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# Assessment of exposure after injection of $^{99m}$Tc-labeled intact monoclonal antibodies and their fragments into humans

**Mostafa Y. A. Mostafa**[1,4] · **Hesham M. H. Zakaly**[1,3] · **Michael Zhukovsky**[1,2]

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**Abstract**
Human pharmacokinetics and internal radiation dosimetry of normal organs after injection with the $^{99m}$Tc-labeled monoclonal antibody (intact and fragments) are simulated by the WinAct program and IDAC (Internal Dose Assessment by Computer) software. The WinAct program is used to calculate the cumulative activity in organs and tissues. The calculated cumulative activity is inputted to the IDAC software, an internal dosimetry program for nuclear medicine based on the International Commission on Radiological Protection (ICRP) adult reference voxel phantom, and the absorbed doses by the organs and tissues are estimated. The obtained absorbed doses for the $^{99m}$Tc-labeled monoclonal antibody (intact and fragments) are compared with the published figures by ICRP-128. The WinAct program method to calculate the cumulative activity is more accurate, as the fraction distribution, $F_s$, is described and calculated for organs, not only for intake, as in the ICRP model, but also for elimination.

**Keywords** Internal exposure · $^{99m}$Tc · Cumulative activity · Monoclonal antibodies · Absorbed dose

## 1 Introduction

Radiopharmaceuticals used in nuclear medical procedures emit α-particles, β-particles, and γ-rays, delivering doses that can possibly lead to detrimental health effects. Several efforts to estimate the internal dose in nuclear medical procedures include the development of dosimetric computer programs and the use of Monte Carlo methods [1–3].

Due to its features, Technetium-99m ($^{99m}$Tc) is the most important radioisotope used in nuclear medicine. Tc-99m labels different pharmaceutical components, which is convenient for specific organ imaging. It has a short half-life (6 h) emitting low-energy γ-rays, minimizing the absorbed dose in patients [4, 5]. $^{99m}$Tc mainly decays by gamma emission (approximately 88% of the time), approximately 98.6% of which are 140.5 keV γ-rays, and the rest consists of 142.6 keV photons. The remaining 12% of the decay consist of internal conversion, involving the ejection of electrons [6]. Photons and particles have different interaction mechanisms with matter, as well as different ranges in tissues [5].

The absorbed dose in patients undergoing diagnostic examinations in nuclear medicine is estimated through calculations based on models of the human body and the radiopharmaceutical's behavior in the body. On the contrary, the radiation risk due to a particular radiopharmaceutical is evaluated with the effective dose calculation. To perform the dosimetric evaluations in nuclear medicine, two main methodologies having the same theoretical considerations are used, one developed by the International Commission on Radiological Protection (ICRP) [7], and the other by the Medical Internal Radiation Dose Committee of the United States Society of Nuclear Medicine [8–10].

Monoclonal antibodies (MAbs) have been a popular means to target cell-surface antigens for therapeutic interventions and diagnostic imaging. MAbs have high affinity for their targets and many have been developed as therapies for human patients. One disadvantage of MAbs is their long serum clearance times; this necessitates protracted imaging

✉ Mostafa Y. A. Mostafa
mostafa_85@mail.ru

1 Department of Experimental Physics, Institute of Physics and Technology, Ural Federal University, Yekaterinburg 620002, Russia

2 Institute of Industrial ecology UB RAS, Sophy Kovalevskoy St., 20, Yekaterinburg 620990, Russia

3 Physics Department, Faculty of Science, Assuit Branch, Al-Azhar University, Assuit 71524, Egypt

4 Department of Physics, Faculty of Science, Minia University, El-Minia, Egypt

efforts spanning multiple days, to clear the background radioactivity [11, 12].

Radiolabeled MAbs are used in nuclear medical research and for the diagnosis and treatment of cancer. These antibodies are used either as the intact molecule (150 kDa) or as fragments F(ab')$_2$ (100 kDa) and F(ab') (50 kDa) [13, 14]. Although the behavior of MAbs varies, there are certain common features that can be distinguished. Directly after intravenous injection, the highest activity is seen in the organs with high vascular perfusion, such as liver, spleen, bone marrow, and kidneys. Organ uptake is mainly a function of the Mab's molecular size, with the intact molecule showing uptake mainly in liver and bone marrow, while smaller fragments concentrate to a greater degree in the kidneys [14]. Moreover, the rate of degradation and elimination is also a function of the molecular size, being faster with smaller fragments [13, 15].

