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Radiation Effective Dose Assessment of [^{51}Mn]- and [^{52}Mn]-chloride

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Abstract: In order to establish the potential of [$^{51/52}$Mn]Cl_2 as safe PET brain tracers, the radiation effective dose (ED) of [^{51}Mn]- and [^{52}Mn]-chloride has been assessed by using biokinetic models in anthropomorphic phantoms. Results showed that [^{52}Mn]-chloride releases one hundred thirty times more radiation dose (ED=1.35 mSv/MBq) than [^{51}Mn]-

chloride (ED=1.02E-02 mSv/MBq). Although the maximum positron energy of ^{52}Mn allows a PET image resolution similar to that of ^{18}F, activities below 15 MBq should be administered.

Keywords: Mn-52 dosimetry; Mn-51 dosimetry; PET brain tracers; [$^{51/52}$Mn]Cl_2 effective dose.

1. Introduction

Manganese in trace amounts is essential for human life. The most stable oxidation state is manganese (II). It has been mainly used in its free ionic form ($MnCl_2$) in animals for manganese-enhanced magnetic resonance imaging (MEMRI)-based techniques, to study tissue anatomy of liver, kidneys, heart, and pancreas (Antkowiak et al., 2008; Hu et al., 2005; Ni' et al., 1997). Due to the ability of Mn^{2+} to enter excitable cells through voltage-gated calcium channels, it can be used to monitor cellular activity, cytoarchitecture and neuronal tract tracing in the brain (Pautler et al., 1998; Murayama et al., 2006). However, elevated ingestion of manganese can produce neurotoxic effects that result in manganism, a neurological syndrome similar to Parkinson's disease (Cersosimo and Koller, 2006).

The much higher sensitivity of positron emission tomography (PET) over MRI enables the use of trace level concentrations of Mn. Radioactive manganese tracers could be used to obtain information typically derived from MEMRI, but with a potential expansion of the methodology to assess tissue function and neuronal connectivity in humans (Saar et al., 2018).

Beta(+)-emitting radionuclides, such as ^{52}Mn ($t_{1/2}$= 5.591 d, β^+= 29.4%, $E(\beta^+)_{avg}$= 241.6 keV), ^{52m}Mn ($t_{1/2}$= 21.1 min, β^+=96.4%, $E(\beta^+)_{avg}$ = 1174 keV) and ^{51}Mn ($t_{1/2}$= 45.59 min, β^+=97.1%, $E(\beta^+)_{avg}$ = 970.2 keV) (Graves et al., 2017a) have been used for preclinical PET imaging. The favorable low maximum positron energy of ^{52}Mn makes PET imaging resolution similar to that of ^{18}F, which has caused a renewed interest in using radioactive manganese as a PET tracer (Topping et al., 2013). Therefore, the development of different production routes for ^{52}Mn and ^{51}Mn by cyclotrons and the

optimization of the radiochemical separation methods were initiated within the framework of the "Multimodal PET/MRI imaging with cyclotron-produced $^{52/51}$Mn and the stable paramagnetic Mn isotopes" (METRICS) research project, by the Legnaro National Laboratories at the National Institute for Nuclear Physics, Italy (LNL-INFN).

Even though several biodistribution preclinical studies of radioactive $MnCl_2$ have been published, only one study reported dosimetry calculations for ^{51}Mn, while the internal radiation dose assessment due to ^{52}Mn administration is pending. In order to establish the potential of radioactive manganese chloride as a safe clinical PET imaging agent, the aim of this work was to assess the radiation effective dose of [^{51}Mn]- and [^{52}Mn]-chloride by using biokinetic models in anthropomorphic phantoms based on human standardized masses defined by ICRP 89 (ICRP, 2002) and tissue-weighting factors recommended by the ICRP 103 (ICRP, 2007) through OLINDA code v2.0.

