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Revision of the affinity constant for perchlorate binding to the sodium-iodide symporter based on *in vitro* and human *in vivo* data

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Abstract

A series of previously published physiologically based pharmacokinetic (PBPK) models describe the effect of perchlorate on iodide uptake by the thyroid, with the mechanism being competitive inhibition of iodide transport by the sodium-iodide symporter (NIS). Hence a key parameter of these models is the affinity of perchlorate for the NIS, characterized as the Michaelis–Menten kinetic constant, K_m. However, when model predictions were compared to published results of a human study measuring radio-iodide uptake (RAIU) inhibition after controlled perchlorate exposures, it was found to only fit the lowest exposure level and underpredicted RAIU inhibition at higher levels. Published *in vitro* data, in which perchlorate-induced inhibition of iodide uptake via the NIS was measured, were re-analyzed. K_m for binding of perchlorate to the NIS originally derived from these data, 1.5 μM, had been obtained using Lineweaver–Burk plots, which allow for linear regression but invert the signal–noise of the data. Re-fitting these data by non-linear regression of the non-inverted data yielded a 60% lower value for the K_m, 0.59μM. Substituting this value into the PBPK model for an average adult human significantly improved model agreement with the human RAIU data for exposures <100 μg kg^{-1} day^{-1}. Thus, this lower K_m value both fits the *in vitro* NIS kinetics and provides better predictions of human *in vivo* RAIU data. This change in K_m increases the predicted sensitivity of humans to perchlorate over twofold for low-level exposures. Published 2016. This article is a U.S. Government work and is in the public domain in the USA.

Keywords

perchlorate; affinity; sodium-iodide; symporter; PBPK; human; thyroid; inhibition

Introduction

Thyroidal uptake of iodide, mediated in large part by the sodium-iodide symporter (NIS), is the first step in the formation of iodinated thyroid hormones, triiodothyronine (T_3) and thyroxine (T_4), which are important for physiological health (e.g., metabolism) and in the

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neurodevelopment of the fetus and neonate (NRC, 2005). A series of physiologically based pharmacokinetic (PBPK) models describing the effect of perchlorate on NIS-mediated iodide uptake have been previously described, beginning with the adult male rat (Merrill *et al.*, 2003), the lactating maternal rat and neonate (Clewell *et al.*, 2003), the adult "average" human (Merrill *et al.*, 2005) and the human "life stage" model, which included lactation (Clewell *et al.*, 2007). The human versions of these models have provided a starting point for a more recent effort to describe the effect of perchlorate on T_3 and T_4 in the pregnant human and her fetus (Lumen *et al.*, 2013). Collaborative efforts between the US FDA and US EPA to extend this biologically based dose–response model to the lactating human mother and infant have been underway for approximately 2 years and are approaching expected completion.

In Merrill *et al.* (2003) the K_m for perchlorate binding to NIS ($K_{m\text{-}NIS,ClO4}$; 1/affinity) was given virtually the same value for thyroid, skin and gastrointestinal (GI) tissues, 1.7 or 1.8 × 10^5 ng l^{-1}. For the rat lactation model, Clewell *et al.* (2003) adjusted these values somewhat, beginning with the K_m as reported by Kosugi *et al.* (1996), 1.5 × 10^5 ng l^{-1}. The study authors stated that, "This value was adjusted slightly to obtain the best fit of thyroid perchlorate to the drinking water data, resulting in a K_m of 2.0 × 10^5 ng/L." In the PBPK model, the code as obtained from Dr. Harvey Clewell, the thyroid $K_{m\text{-}NIS,ClO4}$, was still assigned a value of 1.5 × 10^5 ng l^{-1} while that for skin, GI tract and mammary tissue was 2.0 × 10^5 ng l^{-1}. In personal communication with Dr. Clewell, he indicated that in the process of testing parameters, the table in the draft manuscript might not have been updated. In the US EPA (2009) review, the assumption was made that the values in the model code were used for that analysis.

Considering that the evaluation by Kosugi *et al.* (1996) was in a cellular environment not native to the molecule (i.e., Chinese hamster ovarian [CHO] cells in culture), it is not surprising that some adjustments were required to match the rat PK data. However, this adjustment is inconsistent with the almost identical values across tissues that did fit the dosimetry in the adult male rat (Merrill *et al.*, 2003), as described above. The molecular form of NIS would not be altered by pregnancy or lactation, while other parameters such as permeability and the partition coefficient, which depend on tissue thickness and lipid content, respectively, would be much more likely to change. Thus, it may be that the differential adjustment of $K_{m\text{-}NIS,ClO4}$ for the lactating rat was not necessary to fit the perchlorate PK data.

