004).
- 24 512 28. G. Delgado, C. Muñoz-Torres, T. Orozco-Esquivel, B. Anguiano, and C. Aceves. Total iodine
25 513 quantification in fluids and tissues from iodine- or iodide-supplemented rats by ion
26 514 chromatography following microwave-assisted digestion. *Thyroid*. 25:352-360 (2015).
- 27 515 29. M.E. Gilbert, E.D. McLanahan, J. Hedge, K.M. Crofton, J.W. Fisher, L. Valentin-Blasini, and
28 516 B.C. Blount. Marginal iodide deficiency and thyroid function: Dose-response analysis for
29 517 quantitative pharmacokinetic modeling. *Toxicology*. 283:41-48 (2011).
- 30 518 30. C.P. Shelorand P.K. Dasgupta. Review of analytical methods for the quantification of iodine
31 519 in complex matrices. *Analytica Chimica Acta*. 702:16-36 (2011).
- 32 520 31. X. Sun, L. Lu, L. Shan, Z. Shan, and W. Teng. Iodine storage and metabolism of mild to
33 521 moderate iodine-deficient pregnant rats. *Thyroid*. 27:846-851 (2017).
- 34 522 32. R.W. Leggett. A physiological systems model for iodine for use in radiation protection.
35 523 *Radiation Research*. 174:496-516 (2010).
- 36 524 33. E.D. McLanahan, J.L. Campbell Jr, D.C. Ferguson, B. Harmon, J.M. Hedge, K.M. Crofton, D.R.
37 525 Mattie, L. Braverman, D.A. Keys, M. Mumtaz, and J.W. Fisher. Low-dose effects of
38 526 ammonium perchlorate on the hypothalamic-pituitary-thyroid axis of adult male rats
39 527 pretreated with PCB126. *Toxicological Sciences*. 97:308-317 (2007).
- 40 528 34. R.A. Clewell, E.A. Merrill, K.O. Yu, D.A. Mahle, T.R. Sterner, D.R. Mattie, P.J. Robinson, J.W.
41 529 Fisher, and J.M. Gearhart. Predicting fetal perchlorate dose and inhibition of iodide kinetics
42 530 during gestation: A physiologically-based pharmacokinetic analysis of perchlorate and
43 531 iodide kinetics in the rat. *Toxicological Sciences*. 73:235-255 (2003).
- 44 532 35. R. Leggett. An age-specific biokinetic model for iodine. *Journal of Radiological Protection*.
45 533 37:864 (2017).
- 46 534 36. D. Ramsden, F.H. Passant, C.O. Peabody, and R.G. Speight. Radioiodine uptakes in the
47 535 thyroid studies of the blocking and subsequent recovery of the gland following the
48 536 administration of stable iodine. *Health Physics*. 13:633-646 (1967).
- 49 537 37. E.R. Braverman, K. Blum, B. Loeffke, R. Baker, F. Kreuk, S.P. Yang, and J.R. Hurley.
50 538 *Managing terrorism or accidental nuclear errors, preparing for iodine-131 emergencies: A*

- comprehensive review. International journal of environmental research and public health. 11:4158-4200 (2014).
38. S. Nagataki and S.H. Ingbar. Relation Between Qualitative and Quantitative Alterations in Thyroid Hormone Synthesis Induced by Varying Doses of Iodide. Endocrinology. 74:731-736 (1964).
39. D. Lebsir, L. Manens, S. Grison, P. Lestaevel, T. Ebrahimian Chiusa, D. Suhard, G. Phan, I. Dublineau, K. Tack, M. Benderitter, A. Pech, J.-R. Jourdain, and M. Souidi. Effects of repeated potassium iodide administration on genes involved in synthesis and secretion of thyroid hormone in adult male rats. Molecular and Cellular Endocrinology. 474:119-126 (2018 ~~in press~~).
40. P.B. Zanzonico and D.V. Becker. Effects of time of administration and dietary iodine levels on potassium iodide (KI) blockade of thyroid irradiation by ¹³¹I from radioactive fallout. Health Physics. 78:660-667 (2000).