2. Materials and methods

2.1 Biokinetic data

Biodistribution data in healthy mice after [^{52}Mn]Cl_2 injection (Hernandez et al., 2017)) were used to establish the biokinetic models as described below. Data includes the percent of injected activity per gram of tissue ($[\%\ IA/g]_A$) in all source organs (heart, liver, kidneys, muscle, pancreas and salivary gland) as a function of the time from 1 to 13 days. This time window is suitable to perform trustable and accurate dose assessments for [^{52}Mn]Cl_2. However the first point of these biodistribution data is at 1 h, a value comparable to the half-life of ^{51}Mn (46 min) and could miss details about the accumulation phase for this short half-life isotope. Nevertheless, dynamic PET imaging performed with [^{51}Mn]Cl_2 over a time window of 30 minutes demonstrated that Mn was

accumulated very fast (from 3 to 5 minutes post-injection (p.i.)) in the heart, liver, kidneys, pancreas, muscle and salivary glands and its concentration remained stable for at least 30 min [Graves 2017b]. Therefore, to obtain a more accurate dose assessments for $[^{51}Mn]Cl_2$, the numbers of disintegrations in the different source organs were estimated considering that the uptake values measured by Hernandez et al. (2017) at 1 h p.i were reached already at 5 min p.i.

2.2 Calculation of the number of disintegrations in the source organs

The biodistribution data in the source organs were scaled from mice to humans through the relative mass scaling method, using the following expression, which takes into account the differences in human and animal organ masses with regard to the total body masses (Sparks and Aydogan, 1999):

$$\left(\frac{\%IA}{organ}\right)_H = \left(\frac{\%IA}{organ}\right)_A \cdot \frac{OW_H}{TBW_H} \cdot \frac{TBW_A}{OW_A} \qquad (2)$$

where OW_A and OW_H are the animal and human organ weight, TBW_A and TBW_H are the average total body weight for animal and human, respectively.

As mentioned, Hernandez et al. (2017) provided the animal biodistribution data in $[\%\ IA/g]_A$, so equation (2) is simplified to equation (3), which does not imply the use of animal organ mass:

$$\left(\frac{\%IA}{organ}\right)_H = \left(\frac{\%IA}{g}\right)_A \cdot \frac{OW_H}{TBW_H} \cdot TBW_A \qquad (3)$$

The decay-corrected percent of injected activity in the source organs calculated for humans were plotted as a function of the post-injection time and fitted to a tri-

exponential equation to obtain the organ activity curves. These curves represent the phase of accumulation, retention and elimination of $MnCl_2$ in each source organ. Then, the number of disintegrations in the source organs was calculated by integration of organ activity curves considering the physical half-lives of ^{52}Mn and ^{51}Mn with CoKiMo software (Meléndez-Alafort et al., 2017)

2.3 Calculation of the number of disintegrations in the non-source organs

The total number of disintegrations in the body caused by the injected material was calculated in two different ways, by a conservative estimation, assuming only radioactive decay, and with an estimation based on the human biological half-life stated by Mahoney et al. (Mahoney and Small, 1968) after intravenously injecting ^{54}Mn in man. Mahoney found that Mn is cleared from the body by two exponential components: about 70% of the injected material was eliminated by a "slow" pathway with a biological half-time of 45 days and the rest through a “fast" pathway, with a half-time of 4 days.

Activity in the non-source organs, or remaining organs, was obtained by subtracting the number of disintegrations in the source organs to the total number of disintegrations in the body caused by the $MnCl_2$ injection.

2.4 Dose calculations

Dose calculations were performed with the OLINDA (Organ Level Internal Dose Assessment) software code version 2.0 (Stabin and Farmer, 2012; Stabin et al., 2005). For comparison purposes, the OLINDA code version 1.1 was also used. Version 1.1, makes use of anthropomorphic phantoms based on the Oak Ridge National Laboratory (ORNL) models, which employ geometric shapes to define the organs and calculates the effective dose equivalent (EDE) and the effective dose (ED) using the tissue-weighting

factors recommended by ICRP 26 (1977) and ICRP 60 (1991), respectively. In version 2.0, the geometric models were replaced by the realistic NURBS-type models (Stabin et al., 2012), based on the recently standardized masses defined by ICRP 89 (2002), and the ED is calculated using the new tissue-weighting factors recommended by ICRP 103 (2007). Both versions of OLINDA software use the RADAR method for internal dose estimation (Stabin and Siegel, 2017) and calculate the equivalent dose in each organ according to the general equation:

