



**HAL**  
open science

## 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-02881796v1>**

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  
4  
5 **3** Guillaume Phan<sup>1</sup>, Rym Chioukh<sup>1</sup>, David Suhard<sup>1</sup>, Alexandre Legrand<sup>1</sup>, Charlotte Moulin<sup>1</sup>, Thibaud  
6  
7 **4** Sontag<sup>1</sup>, François Rebière<sup>1</sup>, Céline Bouvier-Capely<sup>1</sup>, Michelle Agarande<sup>1</sup>, Valérie Renaud-Salis<sup>1</sup>, Jean-  
8  
9 **5** René Jourdain<sup>1</sup>

10  
11  
12 **6** Corresponding author: Guillaume Phan, email [guillaume.phan@irsn.fr](mailto:guillaume.phan@irsn.fr)

13  
14  
15  
16 **7** <sup>1</sup> Institute for Radiation Protection and Nuclear Safety, Health Division, 31 avenue de la Division  
17  
18 **8** Leclerc, F-92260 Fontenay-aux-Roses, France

19  
20  
21 **9**

22  
23  
24 **10**

25  
26  
27 **11**

28  
29  
30 **12**

31  
32  
33 **13**

34  
35  
36 **14**

37  
38  
39 **15**

40  
41  
42 **16**

43  
44  
45 **17**

46  
47  
48 **18**

49  
50  
51 **19**

52  
53  
54 **20**

55  
56  
57  
58 **21** Proposed running title: KI pharmacokinetics in the rats

1  
2  
3 **22 Abstract**

4 **23 Purpose** To propose a new and effective dose regimen for stable potassium iodide (KI) repeated  
5 **24** prophylaxis in case of prolonged exposure to radioactive iodine.

6  
7  
8 **25 Methods** The pharmacokinetics of iodine was determined in rats by compartmental analyses after  
9  
10 **26** intravenous and oral administrations of the optimal dose of 1 mg/kg KI, which was previously selected  
11  
12 **27** in a dose-effect study. The thyroid protection against iodine-125 incorporation was followed during  
13  
14 **28** 24h after a single oral dosing of KI. A repeated KI prophylaxis was modeled using initial estimates of  
15  
16 **29** iodine pharmacokinetic parameters.

17  
18  
19  
20 **30 Results** A dose regimen consisting in administrations of 1 mg/kg daily for eight days was selected and  
21  
22 **31** studied. Plasma iodine concentrations predicted by simulation were verified by experimental data and  
23  
24 **32** varied after the third dose of KI between 174 and 1190 µg/l. The inhibition study of iodine-125  
25  
26 **33** binding in the thyroid as a function of the time showed that the protection effect of KI could be  
27  
28 **34** correlated to stable iodine plasma concentrations. Hence, a theoretical decrease in iodine-125 thyroid  
29  
30 **35** uptake from 63% to 88% could be achieved in a 24h-interval between two KI doses.

31  
32  
33  
34 **36 Conclusion** Given the satisfactory levels of thyroid protection, this dose regimen could be envisaged  
35  
36 **37** in order to extent KI indications for repeated prophylaxis.

37  
38  
39  
40 **38 Keywords**

41  
42  
43 **39** Potassium iodide prophylaxis; pharmacokinetics; dose regimen; pharmacokinetic-pharmacodynamic  
44  
45 **40** relationship; rats

46  
47  
48 **41**

49  
50  
51 **42**

52  
53  
54 **43**

55  
56  
57 **44**

## 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

72 correlation has never been fully characterized experimentally or by pharmacokinetic-  
73 pharmacodynamic (PKPD) modeling. In early studies in healthy volunteers, the minimal serum iodide  
74 concentration inducing a thyroid iodine-131 uptake of less than 1.3% was determined around 100 µg/l  
75 (10). In another study, a thyroid iodine-123 uptake of less than 2% in euthyroid volunteers has been  
76 associated with serum iodine concentrations of at least 220 µg/l (9). Hence, in the frame of the  
77 research program PRIODAC co-funded by the French National Research Agency, we undertook to  
78 revise and complete the data on stable KI prophylaxis by conducting pharmacological and  
79 toxicological studies in the rats. An optimal single dose of 1 mg/kg KI has first been determined from  
80 experiment in adult rats and was selected on the basis of the level of thyroid protection against iodine-  
81 125 incorporation as well as on the thyroid distribution and urinary elimination of stable iodine (11).  
82 The purposes of the present work were to study the pharmacokinetics of KI after administration of the  
83 specific dose of 1 mg/kg KI to rats and to assess the duration of the thyroid protective effect of this  
84 dose in order to propose an optimal dose regimen for repeated KI prophylaxis.

## 86 **Materials and Methods**

### 87 *Animals*

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

99 *Chemicals*

1  
2  
3 **100** Stable potassium iodide (I-127) solutions at different concentrations in sterile water pH 7.4 were  
4  
5 **101** prepared and provided by the French Central Armed Forces Pharmacy (Orléans, France). Radioactive  
6  
7 **102** potassium iodide I-125 solution at a concentration of 3700 MBq/ml and with a specific activity of  
8  
9 **103** 643.8 MBq/pg was purchased from Biotrend (Köln, Germany).

