Published in final edited form as:

Int J Toxicol. 2011 December ; 30(6): 611–618. doi:10.1177/1091581811419024.

Biodistribution, toxicology and radiation dosimetry of 5-HT_{1A} receptor agonist Positron Emission Tomography ligand [¹¹C]CUMI-101

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Abstract

Sprague Dawley rats (10/sex/group) were given a single iv dose of CUMI-101 to determine acute toxicity of CUMI-101 and radiation dosimetry estimations were conducted in baboons with [¹¹C]CUMI-101. Intravenous administration of CUMI-101 did not produce overt biologically or toxicologically significant adverse effects except transient hypoactivity immediately post dose in the mid and high dose groups, which is not considered to be a dose limiting toxic effect. No adverse effects were observed in the low dose group. The no observed adverse effect level (NOAEL) is considered to be 44.05 µg/kg for a single iv dose administration in rats. The maximum tolerated dose (MTD) was estimated to be 881 µg/kg for a single iv dose administration. The Medical Internal Radiation Dose (MIRDose) estimates indicate the maximum, permissible single study dosage of [¹¹C]CUMI-101 in human is 52 mCi with testes and urinary bladder as the critical organ for male and female, respectively.

Keywords

PET; toxicity; dosimetry; radioligand

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Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Introduction

Serotonin_{1A} (5-HT_{1A}) receptors belong to the family of G-protein coupled receptors (GPCRs) and contribute to serotonin transmission in brain.¹ 5-HT_{1A} receptors have been implicated in the pathophysiology of mood and anxiety disorders, sexual function, eating disorders, neurodegenerative diseases and in the mechanism of action of antidepressants.²⁻⁹ The density and number of 5-HT_{1A} receptors enables its quantification in living subjects using Positron Emission Tomography (PET).^{10,11} 5-HT_{1A} receptors occur in high and low affinity agonist binding states. In contrast, antagonists bind to the high affinity (HA) and low affinity (LA) conformations of 5-HT_{1A} receptors with comparable affinity. It is the HA state of the receptor which is coupled to G-proteins and therefore agonists provide a measure of functional 5-HT_{1A} receptors.^{12,13} Among the successful antagonist tracers, [¹¹C]WAY-100635 is the most commonly used 5-HT_{1A} ligand for *in vivo* studies in human subjects.¹⁴⁻¹⁶ Several efforts have been made to develop a 5-HT_{1A} receptor agonist imaging agent *in vivo*.¹⁷⁻¹⁹ [*O*-methyl-¹¹C]2-(4-(4-(2-methoxyphenyl)piperazin-1-yl)butyl)-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)dione ([¹¹C]CUMI-101) is the only radiotracer available at present (*K*_i = 0.5 nM; *E*_{max} = 80; *EC*₅₀ = 0.1 nM) (Figure 1).¹³ [¹¹C]CUMI-101 can image high affinity sites in baboons and human subjects.^{12,20} [¹¹C]CUMI-101 is also sensitive to large changes of endogenous 5-HT produced by the administration of citalopram and fenfluramine to baboons.²¹ According to Food and Drug Administration (FDA), the extended single-dose toxicity studies in animals can be used to support single-dose studies in humans. Specifically, this guidance states: "The study should be designed to establish a dose inducing a minimal toxic effect, or alternatively, establishing a margin of safety. To establish a margin of safety, the sponsor should demonstrate that a large multiple (e.g., 100X) of the proposed human dose does not induce adverse effects in the experimental animals. Scaling from animals to humans based on body surface area can be used to select the dose for use in the clinical trial. Scaling based on pharmacokinetic and pharmacodynamic modeling would also be appropriate if such data are available" (Guidance for Industry, Investigators, and Reviewers Exploratory Investigational Drug Application (E-IND), FDA). Since these preclinical studies are needed to demonstrate to the Radioactive Drug Research Committee (RDRC) and FDA that a candidate imaging agent is understood well enough for designing appropriate clinical experiments, most of the work to be conducted to achieve these objectives must be performed and the resulting data analyzed and reported in strict compliance with the FDA's good laboratory practice (GLP) regulations for non-clinical laboratory studies (21 CFR 58). We now report toxicology and dosimetry determinations prior to performing human studies with [¹¹C]CUMI-101. We report toxicology evaluation of CUMI-101 in rats and dosimetry estimations for [¹¹C]CUMI-101 in baboons.