$$D = N_{source} \times DF \tag{4}$$

where N_{source} is the number of disintegrations that occur in the source organ per unit of activity administered (MBq-h/MBq) and DF is a dose factor that depends on the radioisotope, the spatial relationship between the target and the source organ and their tissue composition:

$$DF = \frac{k \sum_i n_i \cdot E_i \cdot \Phi_i \cdot w_R}{m} \tag{5}$$

where m is the mass of the target organ, n_i is the number of i-th nuclear transition per nuclear transformation, E_i is the mean energy of the i-th nuclear transition, Φ_i is the absorbed fraction in the target organ of radiation energy E_i emitted from the source organ, w_R is the radiation-weighing factor assigned to the i-th radiation and k is a constant whose value depends on the units of the included quantities.

3. Results

Number of disintegrations in the source organs

The human percent of injected activity in the main source organs, $[\%\ IA/organ]_H$, was calculated for male and female models through equation (3) on the base of Hernandez's

biodistribution data (Hernandez et al., 2017) using the established values of OW_H and TBW_H of either the ORNL (Cristy and Eckerman, 1987; Stabin et al., 1995) or ICRP 89 (2002) phantoms.

Figure 1 shows $[\%\ IA/organ]_H$ values for ORNL or ICRP 89 phantoms in the most important male source organs plotted for each time p.i. and the organ activity curves obtained after the fitting. Plots show a fast Mn^{2+} uptake for all the organs, followed by a slow clearance, except for the salivary gland, where uptake remains quite stable. The small differences between curves obtained with ORNL and ICRP 89 phantoms are a consequence of the organ weight used by each model. Similar results were obtained when female phantoms were used.

The number of disintegrations in the source organs per MBq of injected activity obtained from the organ activity curves are reported in Table 1 and 2 for $[^{51}Mn]Cl_2$ and $[^{52}Mn]Cl_2$, respectively. The activity reported by Hernandez et al. (2017) as *[%IA/g]* in "heart/blood" was assigned to "heart wall" and "heart contents" using eq.(3) and the respective masses. It was not possible to calculate the number of disintegrations of one source organ for each phantom model: the salivary gland (which is not included in the ORNL phantom model) and muscle (which is not included in the source/target organs of the ICRP 89 phantom model). The number of disintegrations in the remaining organs were calculated either assuming only radioactive decay, without considering a total-body biological clearance (BC) or assuming a total body BC based on the data of Mahoney and Small (Mahoney and Small, 1968). Table 1 and 2 show data for both ORNL and ICRP 89 phantoms for male and female models.

Table 1. Number of nuclear transitions (MBq-hr/MBq) in source organs per MBq of $[^{51}Mn]Cl_2$, for male and female ORNL and ICRP 89 phantoms. The number of disintegrations in the remaining organs has been calculated both with and without the biological clearance (BC) assumption.

Tissue	$[^{51}Mn]Cl_2$			
	Male		Female	
	ORNL	ICRP 89	ORNL	ICRP 89
Heart contents	1.40E-02	1.59E-02	1.63E-02	1.37E-02
Heart wall	9.74E-03	1.03E-02	9.56E-03	9.38E-03
Kidneys	2.78E-02	2.46E-02	2.78E-02	2.64E-02
Liver	9.46E-02	9.02E-02	9.00E-02	8.54E-02
Pancreas	7.46E-03	1.10E-02	8.82E-03	1.15E-02
Muscle	1.63E-01	-	1.27E-01	-
Salivary gland	-	2.72E-03	-	2.71E-03
Remaining (without BC)	7.84E-01	9.41E-01	8.17E-01	9.47E-01
Remaining (with BC)	7.81E-01	9.38E-01	8.14E-01	9.44E-01

The differences between the calculated values for ORNL and ICRP 89 phantoms produced by the organ masses of the different phantoms are mainly relevant for the pancreas (40% increase in the ICRP 89 with regard to ORNL phantoms). In the case of $[^{51}Mn]Cl_2$, the two different hypotheses used to estimate the number of disintegrations in the remaining organs give almost the same results, while larger differences occur in the case of $[^{52}Mn]Cl_2$. These results were expected because the biological clearance has a

negligible effect on the effective half-life of ^{51}Mn, due to its short physical half-life (45.6 min). In the case of ^{52}Mn, the activity in the remaining organs decreases significantly when biological clearance was considered, as a consequence of its larger physical half-life (5.591 d).