In this work, the absorbed dose by "normal" organs after injection of the $^{99m}$Tc-labeled monoclonal antibody (intact and fragments) has been simulated with the WinAct program and IDAC (Internal Dose Assessment by Computer) software. The WinAct program is used to calculate the cumulative activity in the organs and tissues. The calculated cumulative activity is inputted to the IDAC software (version 1.0 and 2.1) and the absorbed doses by the organs are estimated for the $^{99m}$Tc-labeled monoclonal antibody (intact and fragments). The obtained results are compared and discussed with that published by ICRP-128. Moreover, the difference between the two IDAC software versions is presented and discussed.

## 2 Theoretical models and calculations

To use any radiopharmaceutical, the assessment of the absorbed dose by the organs and tissues is required. ICRP-128 provides data on the dynamic behavior of the antibodies, labeled with the radionuclides $^{99m}$Tc, $^{131}$I, $^{111}$In, and $^{123}$I. From this data, we have listed the reference number for MAbs and their respective label in Table 1 [14]. For many widely used radiopharmaceuticals, the corresponding biokinetic parameters $F_s$, $a_i$, $a_j$, $T_i$, and $T_j$ are reported in ICRP publications (ICRP 1987, 1998, 2008, 2015).

The absorbed dose by the organs and tissue is directly estimated with the IDAC software (1.0 and 2.1) using the cumulative activity, which is calculated with Eq. 1:

$$\frac{\tilde{A}_s}{A_0} = F_S \sum_{i=1}^{n} a_i \frac{T_{i,\text{eff}}}{\ln(2)}, \tag{1}$$

where $F_s$ is the fraction of the administered substance that would reach the source organ or tissue after an infinite amount of time if there was no radioactive decay, $a_i$ is the fraction of $F_s$ eliminated with a biological half-time $T_i$ ($\sum a_i = 1$), $n$ is the number of elimination components, and $T_{i,\text{eff}}$ is the uptake effective half-time [14]. The effective half-time can be calculated from the corresponding biological half-time $T_i$ and the functional physical half-life $T_p$[14]:

$$T_{\text{eff}} = \frac{T_i T_p}{T_i + T_p}. \tag{2}$$

Based on these general properties, a set of models can be defined, assuming the principal uptake in the above-mentioned organs and an even distribution of the remainder of the dose in the rest of the body. The antibodies and fragments are metabolized within the body. The technetium thus set free is assumed to be handled by the body according to the biokinetic model for pertechnetate [14]. The contribution from released technetium is calculated as

$$\frac{T_p - T_{\text{eff}}}{T_{\text{eff}}}. \tag{3}$$

The objective of this study is the general assessment of the radiation exposure of organs and tissues, without connection to specific monoclonal antibodies. Therefore, the original averaged data for calculations consist of values of the half-life times of the radiotracer from the bloodstream according to the transition in tissues and organs, 12 h for MAb [16–19], and the biological removal times are (24 and 96 h) and $F_s$ (the fractional distribution to organ or tissue) are obtained from ICRP-128.

### 2.1 IDAC-dose program

IDAC-Dose1.0 (Internal Dose Assessment by Computer), created by Prof. Lennart Johansson at Umeå University in 1987, is the program sanctioned by the ICRP to estimate the radiation risk for diagnostic examinations in nuclear medicine at hospitals. The program has been used to perform dose calculations from different radiopharmaceuticals in ICRP Publications 53, 62, 80, 106, and 128.

A new version, IDAC-Dose 2.1, was developed based on the ICRP's specific absorbed fractions and the computational framework of internal dose assessment given for reference adults in ICRP Publication 133. The program uses the radionuclide decay database of ICRP Publication 107 and considers 83 different source regions irradiating 47 target tissues, setting the effective dose as defined in ICRP Publications 60 and 103.