The original model for perchlorate and iodide dosimetry from which the other life stages and subsequent modeling have largely been extrapolated was that of Merrill *et al.* (2005) for an "average" human adult. The Merrill *et al.* (2005) model should be predictive of perchlorate dosimetry and perchlorate-induced iodide uptake inhibition, perchlorate's initial effect, in healthy young men and women, outside of pregnancy and lactation. A previous evaluation of this model (US EPA, 2009) focused on results at the then-established reference dose, for which the point-of-departure (POD) was the dose of 7 μg kg^{-1} day^{-1}. This POD is the dose at which Greer *et al.* (2002) observed RAIU of 98.2 ± 8.3% of controls (mean ± SE). The Greer *et al.* (2002) data set is of primary importance because controlled perchlorate exposures were administered to a set of human volunteers and the impact on radio-iodide

uptake by the subjects' thyroids was measured during and after the 2-week exposure. Thus, it provides a direct observation of this key initial endpoint in humans with known exposure levels. Hence, evaluating the ability of the model to fit these data is considered a key validation step.

The Merrill *et al.* (2005) model recapitulated the effect measured by Greer *et al.* (2002) at 7 μg kg^{-1} day^{-1} exactly, predicting radio-iodide uptake at 98.2% of control. The US EPA did make several minor modifications to the Merrill *et al.* (2005) model (described in US EPA, 2009), and the results shown here and below are with that modified model. Therefore, for accuracy, it is henceforth referred to as the US EPA (2009) model.

The previous review did not evaluate model behavior at higher doses because the focus was on doses below the POD (7 μg kg^{-1} day^{-1}). Lumen *et al.* (2013) have now extended perchlorate-iodide modeling to a biologically based dose–response model, which predicts the levels of thyroid hormones, T_3 and T_4, in the late-term pregnant mother and fetus. Their results indicate that even though the late-term fetus is considered a very sensitive life stage, exposure levels approximately or somewhat above 7 μg kg^{-1} day^{-1} might not be biologically significant (i.e., might not be considered adverse) for the fetus or mother with adequate iodide intake. While Lumen *et al.* (2013) predicted clearly adverse levels of effect on free T_4 at much higher exposure levels (i.e., 100 μg kg^{-1} day^{-1} perchlorate) for all levels of iodide intake, it now appears that the dose–response for perchlorate for some range above 7 μg kg^{-1} day^{-1} should be evaluated.

Therefore, the US EPA (2009) model was compared to the higher-dose Greer *et al.* (2002) data. This comparison showed that the model significantly underpredicts the effect (overpredicts the RAIU as the percentage of control) at the next two higher doses (20 and 100 μg kg^{-1} day^{-1}; results shown below). A more comprehensive analysis of the discrepancy was then initiated.

To understand why this discrepancy between model prediction and a key data set occurs, US EPA (2009) model predictions were then compared to the blood perchlorate levels in Greer *et al.* (2002). While the perchlorate blood levels were not matched exactly, the differences between model predictions and measured perchlorate blood levels in the study subjects were not sufficient to explain the discrepancy in fits to RAIU inhibition stated above (results not shown). As blood perchlorate levels were predicted reasonably well, the next most important parameter that might explain this discrepancy is the affinity of perchlorate for the NIS, $K_{m\text{-}NIS,ClO4}$, which is central to the prediction of perchlorate's effects on iodide uptake.

As described above, $K_{m\text{-}NIS,ClO4}$ had been given a value of 1.6×10^5 ng l^{-1} by Merrill *et al.* (2005) based on an *in vitro* study by Kosugi *et al.* (1996), who expressed rat NIS in CHO cells. Kosugi *et al.* used a classical but possibly inexact approach for estimating kinetic parameters where (first) reciprocal plots of 1/velocity vs. 1/[substrate] (Lineweaver–Burk plots) are used to estimate an apparent $K_{m\text{-}NIS,iodide}$ (affinity of iodide for the NIS) for each level of inhibitor (perchlorate), then the slope of that relationship is plotted against these perchlorate concentrations, and a final linear regression is used to estimate the inhibition constant for perchlorate, which is assumed to be its K_m (i.e., $K_{m\text{-}NIS,ClO4}$). This approach

was developed when computational power and tools were limited and direct non-linear regression was difficult. However, it also distorts the signal–noise ratio in the data, by magnifying the results with the lowest substrate concentration and velocity and discounting the results for which those are highest. Therefore, a re-analysis of the data from which the current value of $K_{m\text{-}NIS,ClO4}$ was derived, which avoids data signal–noise distortion, is provided here.