Materials and Methods

Synthesis of CUMI-101 and [¹¹C]CUMI-101

The syntheses of CUMI and [¹¹C]CUMI-101 were performed based on a procedure reported previously by us.¹³ In brief, coupling of 2-(4-chlorobutyl)-4-methyl-1,2,4-triazine-3,5(2*H*,4*H*)dione with 2-(piperazin-1-yl)phenol and 1-(2-methoxyphenyl)piperazine provided

desmethyl-CUMI-101 and CUMI-101 respectively. Radiosynthesis of [^{11}C]CUMI-101 was performed by [^{11}C]methylation of desmethyl-CUMI-101 using [^{11}C]MeOTf followed by purification by reverse phase high performance liquid chromatography (RP-HPLC) and C-18 Sep-Pak[®]

Rat Toxicity Study

The toxicity study was carried out in male and female Sprague Dawley rats by SRI International, Menlo Park, CA, in accordance with the FDA “Good Laboratory Practice for Nonclinical Laboratory Studies”, as described in 21 CFR Part 58. All animal studies were approved by SRI’s Institutional Animal Care and Use Committee (IACUC), and were performed in animal facilities that are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC). SRI files assurances with the Public Health Service (PHS) Office of Laboratory Animal Welfare (OLAW) and adheres to PHS standards and practices.

Maximum human dose of CUMI-101 proposed for a single dose is 10 μg per 70 kg person. $10 \mu\text{g}/70 \text{ kg} = 0.143 \mu\text{g}/\text{kg} \times 37$ (human surface area conversion) = $5.286 \mu\text{g}/\text{m}^2$. Scaling for the rat gives $5.286 \mu\text{g}/\text{m}^2 / 6$ (rat surface area conversion) = $0.881 \mu\text{g}/\text{kg}$ as an equivalent human dose; $1000 \times 0.881 = 881 \mu\text{g}/\text{kg}$ as the 1000 $\times$ dose in this study.

Fifty male (7–9 weeks old, 191–264 g) and 50 female (8–10 weeks old, 178–224 g) Sprague Dawley rats supplied from Charles River Laboratories were used in this study. Upon arrival, the rats were quarantined for 3 days. The rats were housed (five per cage) in polycarbonate hanging cages with Sanichip bedding. The animal room was monitored for temperature (65–79°F, 18–26°C) and humidity (30–70%) with a light cycle of 12 h light/12 h dark. The rats were fed with Purina Certified Rodent Chow (#5002; Richmond, IN) ad libitum. Water (purified, reverse osmosis) was provided ad libitum during quarantine and study periods. Male and female rats (ten males and ten females per group) were given CUMI-101 i.v. on Day 1 as a single dose of 881 $\mu\text{g}/\text{kg}$ ($5286 \mu\text{g}/\text{m}^2$; 1,000 times the human dose; Group 2) or as two daily doses of 440.5 $\mu\text{g}/\text{kg}$ per day ($2643 \mu\text{g}/\text{m}^2$; 500 times the human dose; Group 3) or 88.1 $\mu\text{g}/\text{kg}$ ($528.6 \mu\text{g}/\text{m}^2$; 100 times the human dose; Group 4) or 44.05 $\mu\text{g}/\text{kg}$ ($264.3 \mu\text{g}/\text{m}^2$; 50 times the human dose; Group 5). Control rats (ten males, ten females) were given a single i.v. dose of vehicle (at an equivalent volume (5 ml/kg) on Day 1 (Group 1).

Preparation of Dose Formulations

The test article CUMI-101 (also known as CUNBID-101) formulations were prepared by dissolving the appropriate amount of test article in ethanol (Pharmco; Brookfield, CT). Sterile saline was then added to achieve the target concentration in final vehicle formulation of 5% ethanol and 95% saline. Serial dilution using 5% ethanol/95% saline from the stock solution was used to achieve the mid and low doses. The pH was adjusted using 0.1 N HCl (JT Baker, Phillipsburg, NJ; Lot# T40429) to achieve final pH=7. Formulations were stored refrigerated protected from light for 3 days at 3.3°–5.0°C before use. Formulations were brought to room temperature prior to administration to the animals. All dosing formulations were confirmed to be within $\pm 10\%$ of the target concentration for all groups. All dose levels were scaled to surface area for comparison with proposed human dosages.