1 Table I: Kinetics of stable iodine after KI intravenous injection

KI dose (mg/kg)	Mean plasma iodine concentration ± SD (µg/l)		Mean thyroid iodine content ± SD (µg/g)		Mean 24h-cumulated iodine in urines ± SD (µg)	
	0	1	0	1	0	1
Time post KI (h)						
0	86 ± 15	762 ± 282	1067 ± 229	959 ± 296	NA	NA
0.167	82 ± 13	1445 ± 377	861 ± 194	780 ± 361	NA	NA
0.333	78 ± 11	1521 ± 160	708 ± 178	906 ± 206	NA	NA
0.667	69 ± 9	1355 ± 173	596 ± 334	737 ± 205	NA	NA
1	78 ± 5	1171 ± 113	849 ± 137	770 ± 235	NA	NA
2	81 ± 14	846 ± 80	853 ± 275	810 ± 63	NA	NA
4	78 ± 13	615 ± 83	815 ± 317	602 ± 241	NA	NA
6	74 ± 6	598 ± 49	883 ± 229	1037 ± 470	NA	NA
8	74 ± 11	524 ± 166	1141 ± 475	770 ± 259	NA	NA
24	61 ± 2	164 ± 45	846 ± 245	1039 ± 329	19 ± 5	246 ± 58

2 N=5 rats per time point
3 NA : not available

4

5

6

7

8

9

10

11

1

12 Table II: Kinetics of stable iodine after KI oral administration

KI dose (mg/kg)	Mean plasma iodine concentration ± SD (µg/l)		Mean thyroid iodine content ± SD (µg/g)		Mean 24h-cumulated iodine in urines ± SD (µg)	
	0	1	0	1	0	1
Time post KI (h)						
0.25	224 ± 3	891 ± 95	NA	NA	NA	NA
0.5	128 ± 1	903 ± 185	NA	NA	NA	NA
0.75	93 ± 2	988 ± 144	NA	NA	NA	NA
1	148 ± 1	1039 ± 36	NA	NA	NA	NA
1.5	76 ± 12	1021 ± 184	976 ± 346	989 ± 124	NA	NA
2	117 ± 84	853 ± 280	842 ± 215	880 ± 287	NA	NA
2.5	81 ± 3	847 ± 225	956 ± 309	871 ± 198	NA	NA
3	70 ± 16	832 ± 143	1024 ± 284	927 ± 145	NA	NA
3.5	70 ± 6	841 ± 209	860 ± 283	876 ± 198	NA	NA
4	139 ± 97	720 ± 111	856 ± 284	895 ± 231	NA	NA
6	80 ± 29	624 ± 134	692 ± 267	814 ± 298	NA	NA
8	81 ± 27	563 ± 177	841 ± 209	834 ± 258	NA	NA
24	69 ± 8	175 ± 102	814 ± 183	908 ± 233	14 ± 4	173 ± 42
48	70 ± 5	97 ± 36	839 ± 215	985 ± 147	14 ± 2	29 ± 6

13 N=6 rats per time point

14 NA : not available

15

16

17

18

19 Table III: Main stable iodine pharmacokinetic parameters after intravenous injection and oral
 20 administration of 1 mg/kg KI

21

<u>Parameter</u>	<u>Primary parameters</u>	<u>Estimate</u> <u>(coefficient of variation</u> <u>%)</u>	<u>Units</u>
Volume of distribution		0.8038	l.kg ⁻¹
Clearance		0.08637	l. kg ⁻¹ .h ⁻¹
Lag time		0	h
Absorption		5.71297	h ⁻¹
constant First order rate constant of absorption			
Oral bioavailability		89.5629	%
<u>Secondary parameters</u>			
Maximal concentration after intravenous dose		<u>1275.6533 (9.58)</u>	<u>µg.l⁻¹</u>
Elimination half life after intravenous dose		<u>5.4545 (34.96)</u>	<u>h</u>
Maximal concentration after oral dose		<u>993.3562 (2.31)</u>	<u>µg.l⁻¹</u>
Time corresponding to the maximal concentration after oral dose		<u>0.6347 (14.52)</u>	<u>h</u>
Elimination half life after oral dose		<u>8.7531 (11.34)</u>	<u>h</u>

Formatted Table

22 The primary pharmacokinetic parameters were generated by simultaneous fitting of intravenous and
 23 oral plasma data with a mono-compartmental model using the Phoenix modeling tool, and the
 24 secondary parameters were estimated using the classic compartmental analysis tool of WinNonlin
 25 software