Methods and results

The NIS-mediated *in vitro* iodide uptake data of Kosugi *et al.* (1996) were digitized and re-converted to original (non-inverse) units, plotted and used in a non-linear regression. In particular, iodide uptake by CHO cells, in which rat NIS was expressed, had been measured at 0, 3, 10 and 30 μM perchlorate. Assuming competitive inhibition, the rate of uptake was fitted using the equation:

$$V = V_{\max} \times [\mathrm{I}]/\left(K_{m-NIS,\,\mathrm{iodide}} \times \left(1 + [ClO_4^-]/K_{m-NIS,\,ClO_4}\right) + [I]\right).$$

where V is the measured rate of iodide uptake, $V_{\max}$ a fittedmaximum velocity, $[I]$ the iodide concentration and $[ClO_4^-]$ the perchlorate concentration.

As the data of Kosugi *et al.* (1996) were only provided in plots and attempts to contact the author were unsuccessful, the data were digitized and reciprocals taken (as appropriate) to obtain velocity vs. substrate concentrations for each perchlorate level. Because the resolution of the data plots in Kosugi *et al.* (1996) was limited, and the data with the highest velocities and substrate concentrations compressed near the origin of the Lineweaver–Burk plot they provided, the higher iodide concentration data for the 3, 10 and 30 μM perchlorate data were not digitized; the symbols in the Kosugi *et al.* (1996) figure were overlapping and indistinguishable. In particular, concentrations higher than those shown in Fig. 1 below (for each perchlorate level) could not be digitized, and the highest velocity–substrate pair digitized was considered uncertain. Fortunately, the full data set at 0 μM perchlorate was shown on a standard axis plot and could be used. Therefore, estimation of the kinetic parameters was first conducted without using the highest velocity–substrate pairs with perchlorate, but to test sensitivity to those points, estimation was conducted again with them included.

The sum of squared errors between the kinetic equation and the digitized data was minimized in Microsoft Excel using the Solver add-in. The $V_{\max}$ and $K_{m\text{-}NIS,iodide}$ were first estimated using the 0 μM perchlorate data, then those values held constant when fitting $K_{m\text{-}NIS,ClO4}$ to the perchlorate treatment data.

In Fig. 1 the upper set of data and model fit is the Michaelis–Menten fit obtained by non-linear regression for the iodide uptake data in the absence of perchlorate. The value of $K_{m\text{-}NIS,iodide}$ (i.e., affinity for iodide) obtained is 33.4 μM, reasonably close to the value obtained using the inverse/linear-regression method by Kosugi *et al.* (1996), 34.7 μM. However, the value of $K_{m\text{-}NIS,ClO4}$ obtained in this re-analysis, which yields the model fits

shown to the 3, 10 and 30 μM ClO4 data, was 0.59 μM (6×10^4 ng l^{-1}), not 1.5 μM as estimated by Kosugi *et al.* (1996).

As stated above, this value of $K_{m\text{-}NIS,ClO4}$ was estimated without using the top-most point in each perchlorate-exposed data set shown, as these were the most difficult to digitize from the published plot figure. When those top-most points are included, the resulting value of $K_{m\text{-}NIS,ClO4}$ is 0.57 μM, slightly lower. In either case, the value would be rounded to 6×10^4 ng l^{-1} for use in themodel, so the impact of this uncertainty is considered small.

To evaluate the quality of the digitization, the digitized data were plotted in Excel with a transparent background and the plot laid over an image of the original figures; the digitized points aligned almost exactly with the figure (not shown). The traditional analysis used by Kosugi *et al.* (1996) was then repeated with the digitized data. The value of $K_{m\text{-}NIS,iodide}$ using the control (0 μM ClO_4) data, upper most points in Fig. 1, was 31.3, vs. 34.7 μM reported by Kosugi *et al.* (1996). As those data were readily digitized, the difference may be due to the fact that only the mean values shown in Kosugi *et al.* (1996, Fig. 2A) were digitized; error bars for ±1 SD were shown, but not the original data: three measurements per iodide level. Because of the scale in Fig. 2(B) in Kosugi *et al.* (1996), also adjusted to include data from functional rat thyroid cells, the individual points for the CHO cells were also indistinguishable there, though they were for the functional rat thyroid cells.