10  
11  
12 **104** *Experiment protocols*

13  
14  
15  
16 **105** *Experiment 1: Pharmacokinetics of stable iodine after a single intravenous administration of KI*

17  
18  
19 **106** Rats were injected once in the lateral tail vein with either physiological saline or 1 mg/kg of KI  
20  
21 **107** (volume = 0.2 ml of a KI solution at a concentration of 1.75 g/l). The rats were then placed  
22  
23 **108** individually in metabolic cages and euthanized by intracardiac puncture at the corresponding time for  
24  
25 **109** each rat prior to harvesting the blood and the thyroid (5 rats per time point). The sampling times were:  
26  
27 **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  
28  
29 **111** time-point animals.

30  
31  
32  
33  
34 **112** *Experiment 2: Pharmacokinetics of stable iodine after a single oral administration of KI*

35  
36  
37 **113** Rats were administered once orally by esophageal gavage with either physiological saline or 1 mg/kg  
38  
39 **114** of KI (volume = 1 ml of a KI solution at a concentration of 0.35 g/l) using a disposable plastic cannula  
40  
41 **115** (Instech laboratories, Plymouth Meeting, USA). The rats were then placed individually in metabolic  
42  
43 **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  
44  
45 **117** 48 h post KI administration to harvest the blood and the thyroid (6 rats per time point). Urine was  
46  
47 **118** collected from 24-h and 48-h time-point animals.

48  
49  
50  
51 **119** *Experiment 3: Effect of a single oral administration of stable KI on the 24h-thyroid uptake of iodine I-*  
52  
53 **120** *125*

54  
55  
56 **121** Rats were administered once orally by esophageal gavage with either physiological saline or 1 mg/kg  
57  
58 **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

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

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

128 The simulation of different KI dose regimen was performed using Phoenix WinNonlin software  
129 version 6.3 (Certara, Princeton, USA) and the final parameter estimates obtained from the selected  
130 pharmacokinetic model. In order to verify the plasma iodine concentrations at different times during a  
131 repeated administration of KI, groups of rats were administered orally by esophageal gavage with  
132 either physiological saline or 1 mg/kg of KI (volume = 1 ml of a KI solution at a concentration of  
133 0.35 g/l) once a day for up to eight days. The rats were then placed individually in metabolic cages and  
134 euthanized by intracardiac puncture at 6h after three KI administrations (day 3), at 24 h after four KI  
135 administrations (day 5), at 24 h after eight KI administrations (day 9) and 48 h after eight KI  
136 administrations (day 10) to harvest the blood and the thyroid (4 rats per time point).

137 *Iodine analysis in biological samples*

138 After euthanasia of the animals, the thyroid is dissected, rinsed, dried on gauze and weighed. The  
139 blood and the urines are centrifuged using an Eppendorf centrifuge 5810R (4000 rpm, for 20 min at  
140 4 °C). The samples of blood plasma, urines and thyroids are stored at -20 ° C prior to analysis. The  
141 total radioactivity of iodine-125 contained in the thyroids is determined by gamma counting (gamma  
142 multidetector RIASTAR A5410, Packard). The analysis of stable iodine in blood plasma and thyroids  
143 was adapted from a method previously developed for the quantification of iodine in the urines by  
144 inductively coupled plasma mass spectrometry (12). After slow thawing of samples at laboratory  
145 temperature (+ 21 °C), the blood plasma and the urines are diluted respectively 1/100<sup>th</sup> and 1/10 000<sup>th</sup>  
146 with 2% ammonia solution (solution made from the Suprapur® 25% ammonia solution, Merck) and  
147 then stabilized with a sodium thiosulfate solution at 184 mg/l in 2% ammonia. The total iodine content  
148 is determined by direct measurement of three aliquots of each sample by inductively coupled plasma

149 mass spectrometry (ICP-MS, X Series II and iCAP™ Q, Thermo Electron, Courtaboeuf, France) using  
150 the standard addition method. The internal calibration range consists of a standard solution of stable  
151 iodide at 1000 mg/l (Iodides AVS Titrimorm IC Standard, Prolabo). Tellurium Te-125, used as the  
152 second internal standard, is added to the samples at a concentration of 1.25 mg/l from a standard 1000  
153 mg/l solution (Tellurium ICP standard Certipur, Merck). The internal calibration range is constituted  
154 in each sample by the following concentrations: 0, 2, 4, 6, 8, 10 and 12 µg/l of stable iodide. The same  
155 method for determination of stable iodine by ICP-MS is applied to the thyroids after preliminary  
156 mineralization of the samples in a microwave oven (Ethos TC, Milestone, Italy) in 50 ml of ammonia  
157 4M for 30 minutes at 200 °C. A volume of 1 ml of the mineralized solution is then diluted to 1/125th  
158 in 2% ammonia for iodine analysis by ICP-MS. The results of measurements of radioactive iodine I-  
159 125 expressed in number of counts per minute and per gram of tissue (cpm/g) are converted into kilo  
160 Bequerels per gram of tissue (kBq/g) and then as a percentage of injected activity. The results of stable  
161 iodine measurements by ICP-MS in blood plasma, urine and thyroid samples expressed in counts per  
162 second (cps) are converted to µg/l (or ng/ml) of sample after correlation with calibration curves.

### 163 *Statistical and pharmacokinetic analyses*

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



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

184

## 185 Results

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

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

199 The distribution of iodine in the thyroid was quite variable as a function of the time after KI  
200 intravenous injection (Table I). The thyroid iodine content fluctuated from  $596 \pm 334 \mu\text{g/g}$  to  
201  $1141 \pm 475 \mu\text{g/g}$  in control rats and from  $602 \pm 241 \mu\text{g/g}$  to  $1039 \pm 329 \mu\text{g/g}$  in treated rats. Although

1  
2 202 a 19% increase in the thyroid iodine content of the treated rats could be observed at 24h, this  
3  
4  
5 203 difference was not statistically significant.