Table 2. Number of nuclear transitions (MBq-hr/MBq) in source organs per MBq of [^{52}Mn]Cl_2, for male and female ORNL and ICRP 89 phantoms. The number of disintegrations in the remaining organs has been calculated both with and without the biological clearance (BC) assumption.

Tissue	[^{52}Mn]Cl_2			
	Male		Female	
	ORNL	ICRP 89	ORNL	ICRP 89
Heart contents	8.81E-01	1.00E+00	1.03E+00	8.82E-01
Heart wall	6.13E-01	6.47E-01	6.02E-01	5.96E-01
Kidneys	1.98E+00	2.07E+00	2.35E+00	2.24E+00
Liver	7.69E+00	7.32E+00	7.29E+00	6.93E+00
Pancreas	7.70E-01	1.15E+00	8.98E-01	1.20E+00
Muscle	1.77E+01	-	1.39E+01	-
Salivary gland	-	6.00E-01	-	6.01E-01
Remaining (without BC)	1.64E+02	1.81E+02	1.68E+02	1.81E+02
Remaining (with BC)	1.15E+02	1.32E+02	1.19E+02	1.33E+02

Dose Calculations

The absorbed doses in the organs were calculated for [^{51}Mn]Cl_2 and [^{52}Mn]Cl_2 with the OLINDA 1.1 and 2.0 software using the data of Tables 1 and 2, respectively, and the

results are presented in Tables 3 and 4. These tables report, for each radioisotope, the main organ absorbed doses, the values of EDE based on ICRP 26 (1977) and ED based on ICRP 60 (1991) for ORNL phantoms and ED based on ICRP 103 (2007) for ICRP 89 (2002) phantoms, for both male and female models.

[^{51}Mn]Cl_2 absorbed doses calculated with the two different hypotheses concerning the activity in the remaining organs are very similar due to its short half-life. Looking at the dose received by the main organs, it was established that the critical organs are the kidneys, followed by the pancreas and the liver, both for male and female phantoms. In the case of [^{52}Mn]Cl_2, organ absorbed doses calculated without biological clearance were 15 to 35 % higher than the values obtained contemplating the biological clearance. Therefore, ED values for both male and female models increase about 30% when biological removal was not considered. Looking at the dose received by the main organs, it was established that, for both radioisotopes, the critical organ was the pancreas, followed by the kidneys and liver, both for male and female phantoms.

Table 3. The equivalent doses (mSv/MBq) calculated for [^{51}Mn]Cl_2 with the OLINDA v1.1 and v2.0 software for male and female ORNL and ICRP 89 phantoms using the data of Table 1, and values of EDE and ED based on the ICRP 26, 60 and 103. (BC=biological clearance).