IDAC calculates cumulated activities (total number of disintegrations) per administered activity in hours and calculates the absorbed dose and the effective dose. IDAC-Dose2.1 has the ability to calculate the absorbed dose from

**Table 1** Biokinetic data for MAb, labeled with $^{99m}$Tc [14]

| Organ (S) | $F_s$ | $T_b$ (h) | $T_{eff}$ (h) | $a$ | A˜s/A0 (h) | K/d |
|---|---|---|---|---|---|---|
| Intact antibody | | | | | | |
| Kidneys | 0.03 | 24 | 4.81 | 0.5 | 0.23 | 1.50E−02 |
| | | 96 | 5.66 | 0.5 | | |
| Liver | 0.50 | 24 | 4.81 | 0.5 | 3.77 | 2.50E−01 |
| | | 96 | 5.66 | 0.5 | | |
| Spleen | 0.09 | 24 | 4.81 | 0.5 | 0.68 | 4.50E−02 |
| | | 96 | 5.66 | 0.5 | | |
| Red bone marrow | 0.20 | 24 | 4.81 | 0.5 | 1.51 | 1.00E−01 |
| | | 96 | 5.66 | 0.5 | | |
| Other organs and tissues | 0.18 | 24 | 4.81 | 0.5 | 1.36 | 9.00E−02 |
| | | 96 | 5.66 | 0.5 | | |
| Biokinetic data for MAb fragment *F*(ab')2 | | | | | | |
| Kidneys | 0.2 | 12 | 4.00 | 1 | 1.16 | 2.00E−01 |
| Liver | 0.3 | 12 | 4.00 | 1 | 1.73 | 3.00E−01 |
| Spleen | 0.06 | 12 | 4.00 | 1 | 0.35 | 6.00E−02 |
| Red bone marrow | 0.1 | 12 | 4.00 | 1 | 0.58 | 1.00E−01 |
| Other organs and tissues | 0.34 | 12 | 4.00 | 1 | 1.96 | 3.40E−01 |
| Biokinetic data for MAb fragments *F*(ab') | | | | | | |
| Kidneys | 0.4 | 6 | 3.00 | 1 | 1.73 | 4.00E−01 |
| Liver | 0.1 | 6 | 3.00 | 1 | 0.43 | 1.00E−01 |
| Spleen | 0.02 | 6 | 3.00 | 1 | 0.09 | 2.00E−02 |
| Red bone marrow | 0.03 | 6 | 3.00 | 1 | 0.13 | 3.00E−02 |
| Other organs and tissues | 0.45 | 6 | 3.00 | 1 | 1.95 | 4.50E−01 |

1252 different radionuclides of 97 elements. The computer program bases the dose estimations on the Cristy Eckerman stylized family phantoms [20].

## 2.2 Biokinetic model

There are common features in the behavior of antibodies. After intravenous injection, the highest activity is observed in the organs with high vascular perfusion, namely, the liver, spleen, bone marrow, and kidneys [14]. The biokinetic model of the behavior of $^{99m}$Tc, associated with intact antibodies, is shown in Fig. 1. For the whole antibodies, there are two elimination rates. Based on this approach, a model of the radionuclide behavior in the body was developed. Moreover, a simple scheme for antibody fragments *F* (ab)'2 and *F*(ab)' MAb is shown in Fig. 2.

The WinAct program is used to calculate the absorbed dose for the organs and tissues based on the transfer activity fraction from blood to organs, the removal activity rate from organs, and the excretion rate [21]. The input files are created with the transfer coefficient *k*, displayed in Table 1 and calculated as

$$k = f_s * a, \tag{4}$$

where $F_s$ is the fractional distribution to the organs or tissues, and a is the fraction of $F_s$ taken or eliminated with the corresponding half-time; the input file compiles with the program code and the activity is calculated. Figure 3 presents the screen view of a WinAct run.

The output results from the WinAct program are used as input data to the IDAC software (1.0 and 2.1), an internal dosimetry program for nuclear medicine based on the ICRP adult reference voxel phantoms [20–23]. As a result, the absorbed doses by the organs and tissues are estimated.

In cases where the retention function cannot be described by a sum of exponential functions, the cumulated activities are directly derived from the metabolic model. For absorbed dose calculations in nuclear medicine, it has often been assumed that the effective half-time in an organ is equal to the physical half-life. The reason for this approximation is that the substance, in these cases, is labeled with a radionuclide with a physical half-life that is short in comparison with the biological half-time. For short-lived radionuclides, a slow biological excretion may not be apparent, and for absorbed dose calculations, the approximation is sufficiently accurate [14].