26

27

28

29

30

31

32

33

34

35

36

37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59

Table IV: Iodine I-125 uptake in the thyroid and avoided activity compared to control rats as a function of the time post KI dosing and the concentration of stable iodine in plasma

Time post KI (h)	Predicted plasma iodine concentration (µg/l)	Mean iodine I-125 uptake in the thyroid (%IA) ± SD	Mean avoided I-125 activity in the thyroid (% controls) ± SD
1	74	1.78 ± 0.52	NA
2	890	0.37 ± 0.08	87 ± 3
4	755	0.30 ± 0.09	86 ± 3
12	391	0.48 ± 0.14	76 ± 9
16	282	0.74 ± 0.17	66 ± 11
20	203	0.62 ± 0.12	71 ± 5
24	146	0.86 ± 0.16	61 ± 7

N=6 rats per time point
IA : injected activity
NA: not applicable

60
61
62
63
64
65
66
67
68

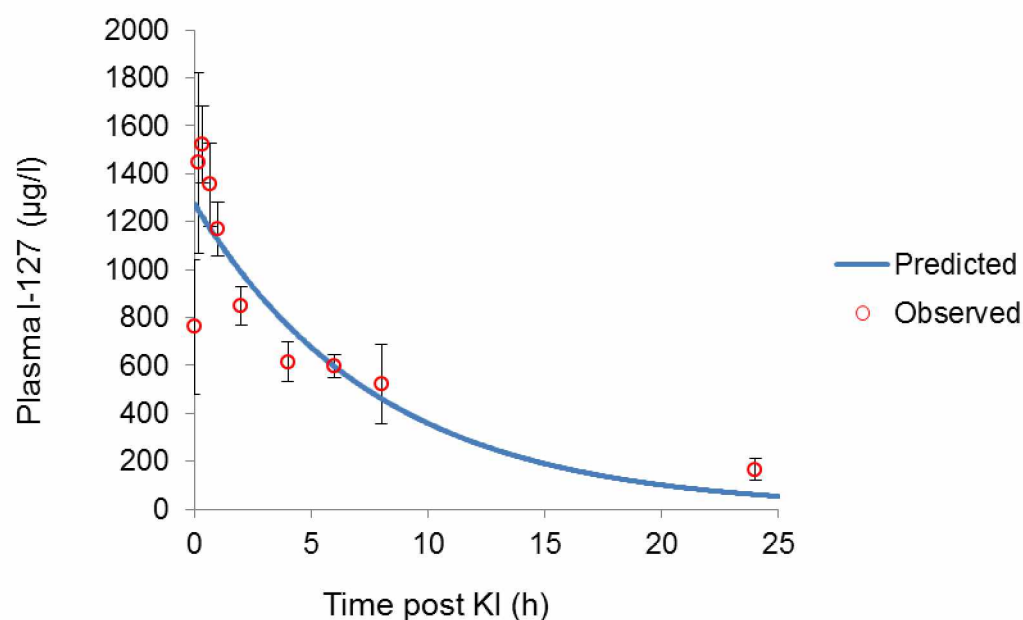
69 Table V: Plasma stable iodine concentrations measured at different times in rats treated by 1 mg/kg KI
70 daily for 8 days and predicted inhibition of I-125 uptake in the thyroid

Sampling time after the beginning of KI repeated prophylaxis	Plasma iodine concentration in treated rats \pm SD ($\mu\text{g/l}$)	Predicted plasma iodine concentration in treated rats ($\mu\text{g/l}$)	Plasma iodine concentration in control rats \pm SD ($\mu\text{g/l}$)	Predicted efficacy of the measured plasma iodine (% inhibition of thyroid uptake)	Predicted efficacy of the theoretical plasma iodine (% inhibition of thyroid uptake)
Day 3	584 \pm 42	751	92 \pm 18	77	79
Day 5	221 \pm 40	155	66 \pm 6	61	50
Day 9	272 \pm 15	151	73 \pm 14	66	50
Day 10	107 \pm 6	77	64 \pm 8	28	7