Target Organ	[^{51}Mn]Cl_2							
	Male				Female			
	Without BC		With BC		Without BC		With BC	
	ORNL	ICRP	ORNL	ICRP	ORNL	ICRP	ORNL	ICRP
Adrenals	1.06E-02	1.67E-02	1.06E-02	1.67E-02	1.39E-02	1.84E-02	1.38E-02	1.83E-02
Brain	8.69E-03	9.30E-03	8.66E-03	9.27E-03	1.12E-02	1.14E-02	1.12E-02	1.14E-02
Breasts	8.29E-03	-	8.26E-03	-	1.08E-02	1.14E-02	1.08E-02	1.14E-02
Esophagus	-	1.10E-02	-	1.09E-02	-	1.33E-02	-	1.32E-02
Eyes	-	9.29E-03	-	9.26E-03	-	1.14E-02	-	1.14E-02
Gallbladder Wall	1.13E-02	1.44E-02	1.13E-02	1.44E-02	1.41E-02	1.49E-02	1.41E-02	1.49E-02
LLI Wall/Left Colon	9.55E-03	1.15E-02	9.52E-03	1.15E-02	1.25E-02	1.37E-02	1.25E-02	1.37E-02
Small Intestine	1.01E-02	1.13E-02	1.01E-02	1.13E-02	1.23E-02	1.33E-02	1.22E-02	1.33E-02
Stomach Wall	9.95E-03	1.20E-02	9.92E-03	1.19E-02	1.29E-02	1.39E-02	1.29E-02	1.39E-02
ULI Wall/Right Colon	1.01E-02	1.15E-02	1.01E-02	1.14E-02	1.31E-02	1.38E-02	1.31E-02	1.38E-02
Rectum	-	1.07E-02	-	1.06E-02	-	1.31E-02	-	1.30E-02
Heart Wall	3.00E-02	3.02E-02	3.00E-02	3.02E-02	3.86E-02	3.56E-02	3.86E-02	3.56E-02
Kidneys	4.71E-02	4.71E-02	4.71E-02	4.71E-02	6.12E-02	5.66E-02	6.12E-02	5.66E-02
Liver	3.36E-02	3.34E-02	3.36E-02	3.34E-02	4.31E-02	4.05E-02	4.31E-02	4.05E-02
Lungs	9.14E-03	1.08E-02	9.11E-03	1.07E-02	1.21E-02	1.33E-02	1.21E-02	1.33E-02
Muscle	6.04E-03	-	6.03E-03	-	7.58E-03	-	7.57E-03	-
Ovaries	9.73E-03	-	9.70E-03	-	1.25E-02	1.32E-02	1.24E-02	1.31E-02
Pancreas	4.78E-02	4.68E-02	4.78E-02	4.68E-02	6.22E-02	5.75E-02	6.22E-02	5.75E-02
Prostate	-	1.07E-02	-	1.06E-02	-	-	-	-
Salivary Glands	-	1.83E-02	-	1.83E-02	-	2.17E-02	-	2.17E-02
Red Marrow	7.57E-03	8.34E-03	7.55E-03	8.32E-03	9.40E-03	1.02E-02	9.37E-03	1.01E-02
Osteogenic Cells	1.25E-02	7.62E-03	1.24E-02	7.59E-03	1.74E-02	8.03E-03	1.74E-02	8.01E-03
Skin	7.69E-03	-	7.66E-03	-	1.01E-02	-	1.00E-02	--
Spleen	9.83E-03	1.11E-02	9.80E-03	1.11E-02	1.29E-02	1.42E-02	1.28E-02	1.42E-02
Testes	8.47E-03	9.67E-03	8.44E-03	9.64E-03	-	-	-	-
Thymus	9.07E-03	1.09E-02	9.04E-03	1.09E-02	1.20E-02	1.31E-02	1.20E-02	1.31E-02
Thyroid	8.71E-03	1.01E-02	8.68E-03	1.00E-02	1.10E-02	1.19E-02	1.10E-02	1.19E-02
Urinary Bladder Wall	9.39E-03	1.06E-02	9.36E-03	1.05E-02	1.10E-02	1.19E-02	1.10E-02	1.19E-02
Uterus	9.81E-03	-	9.78E-03	-	1.24E-02	1.31E-02	1.24E-02	1.31E-02
Total Body	1.10E-02	1.10E-02	1.10E-02	1.10E-02	1.41E-02	1.36E-02	1.41E-02	1.35E-02
EDE (ICRP 26) (mSv/MBq)	**1.65E-02**	**-**	**1.65E-02**	**-**	**2.13E-02**	**-**	**2.13E-02**	**-**
ED (ICRP 60) (mSv/MBq)	**1.10E-02**	**-**	**1.10E-02**	**-**	**1.42E-02**	**-**	**1.41E-02**	**-**
ED (ICRP 103) (mSv/MBq)	**-**	**1.02E-02**	**-**	**1.02E-02**	**-**	**1.37E-02**	**-**	**1.36E-02**

Table 4. The equivalent doses (mSv/MBq) calculated for $[^{52}Mn]Cl_2$ with the OLINDA v1.1 and v2.0 software for male and female ORNL and ICRP 89 phantoms using the data of Table 2, and values of EDE and ED based on the ICRP 26, 60 and 103. (BC= biological clearance).