Observation protocol

All animals were individually identified by ear punch and were observed at least once daily for signs of mortality, morbidity, injury, and availability of food and water. All clinical observations were recorded daily (2–4 hour post dose on the days of dose administration) and more often as clinical effects warranted. Individual body weights were measured and recorded for each animal on Day 1 prior to dosing and at necropsy (Days 3 and 15 for groups 1–5). Food consumption was measured for a period of about 24 hours per cage twice weekly throughout the study.

Clinical pathology

Blood for clinical chemistry and hematology evaluations was collected on Days 3 and 15. Hematology samples were collected using EDTA as anticoagulant. No anticoagulants were used for serum chemistry samples. Animals were killed on Days 3 and 15 (interim and terminal necropsy of groups 1–5) necropsy of group 3) by overdose of sodium pentobarbital (250 mg/kg) administered by i.p. injection. External examination of all body orifices and surfaces and an examination of all cranial, thoracic, and abdominal organs were recorded. All retained tissues and organs were fixed in phosphate-buffered 10% formalin. Organ weights recorded for all survived animals at scheduled sacrifice. These include adrenal glands, brain, heart, kidneys, liver, spleen, thymus, testes and ovaries. Paired organs were combined and weighed together except kidneys.

Histopathology

Histopathology were performed on group 1 (control) and 2 (1000× human dose). Sections of the tissues from animals to be evaluated were embedded in paraffin (5 micron thick) and stained with hematoxylin and eosin by Biopathology Sciences Inc. Each lesion was listed and coded by the most specific topographic and morphologic diagnoses, severity, and distribution using Systemized Nomenclature of Medicine (SNOMED) and National Toxicology Program (NTP) codes as guide. Four step grading system (minimal, mild, moderate and marked) were used to define gradable lesions for comparison between treated and control groups.

Data Analyses

Mean and standard deviation were calculated for body weight, food consumption, organ weights, and clinical pathology data. One-way ANOVA analysis was performed on clinical pathology (LABCAT® module, HE v. 4.42), organ weight data (LABCAT® module OW v3.24). Body weight (LABCAT® In-Life v. 6.2) for Groups 4 and 5 were not compared with those for Groups 1–3 since dosing of Group 4 and 5 animals was initiated different days due to protocol changes in amendments. The values reported as individual food consumption data were calculated from cage totals rather than individual measurements. No statistical analysis was performed on food consumption. In all cases Criteria for Null Hypothesis Rejection was defined as $p < 0.05$.

Dosimetry studies of [^{11}C]CUMI-101 in baboon

Dosimetry estimations in baboons were performed based on protocol developed by us.^{22–24} In brief, fasted animals were immobilized with ketamine (10 mg/kg i.m.) and anesthetized with 1.8% isoflurane via an endotracheal tube. Temperature was kept constant at 37°C with heated water blankets. An intravenous line with 0.9% was maintained during the experiment and used for hydration and radiotracer injection. The ECAT ACCEL PET scanner (CTI-Siemens/ Knoxville, Tennessee, USA) was used to image the baboon's entire body. Two baboons were studied on two separate occasions. Prior to injection, a transmission scan was obtained using 3 Ge-68 rod sources (each, approximately 100 MBq) lasting 3.5 min/bed position using five bed positions needed to cover the entire body. Following a bolus intravenous injection of 187 ± 24.9 MBq of [^{11}C]CUMI-101, with a specific activity of 46.8 ± 29.1 MBq/nmol, five whole body emission scans were performed in two-dimensional mode. Each whole body scan covered the same field of view (FOV) as the transmission scan. Frames increased in duration to compensate for the 20minute half-life of C-11. Total duration of transmission and emission scanning was approximately 120 minutes. The 3D whole body emission scans were reconstructed using Fourier rebinning (FORE) + ordered-subsets expectation maximization (OSEM) using 2 iterations and 8 subsets, using attenuation and scatter corrections as implemented in ECAT 7.2.2 (CTI-Siemens, Knoxville, TN). Images were transferred into the image analysis software Medx 3.3 (Sensor Systems, Inc., Sterling, Virginia). Regions of interest (ROI) were drawn around organs that were identified clearly on all six scans. The absorbed radiation dose was calculated using the Medical Internal Radiation Dose scheme. The area under the curve was obtained by trapezoidal integration of the first 3 Time activity curve (TAC) data points. The organ residence times were then calculated from the ratio of area under the TAC to infinity over the initial total body activity. The MIRDose3 program was used to calculate the total absorbed radiation dose in each organ per injected dose phantom (see above). Using this calibration, the counts in the rest of the body were also estimated. The residence times were extrapolated to the adult male (70 kg) and adult female (57 kg) human phantoms in MIRDose3. The remainder of the blood activity (activity not included in the organ ROIs) was not measured. In the dosimetry calculation, an 'organ' called rest of body was used and its TACs were obtained from the sum of all organ activity subtracted from the total dose, and entered into the MIRDose3 program as 'remainder of the body'.