71 N=4 rats per time point

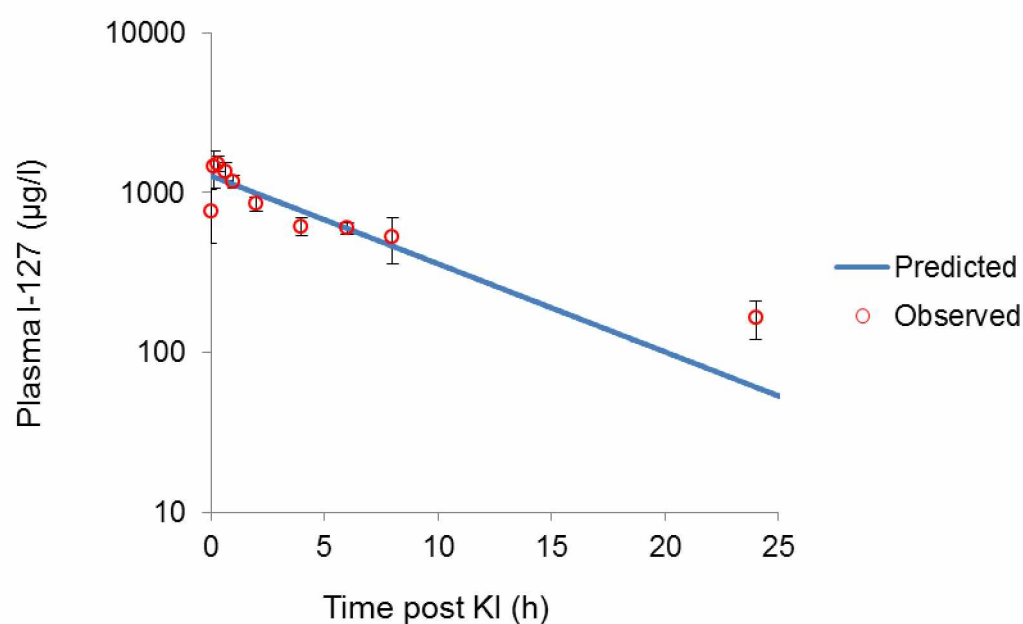
1 Figure 1

2 (A)



3

4 (B)

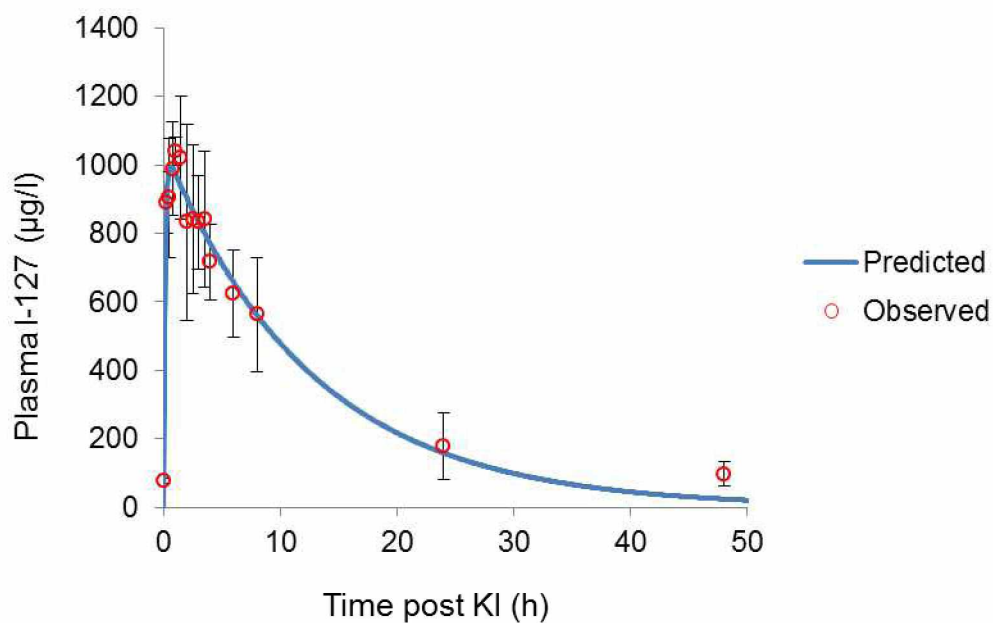


5

6 **Figure 1.** Plasma concentration of stable iodine after intravenous injection of 1 mg/kg KI in the rats;
7 the observed values are the mean of five rats \pm standard deviation and represented by the circles; the
8 predicted values obtained from pharmacokinetic modeling are represented by the curve. Graph (A)
9 represents plasma stable iodine concentrations in linear scale, and graph (B) represents plasma stable
10 iodine concentrations in log scale.