Target Organ	$[^{52}Mn]Cl_2$							
	Male				Female			
	Without BC		With BC		Without BC		With BC	
	ORNL	ICRP	ORNL	ICRP	ORNL	ICRP	ORNL	ICRP
Adrenals	2.50	2.74	1.95	2.27	3.08	3.25	2.42	2.65
Brain	2.03	1.56	1.44	1.15	2.37	1.93	1.7	1.43
Breasts	1.61	-	1.18	-	1.95	1.79	1.44	1.35
Esophagus	-	2.01	-	1.56	-	2.22	-	1.76
Eyes	-	1.55	-	1.14	-	1.93	-	1.43
Gallbladder Wall	2.65	2.73	2.10	2.24	2.95	3.01	2.36	2.41
LLI Wall/Left Colon	2.44	2.49	1.78	1.90	3.05	2.92	2.23	2.22
Small Intestine	2.70	2.50	1.98	1.88	2.75	2.72	2.05	2.07
Stomach Wall	2.41	2.38	1.81	1.87	2.92	2.86	2.22	2.21
ULI Wall/Right Colon	2.64	2.47	1.95	1.89	3.21	2.99	2.38	2.26
Rectum	-	2.36	-	1.74	-	2.87	-	2.12
Heart Wall	2.12	2.17	1.75	1.82	2.60	2.63	2.16	2.16
Kidneys	2.90	2.98	2.50	2.58	3.57	3.60	3.1	3.12
Liver	2.63	2.67	2.33	2.37	3.24	3.30	2.85	2.90
Lungs	1.91	1.88	1.44	1.44	2.4	2.38	1.83	1.82
Muscle	1.71	-	1.28	-	2.08	-	1.57	-
Ovaries	2.50	-	1.83	-	2.96	2.93	2.18	2.17
Pancreas	3.28	3.46	2.80	3.00	4.06	4.26	3.49	3.70
Prostate	-	2.33	-	1.72	-	-	-	-
Salivary Glands	-	2.45	-	2.01	-	2.73	-	2.27
Red Marrow	2.05	1.96	1.52	1.47	2.54	2.44	1.89	1.84
Osteogenic Cells	2.52	2.09	1.83	1.55	3.01	2.52	2.21	1.88
Skin	1.27	-	0.94	-	1.61	-	1.19	-
Spleen	2.35	2.24	1.77	1.71	2.87	2.82	2.19	2.18
Testes	1.81	1.82	1.32	1.33	-	-	-	-
Thymus	1.92	1.94	1.44	1.49	2.45	2.45	1.84	1.87
Thyroid	1.92	1.95	1.41	1.45	2.15	2.14	1.58	1.60
Urinary Bladder Wall	2.33	2.32	1.70	1.70	2.00	2.11	1.48	1.56
Uterus	2.56	-	1.87	-	2.92	2.89	2.15	2.14
Total Body	1.86	1.85	1.40	1.37	2.33	2.25	1.75	1.70
EDE (ICRP 26) (mSv/MBq)	**2.32**	**-**	**1.79**	**-**	**2.81**	**-**	**2.18**	**-**
ED (ICRP 60) (mSv/MBq)	**2.15**	**-**	**1.62**	**-**	**2.58**	**-**	**1.95**	**-**
ED (ICRP 103) (mSv/MBq)	**-**	**1.74**	**-**	**1.35**	**-**	**2.31**	**-**	**1.79**

4. Discussion

Extreme care should be taken into account when using biodistribution data from animals to predict doses to humans, as, for example, extrapolated animal data tend to underpredict human organ self-doses (Sparks and Aydogan, 1999). Nevertheless, the estimated doses for ^{51}Mn and ^{52}Mn radioisotopes obtained in this work from preclinical data can be considered a first approach to predict the dosimetric behavior in humans, since appropriate scaling parameters were taken into account (mass organs, whole-body total weight and biokinetic data). At this point, the obtained dosimetric estimations are useful to consider or not the application of [^{51}Mn]Cl_2 and [^{52}Mn]Cl_2 in human beings, as discussed below.