Results

Mortality/Morbidity and Clinical Observations

All animals survived until their scheduled sacrifice. Almost all male and female rats in the mid and high dose groups (Groups 2–4) displayed slight to moderate hypoactivity (severity 1–2 on a 0–4 scale) on Day 1 immediately after dose administration. The severity of the hypoactivity appeared to be dose dependent, with 19 of 20 animals in the high dose group (Group 2) having moderate hypoactivity. The animals recovered from the hypoactivity within a few hours after dose administration and appeared normal by the last time point at which clinical observations were performed on Day 1. All animals, except one female in Group 3, in the mid and high dose (Group 2 to 4) also displayed tachypnea (rapid breathing) immediately after dosing on Day 1; some animals also had shallow breathing. These animals

recovered by the next day. Rats in the low dose group at 44.05 µg/kg (50× human dose) and the control group did not exhibit hypoactivity and tachypnea after dose administration.

Body weight and food consumption

No test article related changes in body weights and food consumption were observed in the treated groups compared with the control group.

Clinical pathology

Clinical pathology (hematology and clinical chemistry) was evaluated on Days 3 and 15 (2 and 14 days after dose administration respectively). All of the changes were sporadic, were not clearly dose related, and generally represented small changes within the normal ranges for Sprague Dawley rats. Therefore, none of these changes were considered to be of toxicological significance.

Organ Weights

Brain weight in the males of Group 2 at the terminal sacrifice on Day 15 was slightly decreased compared with the controls. The change was not correlate microscopic evaluation and is considered to be a sporadic variation.

Histopathology

All tissues (~45 per animal) were examined histopathologically from all rats in Groups 1 (the controls) and 2 (high dose, 1000× human dose). Minor differences in type, incidence, and severity of findings exist between and within these two study groups, but no finding varies consistently and no variation is attributed to the test compound. The findings are generally similar to those commonly encountered as background findings for male and female rats of this strain and general age group. The gross stomach mass in Group 1 female #11 is histologically a hematoma on the serosal aspect of the stomach, an incidental finding. Inflammation in the heart is compatible with murine progressive cardiomyopathy, a commonly encountered background lesion in young rats of this strain. No histopathology examination was made of any tissues from rats in Groups 3, 4, or 5 because lesions at the highest dose were not considered test article related.

Biodistribution of [¹¹C]CUMI-101 in baboons

All animals tolerated the study and there were no discernable effects of the radiotracer injections on systolic or diastolic blood pressure, heart rate, respiratory rate, or rectal temperature. The whole body biodistribution of [¹¹C]CUMI-101 is shown in Figure 2.

Several organs were clearly identifiable based on location by the administration of [¹¹C]CUMI-101. A time-activity curve generated from some of the regions is illustrated in Figure 3. The area under the curve was calculated as the sum of the trapezoidal integration and the integral of the exponential functions from time zero to infinity. The residence times are shown in Table 1 with the liver having the highest residence time. Residence times were then used as input to the MIRDose3 program. Table 2 and 3 gives the dosimetry estimates for the 70 kg adult and adult female (57 kg) respectively. The data indicate elimination of [¹¹C]CUMI-101 via the hepatobiliary and renal systems. Testes for adult male and urinary

bladder for female received the highest estimated radiation dose and were the critical organ ($1.00\text{E}-02$ mGy/MBq and $2.03\text{E}-02$ rad/mCi, respectively) estimates for adult human males and females and validate the baboon as a substitute for human subjects.