6  
7 204 The total excreted amount of iodine recovered in the urines 24h post KI dosing was about  $246 \pm 58 \mu\text{g}$   
8  
9 205 whilst the control rats excreted about  $19 \pm 5 \mu\text{g}$  (Table I). This amount of iodine excreted in treated  
10 206 rats accounted for about 84% of the injected dose of  $269 \mu\text{g}$  iodine from  $350 \mu\text{g}$  KI.

11  
12  
13 207

14  
15  
16 208 *Pharmacokinetics of stable iodine after a single oral administration of KI (Experiment 2)*

17  
18  
19 209 The mean stable iodine plasma concentrations at different sampling times post KI oral gavage are  
20  
21 210 presented in the table II and the figure 2. ~~The pharmacokinetic modeling showed that these data were~~  
22  
23 211 ~~best fitted by a one-compartment model with first order rate distribution and elimination processes~~  
24  
25 212 ~~since the related statistic parameters (AIC=151.42; SBC=153.34) were better than those of other~~  
26  
27 213 ~~models tested such as the two-compartment model (AIC=152.42; SBC=155.61). The subsequent~~  
28  
29 214 ~~predicted plasma values were generated with the selected model and represented by the curve in the~~  
30  
31 215 ~~figure 2 and the main pharmacokinetic parameters were calculated and presented in the table III. The~~  
32  
33 216 ~~one compartmental model was also selected, as it was associated with lower AIC and SBC values~~  
34  
35 217 ~~(AIC=151.42; SBC=153.34) compared with the two compartment model (AIC=152.42; SBC=155.61),~~  
36  
37 218 ~~still providing an adequate description of the data, as shown in figure 2 where observations and model~~  
38  
39 219 ~~predictions appear superimposed.~~ According to this model, iodine is absorbed rapidly and reaches a  
40  
41 220 peak plasma level of about  $993 \mu\text{g/l}$ , approximately 38 minutes after oral administration. In addition,  
42  
43 221 the plasma concentration of iodine 24 hours after dosing (predicted value of  $158 \mu\text{g/l}$  and measured  
44  
45 222 value of  $175 \pm 102 \mu\text{g/l}$ ) remains approximately two times higher than the iodine concentration in the  
46  
47 223 control rats ( $69 \pm 8 \mu\text{g/l}$ ). The concentrations then decreased with a half-life of about 8.8 hours to the  
48  
49 224 value of the control rats after 33 hours. ~~The first order rate constants which were derived after~~  
50  
51 225 ~~simultaneous fitting of intravenous and oral data by a population approach are presented.~~ Parameter  
52  
53 226 estimates resulting from the simultaneous analysis of the intravenous and oral data are listed in the  
54  
55  
56  
57  
58  
59 227 table III.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
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  
60  
61  
62  
63  
64  
65

**228** 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  
**229** 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  
**230** time. As after intravenous injection of KI, this parameter did not significantly differ as a function of  
**231** the time post KI dosing compared with control rats, although it tended to increase by 10% at 24h and  
**232** by 15% at 48h in treated rats (Table II).

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

**238**  
**239** *Effect of a single oral administration of stable KI on the 24h-thyroid uptake of iodine I-125:*

**240** *Pharmacokinetic-pharmacodynamic correlation (Experiment 3)*

**241** The measurements of thyroid I-125 activity as a function of time after oral administration of  
**242** 1 mg/kg KI are shown in Table IV and the Figure 3. The theoretical stable iodine plasma  
**243** concentrations corresponding to the same observation times and which were obtained in the  
**244** pharmacokinetic studies are reported in the same table as well as in Figure 3 for comparison purpose.  
**245** These results showed that the efficacy of a single dose of KI in terms of avoided iodine I-125 activity  
**246** in the thyroid compared with the control rats, was comprised between 87% (at 2 hours) and 61% (at 24  
**247** hours). A decrease in iodine-125 avoided activities in the thyroid (expressed as a percentage of thyroid  
**248** uptake in control rats) and in stable iodine plasma concentrations can be observed as a function of time  
**249** from 1 hour after KI administration. This observation supports the hypothesis of a correlation between  
**250** the efficacy of stable iodine and its concentration in plasma. In addition, a decrease in iodine-125  
**251** uptake in the thyroid of the treated rats (expressed as a percentage of the initial injected activity) is  
**252** observed as a function of increasing stable iodine plasma concentrations.

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

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

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

(Equation 1)

261 Where

262  $C$ : stable iodine plasma concentration

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

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

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

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

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

(Equation 2)

272 Where

273  $C$ : stable iodine plasma concentration

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

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

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

281 be more than 94% (Figure 5). This kinetic modeling of the protective effect of stable KI can be  
282 exploited to verify the efficacy of the selected dose of 1 mg/kg KI by correlating stable iodine plasma  
283 concentrations to a predicted effect. Thus, a minimum plasma concentration of 174  $\mu\text{g/l}$  of stable  
284 iodine would be associated with an uptake of 0.89% of the injected activity (Figure 4), which would  
285 represent a 63% decrease in the uptake of iodine-125 compared with control rats (Figure 5). Similarly,  
286 a maximum plasma concentration of 1190  $\mu\text{g/l}$  of stable iodine would be associated with an uptake of  
287 0.23% of the injected activity and a theoretical reduction of 88% of the uptake in control rats. Finally,  
288 an efficacy of 75% reduction in the uptake of iodine-125 can be associated with an interpolated  
289 concentration value of approximately 340  $\mu\text{g/l}$  (Figure 5). In terms of kinetics, the predicted stable  
290 plasma iodine concentrations were higher than 500  $\mu\text{g/l}$  for about 10 hours after KI dosing. Therefore,  
291 repeated KI prophylaxis with daily dose of 1 mg/kg would theoretically be more than 75% effective  
292 for 10 hours (75% to 88%) and comprised between 63% and 75% from 10 hours to 24 hours post  
293 dosing.