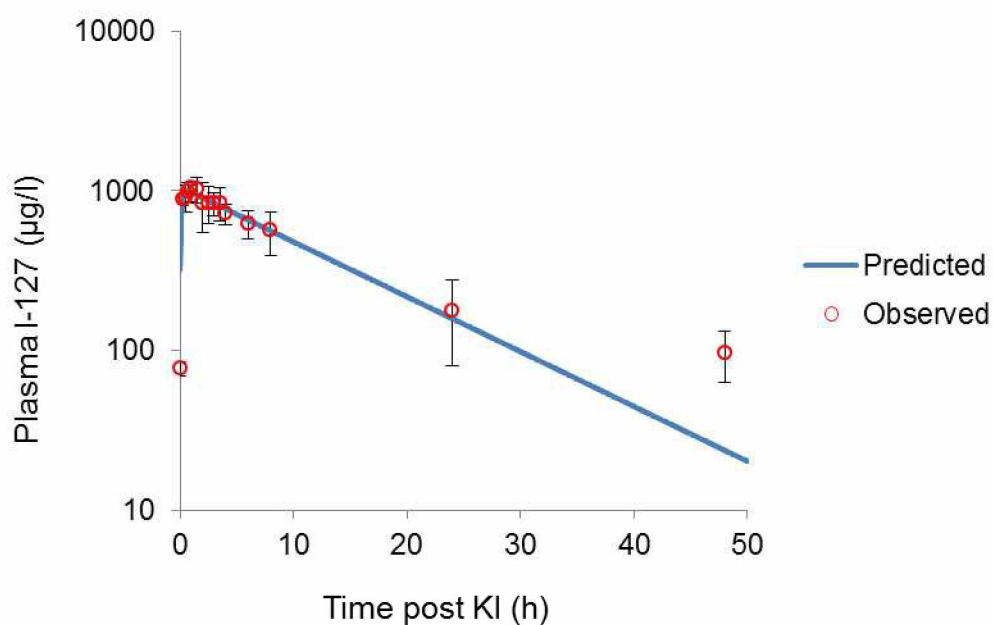
11 Figure 2

12 (A)



13

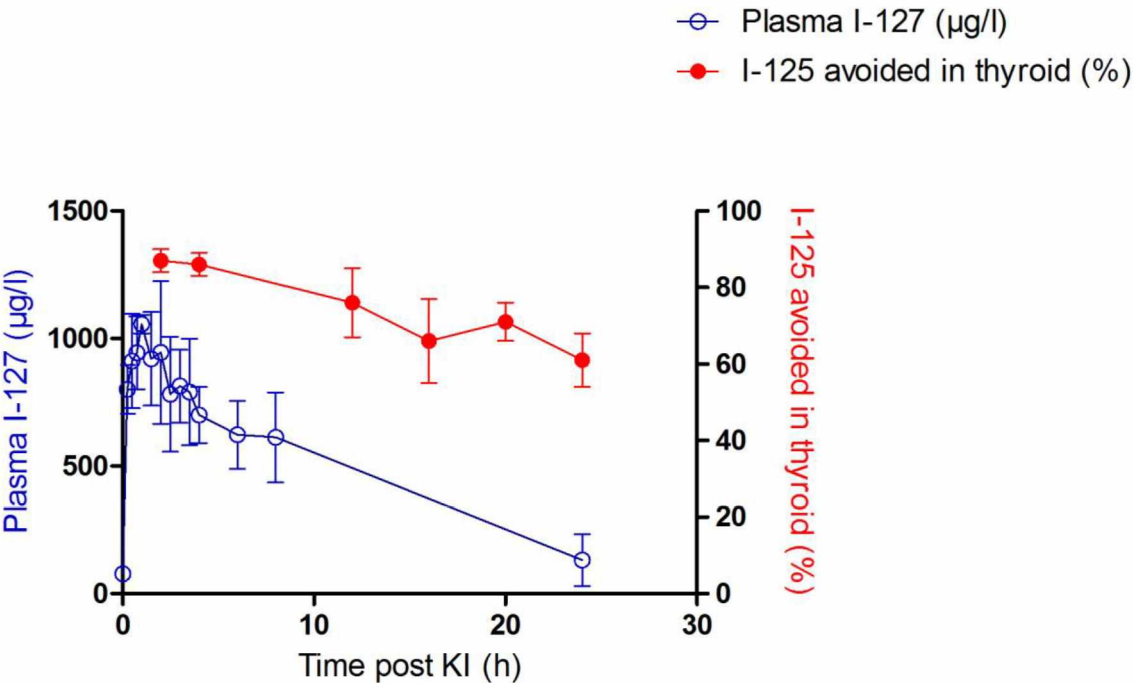
14 (B)