Discussion

All animals evaluated in the rat toxicity study survived until their scheduled necropsy. Male and female rats in the mid and high dose groups (Groups 2–4) displayed slight to moderate hypoactivity on Day 1 immediately after dose administration. The severity of the hypoactivity appeared to be dose dependent, with the highest severity observed in the high dose group (Group 2). The animals recovered from the hypoactivity within a few hours and appeared normal by the last time point at which clinical observations were performed on Day 1. Rats in the low dose group at $44.05\text{ }\mu\text{g/kg}$ ($264.3\text{ }\mu\text{g/m}^2$, $50\times$ human dose) and control group did not exhibit hypoactivity after dose administration. No drug-related effects were found for clinical pathology, body weights, food consumption, organ weights, and macroscopic and microscopic evaluations. In conclusion, iv administration of CUMI-101 to male and female Sprague Dawley rats once or twice a day did not produce overt biologically or toxicologically significant adverse effects other than hypoactivity in the mid and high dose groups. The hypoactivity is not considered to be a dose-limiting toxic effect. No adverse effects were observed in the low dose group. The no observed adverse effect level (NOAEL) is considered to be $44.05\text{ }\mu\text{g/kg}$ ($264.3\text{ }\mu\text{g/m}^2$) for administration of a single iv dose. The maximum tolerated dose (MTD) is considered to be at least $881\text{ }\mu\text{g/kg}$ ($5286\text{ }\mu\text{g/m}^2$) for administration of a single iv dose.

The [^{11}C]CUMI-101 was well tolerated in the animals, with no meaningful changes in any vital signs. Our study show the single study maximal radiation exposure calculated by our group in male baboon studies involving [^{11}C]CUMI-101, will remain below the 21 CFR 361.1 dose limit for research subjects which is 26 mCi in males and 26 mCi in females (i.e., calculation based upon the testes and the bladder as the critical organ respectively; 3 rads per single study for the whole body, active blood forming organs, lens of the eyes and gonads; 5 rads for other organ per single study limit). The maximum annual dose limit (15 rads) is 135 mCi in males and 170 mCi in females. Thus, the dose of 52 mCi in males and 52 mCi in females per year (dosage for two PET sessions) is below this limit. The favorable toxicology and dosimetry findings make [^{11}C]CUMI-101 suitable for human use. Dosimetry findings will need to be validated in human subjects.

Acknowledgments

This work was partially supported by research grant from the National Institute of Health (K08 MH76258-01A1). We thank National Institute of Mental Health Toxicology screening program for financial support for Toxicology studies.

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R = CH₃; CUMI-101
R = ¹¹CH₃; [¹¹C]CUMI-101
CAS RN# 903528-74-5

Figure 1.
Chemical structures of CUMI-101 and [¹¹C]CUMI-101

Figure 2. Whole body $[^{11}\text{C}]$ CUMI-101 image of baboon. Left to right: frame 1, 2, 4, 8 (Midtime 0.75, 4.38, 13.65 and 80.18 minutes) , top: coronal images, bottom: transaxial images

Figure 3.

Time activity curves of $[^{11}\text{C}]\text{CUMI-101}$ in different organs of baboon. (The blue curves (dotted lines) are decay corrected and the red curves (dashed and solid lines) are non-decay-corrected TACs for each organ).

Table 1Average residence time of [^{11}C]CUMI-101 in baboon (unit: Bq·h/Bq)

Remainder	2.92E-01
Liver	7.02E-02
Lungs	2.58E-02
Small Intestine	2.07E-02
Urinary Bladder content	1.99E-02
Brain	1.84E-02
Kidneys	1.25E-02
Red Marrow	8.01E-03
Stomach	7.20E-03
Pancreas	4.91E-03
Heart Wall	3.73E-03
Spleen	3.68E-03
Gall Bladder Content	1.10E-03
Thyroid	3.94E-04
Eyes	2.56E-04