294  
295 *Simulation and experimental verification of repeated daily oral administrations of stable KI*  
296 *(Experiment 4)*

297 Based on the results of the kinetic study of stable KI protective effect for 24h (experiment 3), a dose of  
298 1 mg/kg KI once daily could be pertinent and simple enough to ensure a good compliance in case of  
299 prolonged KI prophylaxis. Hence this dose regimen was simulated with the pharmacokinetic software  
300 and tested in rats in order to check the concordance between the measured iodine plasma  
301 concentrations during or at the end of repeated prophylaxis and the values predicted by modeling. The  
302 simulation of iodine plasma concentrations during a daily repeated oral administration of 1 mg/kg KI  
303 was performed using the final estimates of iodine first order rate constants such as the volume of  
304 distribution (~~0.8040~~0.8038  $\text{l.kg}^{-1}$ ), the absorption rate ( $5.71 \text{ h}^{-1}$ ) and the elimination rate ( $0.0864 \text{ h}^{-1}$ )  
305 which were determined by non-compartmental analysis of plasma data after single oral administrations  
306 of KI (experiment 2). The plasma concentration measurements at different sampling times during  
307 repeated prophylaxis were interpreted using the mathematical model obtained in the 24h-kinetic study

1  
2 309 of the protective effect of 1 mg/kg KI (experiment 3). The simulation of iodine plasma concentrations  
3 during a repeated KI prophylaxis and the plasma samples measurements are presented in Table V and  
4 310 Figure 6.

5  
6  
7 311 According to this simulation, the steady-state has been achieved after the third dose of KI and plasma  
8 iodine concentrations varies between a maximum concentration of approximately 1190  $\mu\text{g/l}$  and a  
9 312 minimal concentration of approximately 174  $\mu\text{g/l}$  (before a subsequent KI administration) (Figure 6).  
10 313 Hence, this dose regimen makes it possible to maintain concentrations at least two times higher than  
11 314 the concentration of the control rats (about 77  $\mu\text{g/l}$ ) throughout the duration of the treatment.  
12  
13  
14  
15  
16  
17  
18

19 316 The values of the average iodine plasma concentrations measured in the control rats were uniform  
20 317 regardless of the sampling time (Table V, Figure 6). With the exception of the measurements in the  
21 318 rats at day 9 (ie 24 hours after the 8th dose of KI) which was higher than the expected theoretical  
22 319 value, the mean values of the concentrations measured at the other times in the treated rats (day 3  
23 + 6h, day 5 and day 10) were consistent and of the same order of magnitude as the predicted values.  
24  
25  
26  
27  
28  
29  
30  
31 321 These results validated the selected dose regimen model.

32  
33  
34 322

### 35 36 37 323 Discussion

38  
39  
40 324 For many years, the absence of analytical methods for the direct determination of iodide anion or  
41 325 stable iodine in blood and organs represented an obstacle to research on the pharmacodynamics and  
42 326 pharmacokinetics of iodine (18). Hence, the development of biokinetic or pharmacokinetic models for  
43 327 iodine was mainly based on studies using radioisotopes of iodine which are toxic elements (3, 19, 20)  
44 328 and on computational modeling (21, 22). Former alternative methods for the quantification of stable  
45 329 iodine in organs and blood were either indirect and dependent on the measurement of iodine in other  
46 330 biological matrixes such as the urines (23, 24), or were based on the Sandell-Kolthoff colorimetric  
47 331 reaction after digestion methods of the samples which could lead to a loss of iodine (25, 26). Recently,  
48 332 more sensitive methods for direct determination of iodine based on ion chromatography (18, 27-29) or  
49 333 capillary electrophoresis coupled to mass spectrometry were developed (30), but very few studies have  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65

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

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

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
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  
60  
61  
62  
63  
64  
65

360 In the present study, the early plasma iodine measurement around 800 µg/l after intravenous dosing  
361 may suggest a short infusion instead of a bolus dose although the injection was performed in less than  
362 five seconds and no retention at the injection site was observed. As an explanation, it was assumed  
363 that the maximal plasma concentration was not yet reached in all animals euthanized soon after the  
364 intravenous bolus. As far as the pharmacokinetics of iodine was concerned, it is interesting to note that  
365 the elimination half-life value determined in the rats after KI oral administration of about 8.75±1 h was  
366 comparable with the data in the literature: an 8.27 h iodine plasma elimination half-life was  
367 determined in a study in which iodine was determined in rat serum samples by ion chromatography  
368 (28).

369 The bioavailability value of 90% determined in the present study was consistent with available data in  
370 the literature indicating a bioavailability of iodides higher than 90% and up to 99% depending on the  
371 diet (32). The pharmacokinetic modeling of iodine after intravenous or oral administration were both  
372 consistent, as attested by the statistics. More complicated biokinetic or pharmacokinetic models with  
373 larger number of compartments have been published so far in order to describe the metabolism of  
374 dietary iodine or to estimate radiation dose induced by radioiodine incorporation in the thyroid (19, 29,  
375 32, 34, 35). Besides, a limited number of biokinetic models have been dedicated to stable iodine as a  
376 thyroid blocking agent (21, 22, 36). Anyhow, the kinetic models and the analysis of plasma data in the  
377 present work were sufficient for the determination of the main pharmacokinetic parameters (volume of  
378 distribution, absorption constant and elimination constant) which were useful to model and to study  
379 iodine plasma concentrations as a function of the time during a repeated KI prophylaxis.