15

16 **Figure 2.** Plasma concentration of stable iodine after oral administration of 1 mg/kg KI in the rats; the
17 observed values are the mean of six rats \pm standard deviation and represented by the circles; the
18 predicted values obtained after pharmacokinetic modeling are represented by the curve. Graph (A)
19 represents plasma stable iodine concentrations in linear scale, and graph (B) represents plasma stable
20 iodine concentrations in log scale.

21 Figure 3



22
23 **Figure 3.** Iodine-125 avoided activities in the thyroid (expressed as percentages of controls) and
24 plasma stable iodine concentration as a function of the time after oral administration of 1 mg/kg KI;
25 the observed values are the mean of six rats \pm standard deviation; the avoided I-125 activities are
26 represented by the closed circles (right Y-axis); the plasma stable iodine concentrations are
27 represented by the open circles (left Y-axis).

Figure 4

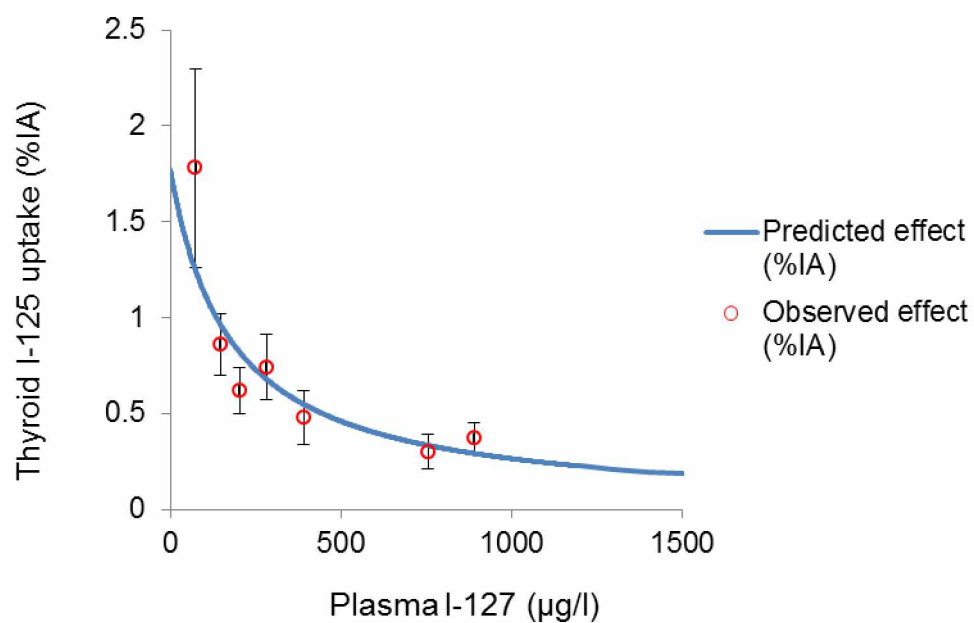


Figure 4. Iodine-125 uptake in the thyroid (expressed as percentages of injected activity) as a function of plasma stable iodine concentration; the observed values are the mean of six rats \pm standard deviation and represented by the circles; the inhibition function is represented by the curve.