As expected, results showed that the biological half-life of manganese has a significant effect on the effective half-life of the radioisotopes. Comparison of the values calculated considering or disregarding biological clearance demonstrated that, in the second case, the overestimation of the dose was more evident with the long half-life isotope ^{52}Mn than with the short physical half-life isotope ^{51}Mn (see table 3 and 4).

In general, the calculated [^{51}Mn]Cl_2 equivalent doses are lower using the ORNL than the ICRP 89 phantoms, except for the osteogenic cells (see table 3). For [^{52}Mn]Cl_2 equivalent doses do not show a general trend, in some cases (for example, the pancreas) values are lower for the ORNL phantoms; in other cases they are higher (see table 3). However, for both isotope ED values calculated with Olinda 1.1, using the ORNL phantoms, were higher than the ED calculated with Olinda 2.0, using the ICRP 89 phantoms, especially for males. These results are explained by the fact that the adult male ORNL phantom is indeed hermaphroditic (Cristy and Eckerman, 1987); then, the presence of female

organs such as ovaries, uterus and breasts in the ORNL phantom can contribute to the increment of effective dose values when Olinda 1.1 was used.

Female effective doses calculated for both isotopes (^{51}Mn and ^{52}Mn) are about 30% higher than male ED. This result is in agreement with those reported for other radiopharmaceuticals (Stabin, 1997). The reason is well-known and it is related with the female's overall body and organ sizes, which are smaller and closer than those of males. In addition, female gonads are inside the body, near to several source organs such as urinary bladder, liver, kidneys, stomach and intestines. Therefore, to avoid an over or underestimation of the dose, the most accurate ICRP 89 phantoms and the correct female or male model must always be used for ED calculations.

Currently, only one work (Graves et al., 2017b) has reported the dosimetry predictions for ^{51}Mn. Graves *et al.* (2017b) calculated the number of nuclear transitions in source organs using a simplified kinetic model, assuming an instant compartment localization equal to the *[% IA/organ]* measured *ex vivo* at 90 min p.i. and an effective organ clearance half-life (T_{eff}) equal to the radioactive half-life of ^{51}Mn. They calculated the EDE with OLINDA 1.1 for the standard adult and reported EDE values of 36.2 μSv/MBq and 42.2 μSv/MBq for male and female phantoms, respectively. These values are about two times higher than the EDE values calculated in our work using more accurate biokinetic models based on the biodistribution data reported by Hernandez et al. (2017) (see Table 3). Although these values cannot be directly compared because they were obtained using very different kinetic models, Graves' values are useful to establish the order of magnitude of ^{51}Mn doses.

Pagani et al. (1997) calculated the ED (ICRP 60) for 25 alternative positron-emitting radionuclides with potential clinical applications, including ^{51}Mn and ^{52}Mn. To calculate the dose, authors used a very simple hypothesis of uniform distribution of the radionuclide in the whole body of a standard adult male with biological half-lives of 1 h, 10 h or 100 h, obtaining values of 6.64, 10.9 and 11.7 μSv/MBq for ^{51}Mn and 16.0, 150 and 924 μSv/MBq for ^{52}Mn, respectively. Values calculated by Pagani et al. (1997) for ^{51}Mn are similar to the values obtained in this work, showing that, for this short-lived radioisotope, organ localization has a poor effect in ED estimation (see Table 3). The ED values reported by Pagani et al. (1997) for ^{52}Mn are instead quite lower than the values calculated in our work (see Table 4). In the case of radioisotopes with a prolonged physical half-life, like ^{52}Mn, the biological half-life has a significant influence on the dose assessment, as it was demonstrated above; therefore, the use of a radioisotope of manganese with biological half-life of several days gives much higher values than those assumed by Pagani et al. (1997), which make a considerable difference in the calculated ED.