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



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

412

1  
2  
3 **413 Conclusion**

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

32  
33  
34  
35 **428 Acknowledgments**

36  
37  
38 **429** The authors are thankful to the Central Army Pharmacy for providing solutions of KI, Dr Delphine  
39  
40 **430** Denais-Lalieve (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  
45 **432 Declaration of conflicting interests**

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  
54 **435 Funding**

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).

- 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 <sup>131</sup>I and <sup>133</sup>I 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 Pregnancy<sup>1</sup>. *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*

539 comprehensive review. *International journal of environmental research and public health*.  
11:4158-4200 (2014).

1 540

2 541 38. S. Nagataki and S.H. Ingbar. Relation Between Qualitative and Quantitative Alterations in  
3 542 Thyroid Hormone Synthesis Induced by Varying Doses of Iodide. *Endocrinology*. 74:731-736  
4 543 (1964).

5 544 39. D. Lebsir, L. Manens, S. Grison, P. Lestaevel, T. Ebrahimian Chiusa, D. Suhard, G. Phan, I.  
6 545 Dublineau, K. Tack, M. Benderitter, A. Pech, J.-R. Jourdain, and M. Souidi. Effects of  
7 546 repeated potassium iodide administration on genes involved in synthesis and secretion of  
8 547 thyroid hormone in adult male rats. *Molecular and Cellular Endocrinology*. 474:119-126  
9 548 (2018 ~~in press~~).

10 549 40. P.B. Zanzonico and D.V. Becker. Effects of time of administration and dietary iodine levels  
11 550 on potassium iodide (KI) blockade of thyroid irradiation by <sup>131</sup>I from radioactive fallout.  
12 551 *Health Physics*. 78:660-667 (2000).

13 552

14 553

15

16

17

18

19

20

21

22

23

24

25

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

60

61

62

63

64

65

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

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 (coefficient of variation %)</u>	<u>Units</u>
Volume of distribution		0.8038	l.kg <sup>-1</sup>
Clearance		0.08637	l. kg <sup>-1</sup> .h <sup>-1</sup>
<u>Lag time</u>		0	h
<u>Absorption constant</u>		5.71297	h <sup>-1</sup>
<u>First order rate constant of absorption</u>			
Oral bioavailability		89.5629	%
<u>Secondary parameters</u>			
<u>Maximal concentration after intravenous dose</u>		<u>1275.6533 (9.58)</u>	<u>µg.l<sup>-1</sup></u>
<u>Elimination half life after intravenous dose</u>		<u>5.4545 (34.96)</u>	<u>h</u>
<u>Maximal concentration after oral dose</u>		<u>993.3562 (2.31)</u>	<u>µg.l<sup>-1</sup></u>
<u>Time corresponding to the maximal concentration after oral dose</u>		<u>0.6347 (14.52)</u>	<u>h</u>
<u>Elimination half life after oral dose</u>		<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 ( $\mu\text{g/l}$ )	Mean iodine I-125 uptake in the thyroid (%IA) $\pm$ SD	Mean avoided I-125 activity in the thyroid (% controls) $\pm$ SD
1	74	$1.78 \pm 0.52$	NA
2	890	$0.37 \pm 0.08$	$87 \pm 3$
4	755	$0.30 \pm 0.09$	$86 \pm 3$
12	391	$0.48 \pm 0.14$	$76 \pm 9$
16	282	$0.74 \pm 0.17$	$66 \pm 11$
20	203	$0.62 \pm 0.12$	$71 \pm 5$
24	146	$0.86 \pm 0.16$	$61 \pm 7$

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

60  
61  
62  
63  
64  
65  
66  
67  
68

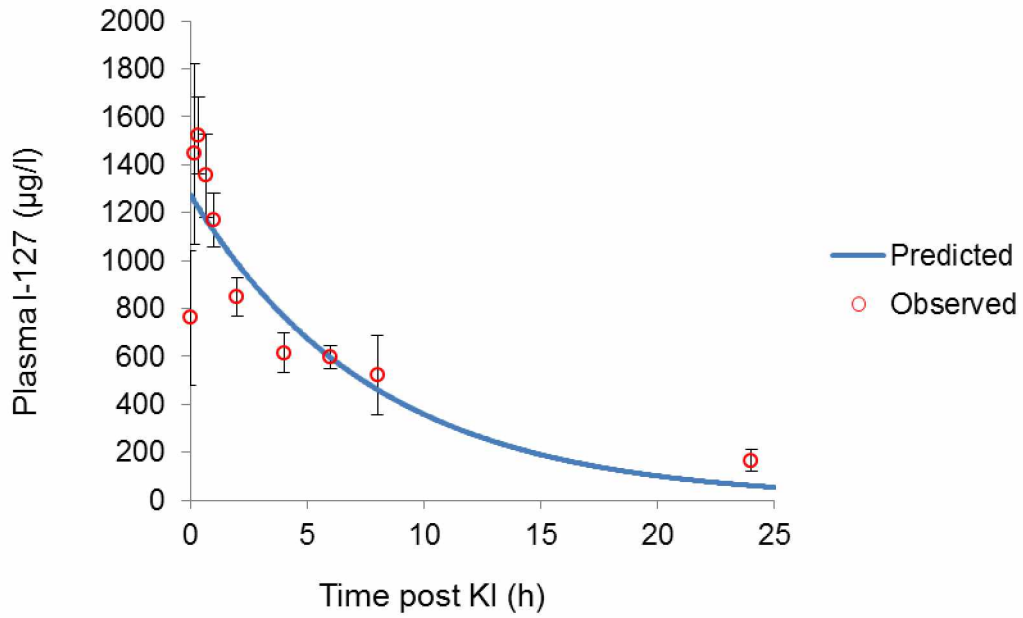
69 Table V: Plasma stable iodine concentrations measured at different times in rats treated by 1 mg/kg KI  
70 daily for 8 days and predicted inhibition of I-125 uptake in the thyroid