Figure 5

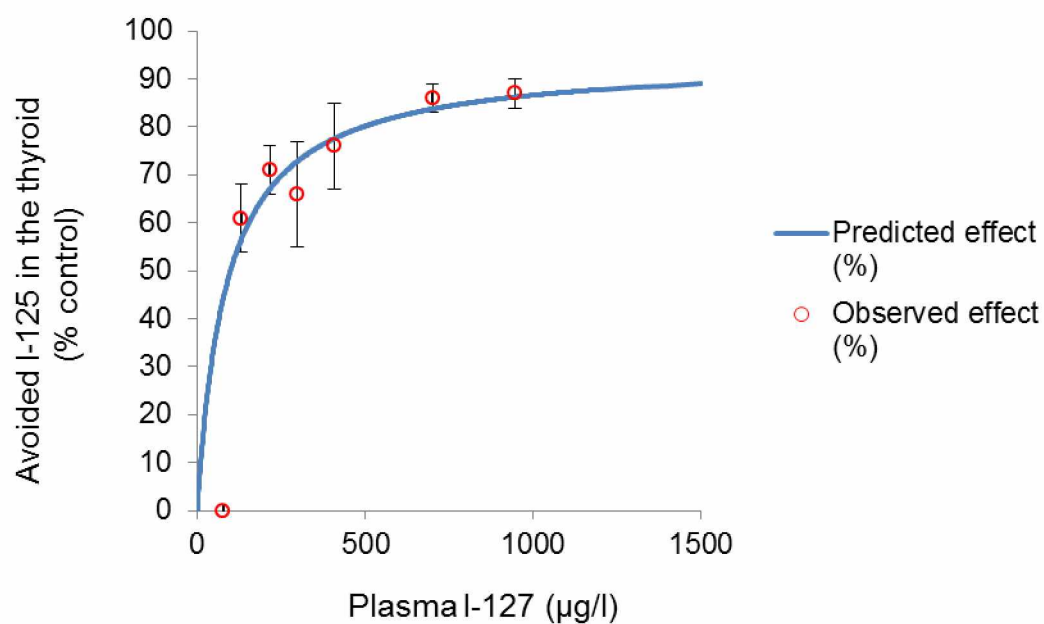
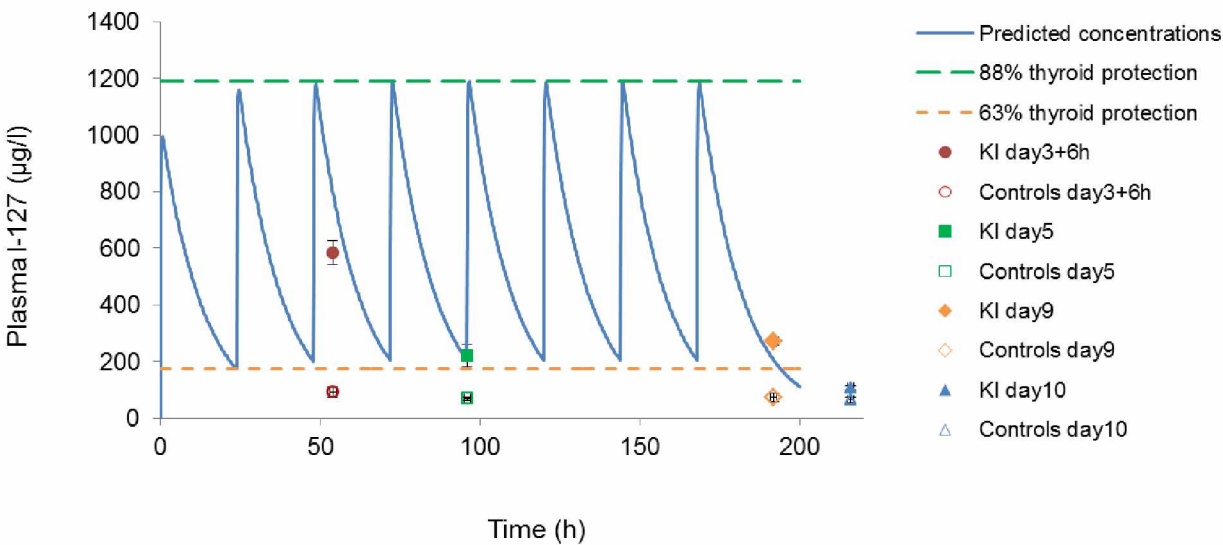


Figure 5. Avoided iodine-125 activity in the thyroid compared with the uptake in control rats (expressed as percentages of uptake in control rats) as a function of plasma stable iodine concentration; the observed values are the mean of six rats \pm standard deviation and represented by the circles; the specific binding function is represented by the curve.

79 Figure 6



80
81 **Figure 6.** Plasma iodine concentrations measured at different times in rats treated by 1 mg/kg of KI
82 daily for eight days; the observed values are the mean of four rats \pm standard deviation; the predicted
83 concentrations obtained after pharmacokinetic modeling are represented by the curve; horizontal dotted
84 lines represent concentration levels associated to relevant percentage of uptake inhibition and thyroid
85 protection.