When the reciprocal values ($1/V$ vs. $1/[S]$) from Kosugi *et al.* (1996, Fig.3A) for 3–30 μM ClO_4^- were re-analyzed by linear regression, the slopes for 3 and 30 μM ClO_4^- were reasonably close to those reported by Kosugi *et al.*: 19.8 and 163.8 (this analysis) vs. 19.9 and 169.2 (Kosugi *et al.*). For 0 μM ClO_4^- the test re-analysis yielded 7.95 vs. 8.12, again quite close. However, for 10 μM ClO_4^- the slope obtained by re-analysis is only 52.8, compared to 67.4 shown by Kosugi *et al.* When the slopes obtained from the digitized data were used in a Lineweaver–Burke analysis, the value of "KI" obtained was 0.87 μM, intermediate between 1.5 μM (Kosugi *et al.*, 1996) and 0.59 μM (non-linear analysis described above). When the slope of 67.4 was used instead of 52.8, but all other slopes as estimated from the digitized data, the KI obtained was 1.6 μM. Visual inspection of Fig. 3(A) from Kosugi *et al.* (1996) reveals that the actual slope of the regression line shown cannot be more than 55, so "67.422" appears to be a transcription error. Thus, the difference between the "KI" reported by Kosugi *et al.* (1996) and obtained here appears to be due to two factors, i.e., (1) use of inverse concentration vs. velocity plots, which changes the weighting of the data, and (2) a transcription error for the $1/V$ vs. $1/[S]$ slope for the 10 μM ClO_4^- results.

The revised vs. original values of $K_{m\text{-}NIS,ClO4}$ (i.e., 6×10^4 vs. 1.6×10^5 ng l^{-1}) were then evaluated by comparing model predictions with the US EPA (2009) perchlorate/iodide PBPK model (revised from Merrill *et al.*, 2003) using these alternate values for the corresponding model parameter, KM_TP, to the data of Greer *et al.* (2002). Briefly, Greer *et al.* (2002) dosed healthy adult human with 7, 20, 100 or 500 μg kg^{-1} day^{-1} perchlorate, divided into four oral boluses, which were ingested at 4 h intervals for 14 days. RAIU analysis was conducted on each subject at four time-points spanning the study. The data

considered here are the 24 h RAIU data collected on the 14th day of the study (last day of dosing). A perchlorate ingestion schedule exactly matching that of Greer *et al.* (2002) was simulated using the US EPA (2009) PBPK model, with an intravenous administration of radio-iodide at the start of the 14th day, and the predicted radio-iodide content in the thyroid calculated at the end of the 14th day (i.e., the RAIU). The ratio of predicted RAIU at various simulated perchlorate exposures to RAIU with zero perchlorate was then calculated, and compared to the corresponding data of Greer *et al.* (2002). Results are shown in Fig. 2.

When the revised, lower value of $K_{m\text{-}NIS,ClO4}$ is applied in the US EPA (2009) perchlorate model, it provides much better agreement with the Greer *et al.* (2002) data as high as 100 μg kg^{-1} day^{-1} (Fig. 2). While the predicted uptake at 7 μg kg^{-1} day^{-1} is thereby reduced from 98% to 95% (inhibition increased from 2 to 5%), this is still within 1 SE of the value reported by Greer *et al.* (2002), 98.2 ± 8.3% of controls.

At 20 μg kg^{-1} day^{-1}, using $K_{m\text{-}NIS,ClO4} = 1.6 \times 10^5$ ng l^{-1} yielded a predicted RAIU of 95.6% of control (i.e., 4.4% inhibition), and using the revised value of 6×10^4 ng l^{-1} yielded a predicted RAIU of 87.4% of control, or 12.6% inhibition. Thus, the change increases the predicted RAIU inhibition by almost threefold in the range of the Greer *et al.* (2002) data that may be relevant to human health risk assessment. While the response at 500 μg kg^{-1} day^{-1} is overpredicted, the error is only slightly higher than the error (underprediction of response) with the previously used K_m. The dose of 500 μg kg^{-1} day^{-1} is sufficiently high, resulting in more than 60% RAIU inhibition, that upregulation of NIS or other compensatory changes in the thyroid may have occurred, which are not included in the model. Such changes would have reduced the effect compared to model predictions. Hence, the model with the revised $K_{m\text{-}NIS,ClO4}$ should not be used to simulate dose levels much higher than 100 μg kg^{-1} day^{-1}.