^{51}Mn decays with the consequent formation of a radioactive daughter, ^{51}Cr (half-life=27.7 days), that should be taken into consideration for a correct dosimetry calculation. Olinda version 2.0 allows the calculation of the total dose of an isotope that decays, producing other radioactive species, considering that the daughter presents the same biodistribution profile. Calculated ^{51}Mn ED values with this option were, however, the same of those obtained disregarding the formation of ^{51}Cr, confirming that the accumulation of activity is only a small fraction of that of the parent.

^{52}Mn has the advantage over ^{51}Mn to provide higher PET image resolution (0.63 mm vs. 2.9 mm (Pagani et al., 1997)) due to the lower positron energy ($E(\beta^+)_{avg}$= 241.6 keV vs. 970.2 keV). In spite of the large ratio of high-energy gamma emissions (744 keV, 936 keV, and 1434 keV) per each β^+ particle , [^{52}Mn]-chloride radiation dose is only 2.7-fold greater than that reported for ^{89}Zr ($t_{1/2}$ = 3.3 d; 23% positron emissions: $E(\beta^+)_{avg}$ =396.9 keV; spontaneous gamma decay= 908.97 keV) which, conjugated to the trastuzumab protein, is currently being used in clinical studies (Bensch et al., 2018; Laforest et al., 2016).

In contrast, ^{51}Mn ED is comparable to the ED of ^{18}FDG (0.0192 mSv/MBq; gender-averaged value)(Stabin and Siegel, 2017), and about two orders of magnitude lower than that of ^{52}Mn. Table 5 shows that at an administered activity of 15 MBq, the effective dose due to ^{52}Mn would be below 27 mSv in women and 20 mSv in men, which is not quite different than that reported for ^{89}Zr-Trastuzumab (17.54 mSv) and ^{124}I ($t_{1/2}$ =4.2 d; 23% positron emission: $E(\beta^+)_{avg}$ =819 keV; 602 keV gamma emission)(35 mSv) in patients (Foss et al., 2018; Laforest et al., 2016). Nevertheless, the potential of ^{52}Mn low energy positron emission could be exploited by attaching it to receptor-specific molecules that could improve its pharmacokinetic properties.

Table 5. ED (ICRP 103) constant values (mSv/MBq) of ^{18}FDG (Stabin and Siegel, 2017), [^{51}Mn]Cl_2 and [^{52}Mn]Cl_2, calculated with the biological clearance assumption and effective dose (mSv) due to the assumed injected activity (MBq).

Compound	ED (ICRP 103) constant (mSv/MBq)		**Injected dose (MBq)**	**Patient ED (mSv)**	
	Male	**Female**		**Male**	**Female**
[^{18}F]FDG	1.60E-02	2.06E-02	370	5.9	7.6
[^{51}Mn]Cl_2	1.02E-02	1.36E-02	370	3.8	5.0
[^{52}Mn]Cl_2	1.35	1.79	15	20.3	26.9

5. Conclusions

Despite the limitations of using biodistribution data from animals to predict human doses, this work provides a first indication of the effective dose due to [^{51}Mn]- and [^{52}Mn]-Cl_2 in human beings.

The higher sensitivity of PET over MRI enables the use of low concentrations of manganese for imaging studies. However, dosimetric calculations performed in this work demonstrate that, due to the relatively high [^{52}Mn]Cl_2 effective dose, the usefulness of [^{52}Mn]-chloride as a PET brain imaging agent is limited. Based on the values of effective dose, it is possible to conclude that [^{51}Mn]-chloride could successfully be used for diagnosis by PET imaging.

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Figure Captions

Figure 1 $(\%IA/organ)_H$ values for ORNL (a) and ICRP 89 (b) phantoms in the most important male source organs (kidneys, liver, and muscle (left scale), heart contents, pancreas and salivary gland (right scale) plotted for each time p.i. and the organ activity curves obtained after the fitting.