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

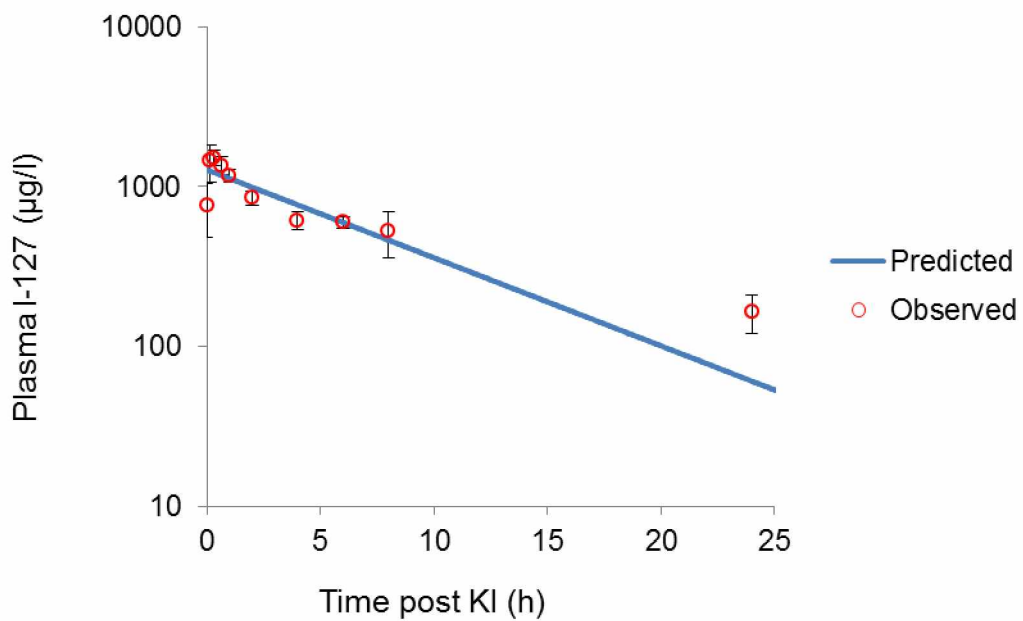
1 Figure 1

2 (A)



3

4 (B)

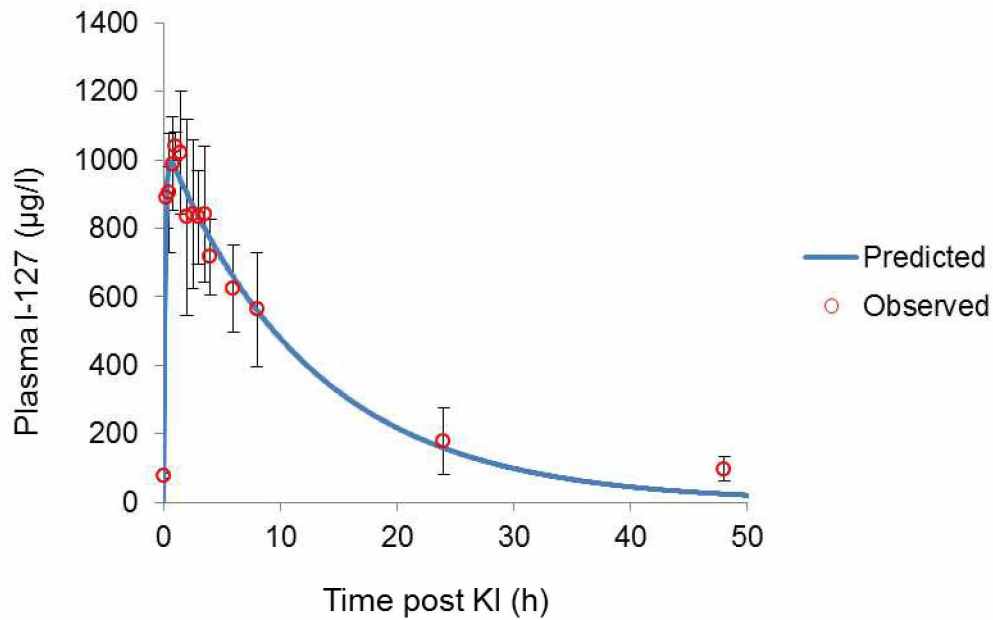


5

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.