Discussion

Previous analysis and evaluation of the perchlorate/iodide PBPK model focused on its ability to match the RAIU measured by Greer *et al.* (2002) at the effective NOEL of 7 μg kg^{-1} day^{-1}, given the recommendation that this level be used as a POD by the NRC (2005). However, from examining Fig. 2 and noting that at the next higher dose, 20 μg kg^{-1} day^{-1}, the average response is 16.4%RAIU inhibition vs. 1.8% inhibition at 7 μg kg^{-1} day^{-1} – an increased response of nine-fold vs. an increased dose of threefold – it is clear that the response at 7 μg kg^{-1} day^{-1} is not predictive of that next dose level. The PBPK model simulation with $K_{m\text{-}NIS,ClO4}=1.6 \times 10^5$ ng l^{-1} matches the average measured response at 7 μg kg^{-1} day^{-1} almost exactly, but like this arithmetic (linear) extrapolation underpredicts the response at the next two higher doses, responses that are significantly different from controls. So the discrepancy between model predictions for low- vs. high-dose data, i.e., that the model fits the 7 μg kg^{-1} day^{-1} data but not the higher doses is reflected in the relative levels of inhibition of the data, which show a much greater than proportionate increase from the lowest to the next higher dose.

As the revised value for $K_{m\text{-}NIS,ClO4}$ was obtained from fitting *in vitro* data, and model simulations based on it were compared to the human *in vivo* data (Greer *et al.*, 2002)without

further adjustment, the later comparison is effectively a validation of the *in vitro* based derivation. Using this value, the PBPK model fits the *in vivo* RAIU data quite well for exposures up to 100 μg kg^{-1} day^{-1} (Fig. 2).

An issue to be considered in subsequent application of this parameter is its applicability to other life stages and other tissues. As the molecular form of the NIS, which in large part determines the binding affinity of perchlorate, does not vary between tissues and life stages, it would seem reasonable to assume that $K_{m\text{-}NIS,ClO4}$ does not vary among these, unless the PK data clearly show that this assumption is not valid. As noted in the Introduction, Clewell *et al.* (2003) adjusted the K_m when fitting the model to the rat lactation PK data, assigning it a 33% larger value in skin, GI tract and mammary tissue than the thyroid. However, it is not clear that this choice to assign a different value in non-thyroid tissues is appropriate for human predictions. In particular, one can question the use of a higher value for transfer to breast milk and competition with iodide in that process, compared to iodide uptake in the thyroid, when the K_m for *iodide* on NIS is assumed the same for transfer to breast milk as for uptake into thyroid. The extrapolation of the difference in perchlorate $K_{m\text{-}NIS,ClO4}$ values from the Clewell *et al.* (2003) rat lactation model is also uncertain, as NIS in humans is not identical to NIS in rats. Further, this choice results in a lower estimated effect on the breast-fed infant than assuming equality of $K_{m\text{-}NIS,ClO4}$ for milk and thyroid transfer (i.e., that the milk transfer $K_{m\text{-}NIS,ClO4}$ is as low as the thyroid value). While the analysis described here does not address lactation, the US EPA (2009) version of the model applied here assigned the same value of $K_{m\text{-}NIS,ClO4}$ to the other two tissues in which it is included for the average adult model, skin and GI tract, as used in the thyroid.

Like the lactation model, the Clewell *et al.* (2007) human pregnancy model used a lower $K_{m\text{-}NIS,ClO4}$ for the maternal and fetal thyroid (1.6×10^5 ng l^{-1}) than other tissues (2×10^5 ng l^{-1}). As the end-of-pregnancy analysis is conducted with the model at steady state (or close to it), values of $K_{m\text{-}NIS,ClO4}$ for the skin and GI tract will have little effect on those predictions. For the pregnant rat, Clewell *et al.* (2003) used identical values for $K_{m\text{-}NIS,ClO4}$ in all tissues. Thus, any data from the rat on disposition of perchlorate across the rat placenta vs. thyroid do not indicate a differential value of $K_{m\text{-}NIS,ClO4}$ from the thyroid. Therefore, for human pregnancy predictions it again seems appropriate to assume consistency, equality of $K_{m\text{-}NIS,ClO4}$ across all tissues of the pregnant mother and fetus and, in particular, to use the value for the adult thyroid, whose value can be tested by comparing model predictions with experimental observations of iodide uptake inhibition in adult humans.