Table 2Dosimetry estimation of [^{11}C]CUMI-101 extrapolated to adult male

Organ	mGy/MBq	mrads/mCi	mrads/ID	% Limit
Adrenals	3.47E-03	1.28E+01	3.34E+02	6.7
Brain	4.54E-03	1.68E+01	4.37E+02	8.7
Breasts	2.00E-03	7.40E+00	1.92E+02	3.8
Gallbladder Wall	6.11E-03	2.26E+01	5.88E+02	11.8
LLI Wall	2.85E-03	1.05E+01	2.74E+02	5.5
Small Intestine	8.26E-03	3.06E+01	7.95E+02	15.9
Stomach Wall	1.15E-02	4.25E+01	1.11E+03	22.1
ULI Wall	3.42E-03	1.27E+01	3.29E+02	6.6
Heart Wall	4.76E-03	1.76E+01	4.58E+02	9.2
Kidneys	1.28E-02	4.74E+01	1.23E+03	24.6
Liver	1.28E-02	4.74E+01	1.23E+03	24.6
Lungs	7.76E-03	2.87E+01	7.47E+02	14.9
Muscle	2.30E-03	8.51E+00	2.21E+02	4.4
Pancreas	1.55E-02	5.74E+01	1.49E+03	29.8
Red marrow	2.83E-03	1.05E+01	2.72E+02	9.1
Osteogenic Cells	2.60E-03	9.62E+00	2.50E+02	5.0
Skin	1.79E-03	6.62E+00	1.72E+02	3.4
Spleen	7.07E-03	2.62E+01	6.80E+02	13.6
Testes	1.00E-02	3.70E+01	9.62E+02	32.1
Thymus	2.32E-03	8.58E+00	2.23E+02	4.5
Thyroid	5.65E-03	2.09E+01	5.44E+02	10.9
Urinary Bladder Wall	1.51E-02	5.59E+01	1.45E+03	29.1
Lens of the Eye	6.31E-03	2.33E+01	6.07E+02	20.2
Total Body	2.84E-03	1.05E+01	2.73E+02	
	mSv/MBq	mrem/mCi	mrem/ID	
Effective dose equivalent	8.20E-03	3.03E+01	7.89E+02	
Effective dose	7.10E-03	2.63E+01	6.83E+02	22.8
Effective dose	7.10E-03	2.63E+01	6.83E+02	22.8

Table 3Dosimetry estimation of [^{11}C]CUMI-101 extrapolated to adult female

Organ	mGy/MBq	mrads/mCi	mrads/ID	% Limit
Adrenals	4.38E-03	1.62E+01	4.21E+02	8.4
Brain	5.28E-03	1.95E+01	5.08E+02	10.2
Breast	2.55E-03	9.44E+00	2.45E+02	4.9
Gallbladder Wall	7.11E-03	2.63E+01	6.84E+02	13.7
LLI Wall	3.61E-03	1.34E+01	3.47E+02	6.9
Small Intestine	9.68E-03	3.58E+01	9.31E+02	18.6
Stomach Wall	1.66E-02	6.13E+01	1.59E+03	31.9
ULI Wall	4.28E-03	1.58E+01	4.12E+02	8.2
Heart Wall	6.19E-03	2.29E+01	5.95E+02	11.9
Kidneys	1.41E-02	5.22E+01	1.36E+03	27.1
Liver	1.69E-02	6.25E+01	1.63E+03	32.5
Lungs	9.83E-03	3.64E+01	9.46E+02	18.9
Muscle	2.89E-03	1.07E+01	2.78E+02	5.6
Ovaries	3.83E-03	1.42E+01	3.68E+02	12.3
Pancreas	1.75E-02	6.48E+01	1.68E+03	33.7
Red marrow	3.20E-03	1.18E+01	3.08E+02	10.3
Osteogenic Cells	3.10E-03	1.15E+01	2.98E+02	6.0
Skin	2.25E-03	8.33E+00	2.16E+02	4.3
Spleen	8.60E-03	3.18E+01	8.27E+02	16.5
Thymus	2.98E-03	1.10E+01	2.87E+02	5.7
Thyroid	6.70E-03	2.48E+01	6.45E+02	12.9
Urinary Bladder Wall	2.03E-02	7.51E+01	1.95E+03	39.1
Uterus	4.10E-03	1.52E+01	3.94E+02	7.9
Lens of the Eye	7.36E-03	2.72E+01	7.08E+02	23.6
Total Body	3.56E-03	1.32E+01	3.42E+02	
	mSv/MBq	mrem/mCi	mrem/ID	
Effective dose equivalent	7.90E-03	2.92E+01	7.60E+02	
Effective dose	6.75E-03	2.50E+01	6.49E+02	21.6