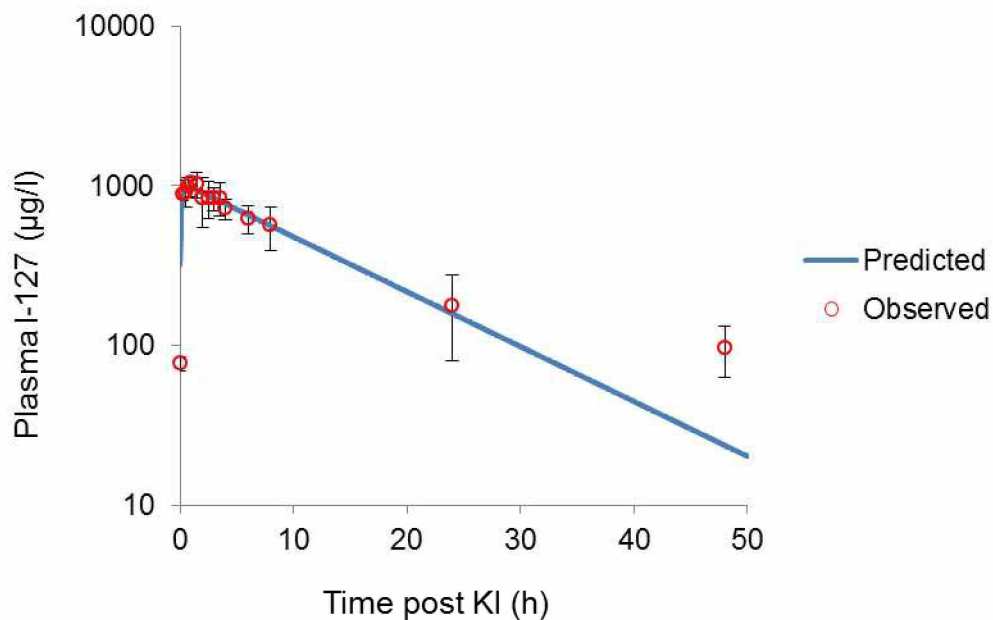
11 Figure 2

12 (A)



13

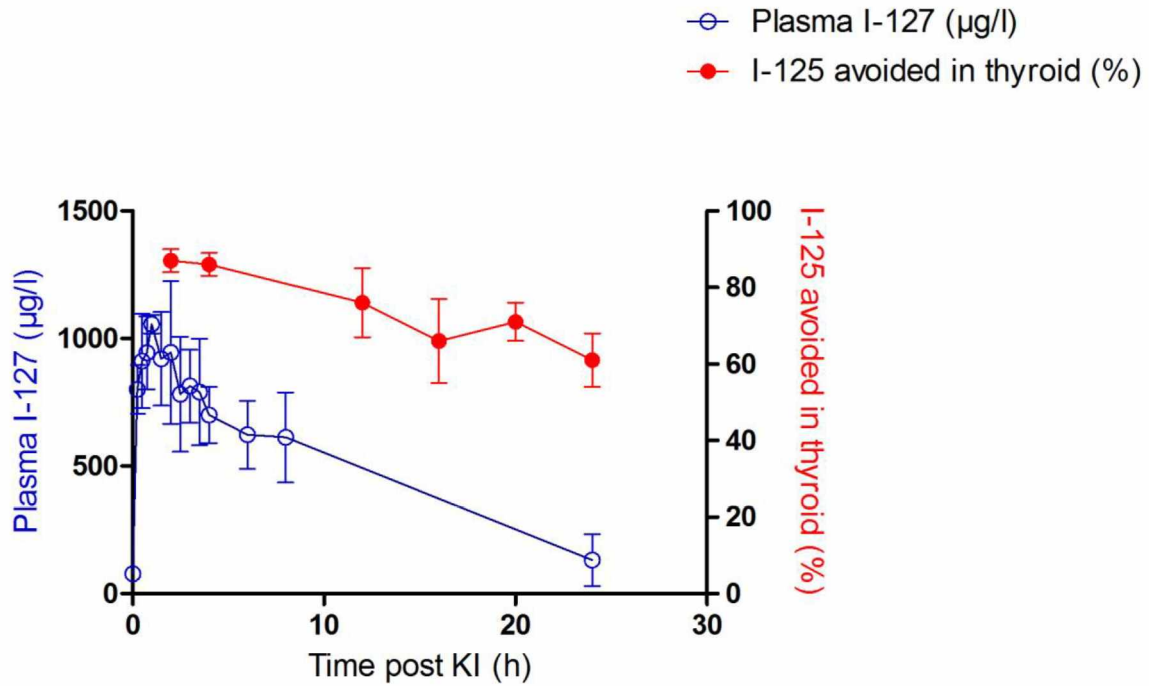
14 (B)



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).