In conclusion, re-analyzing the *in vitro*, NIS-mediated iodide uptake data that could be obtained from Kosugi *et al.* (1996) using a non-linear regression of the non-inverted data (vs. linear regressions of 1/velocity vs. 1/concentration values), resulted in a revised value for the affinity of perchlorate for the NIS of 0.59 μM. This is 2.5-fold lower than the value obtained by Kosugi *et al.* (1996) through linear regression of the inverted data, 1.5 μM. In part, the difference may be due to a transcription error of the regression slope from the 10 μM ClO_4^- inhibition data, where an attempt to reproduce the original results showed the largest discrepancy. When used in a PBPK model, which predicts the dosimetry of perchlorate and its effect on RAIU (US EPA (2009), adapted from Merrill *et al.* (2005) with minor changes), the model predictions of human RAIU data (Greer *et al.*, 2002) were clearly improved for

exposures levels of 20 and 100 μg kg^{-1} day^{-1} perchlorate, and remained within 1 SE of the observation at 7 μg kg^{-1} day^{-1} perchlorate. Use of the revised affinity is expected to improve the accuracy of predictions of perchlorate's effects for exposures up to 100 μg kg^{-1} day^{-1} across all human life stages.

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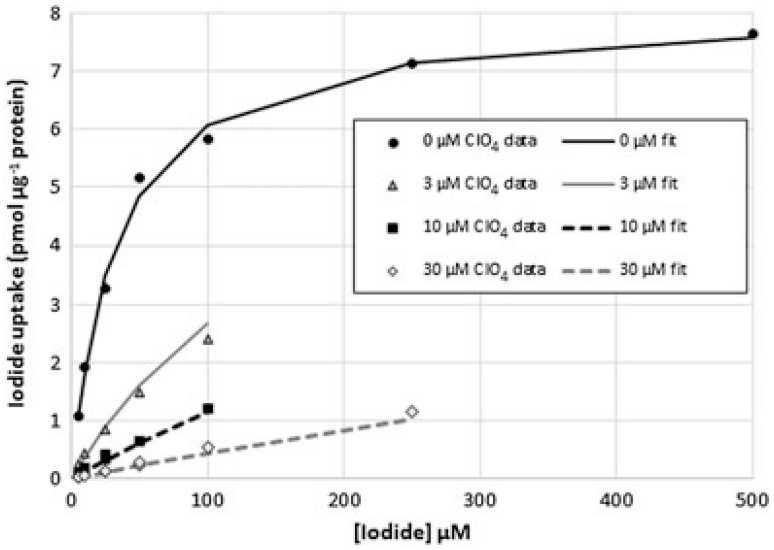

Figure 1.

Fit of competitive-inhibition Michaelis–Menten kinetic model to data of Kosugi *et al.* (1996) for NIS-mediated iodide uptake, with inhibition by perchlorate.

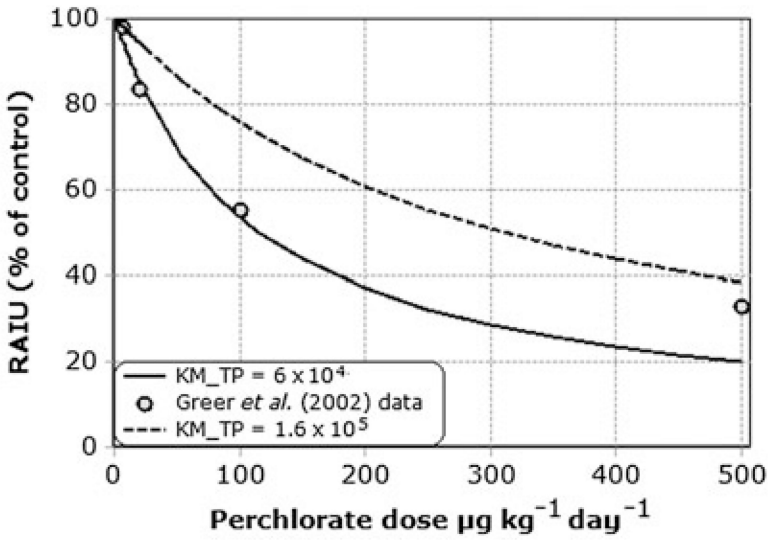

Figure 2.

Predicted RAIU levels (curve) for the average adult using the US EPA (2009) physiologically based pharmacokinetic model, but with $K_{m\text{-}NIS,ClO4}$ (KM_TP) = 6×10^4 or 1.6×10^5 ng l^{-1}. Data points from Greer *et al.* (2002). RAIU, radio-iodide uptake.