28

29

30

31

32

33

34

35

36

37

38

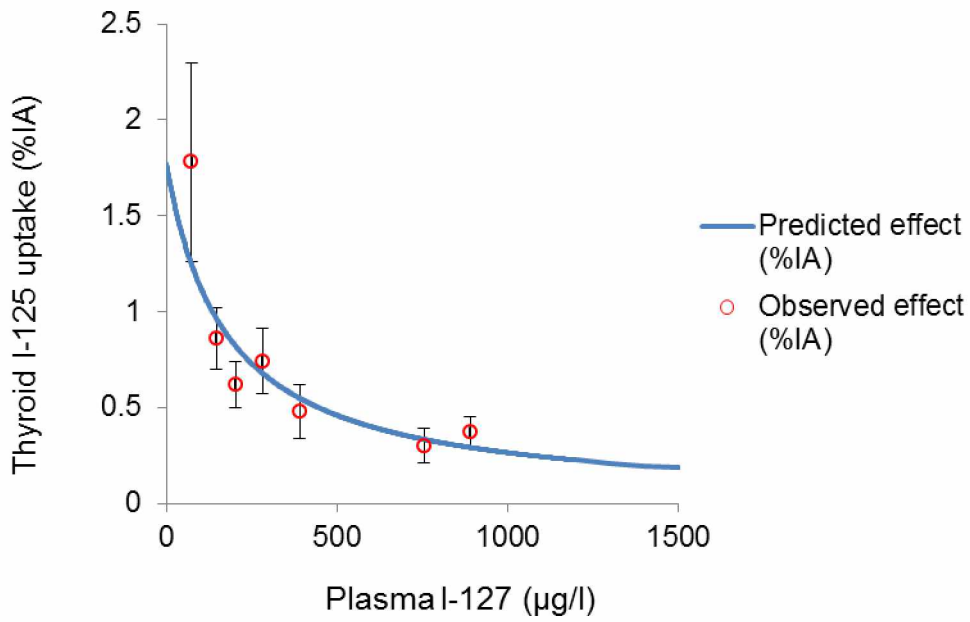
39

40

41

42 Figure 4

43



44

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

48

49

50

51

52

53

54

55

56

57

58

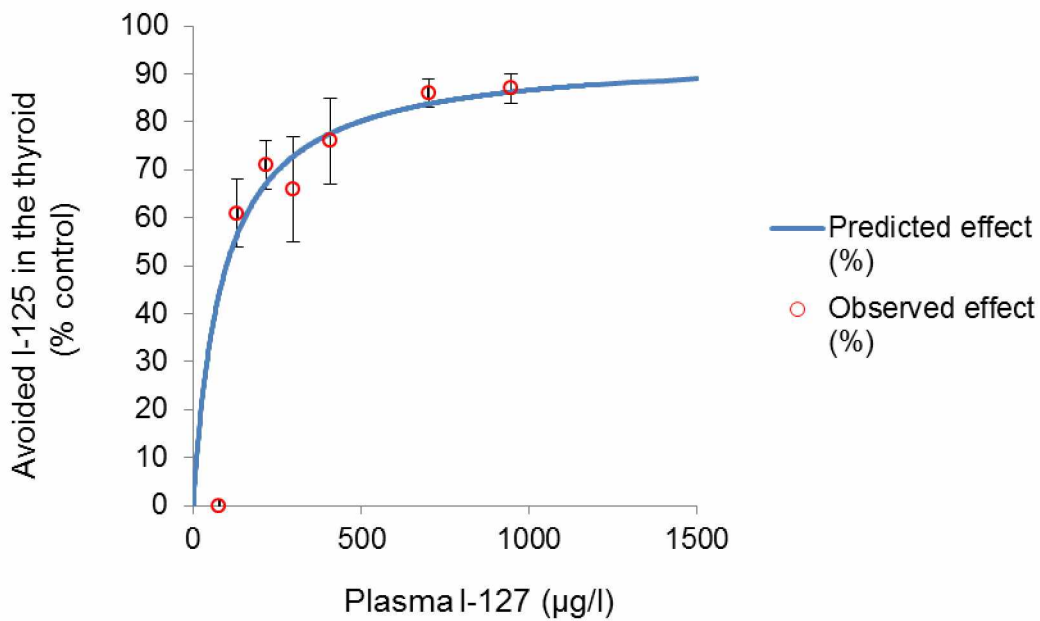
59

60

61

62 Figure 5

63



64

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

69

70

71

72

73

74

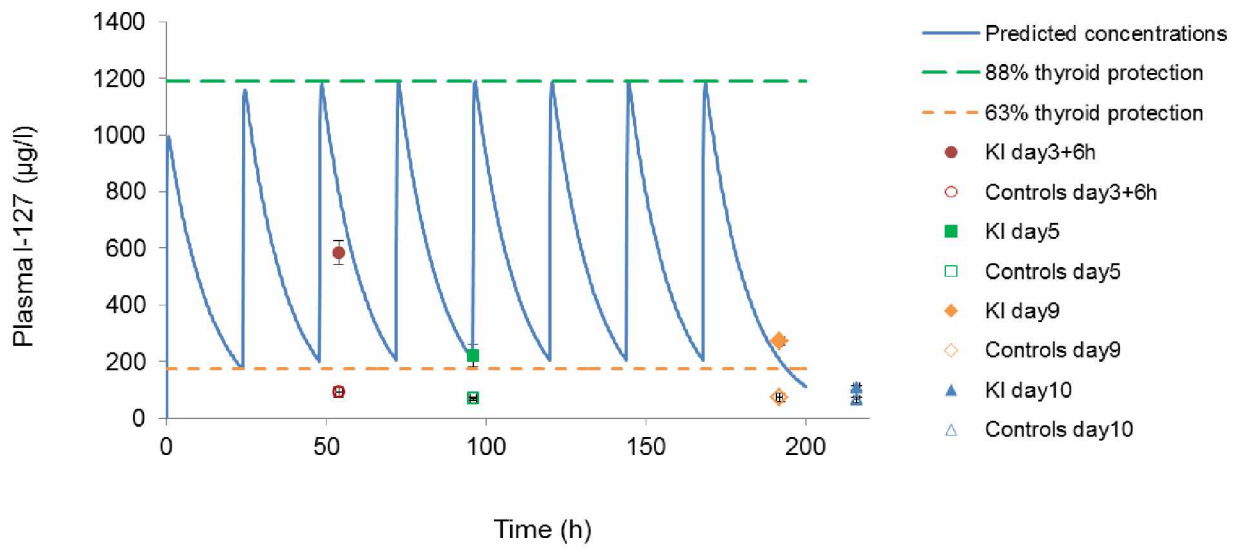
75

76

77

78

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 ± 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.