The absorbed doses are compared for $^{99m}$Tc associated with intact antibodies and fragments as:

- ICRP-128 reported for $^{99m}$Tc, associated with intact antibodies and fragments with the IDAC software (1.0).
- Calculation of $^{99m}$Tc, associated with intact antibodies and fragments with the IDAC software (2.1) using the listed cumulative activity in ICRP-128 (Table 1).
- Calculation of $^{99m}$Tc, associated with intact antibodies and fragments with the IDAC software (1.0) using the cumulative activity from the WinAct program calculations based on the presented biokinetic model.

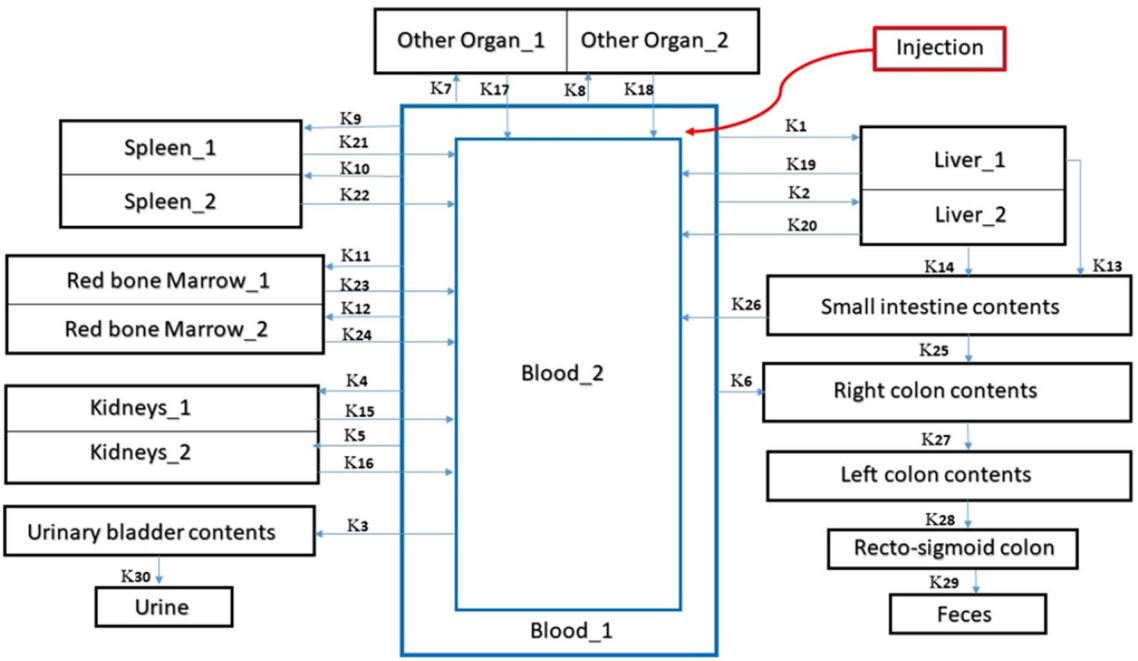


**Fig. 1** Biokinetic model of the behavior of $^{99m}$Tc, associated with intact antibodies

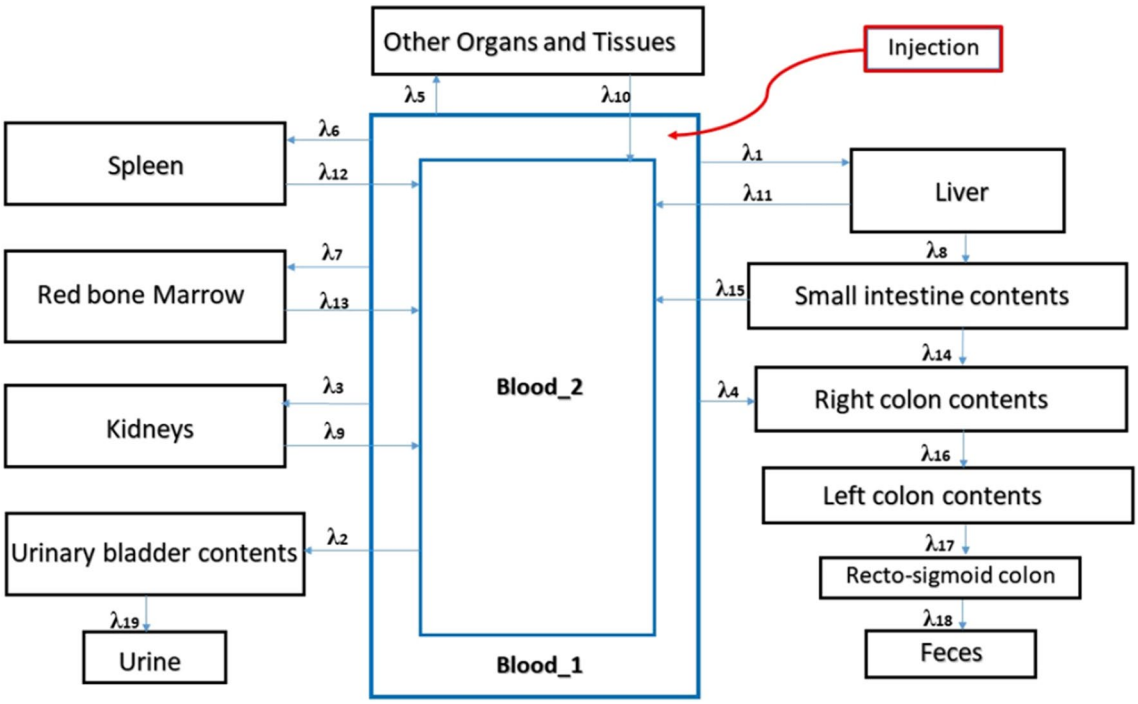


**Fig. 2** Biokinetic model $^{99m}$Tc, associated with the MAb fragments

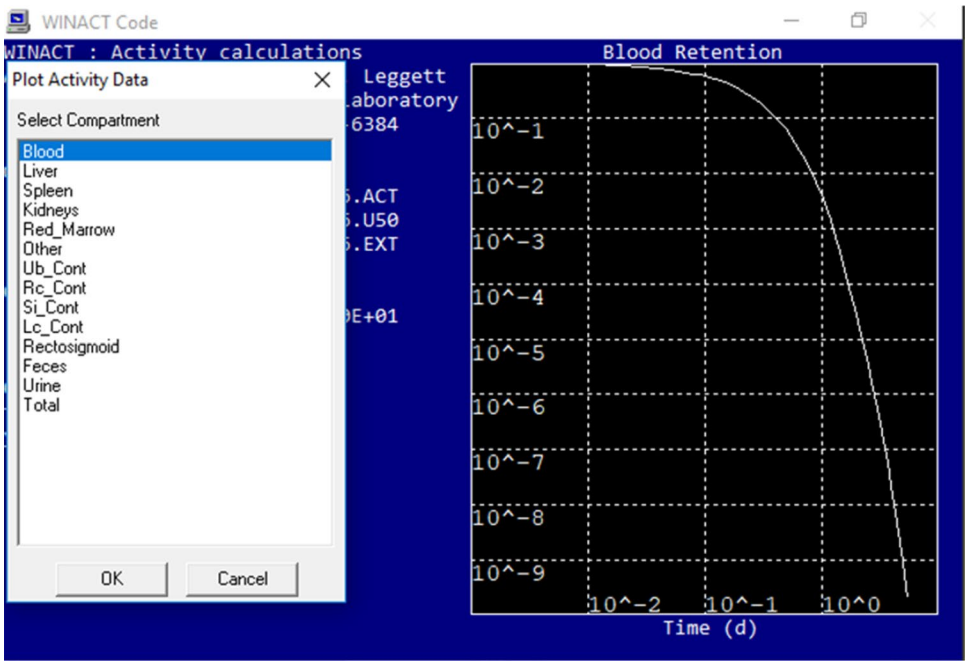


**Fig. 3** Screen view of a WinAct run, the *Y*-axis representing the activity

- Calculation of $^{99m}$Tc, associated with intact antibodies and fragments with the IDAC software (2.1) using the cumulative activity from the WinAct program calculations based on the presented biokinetic model.

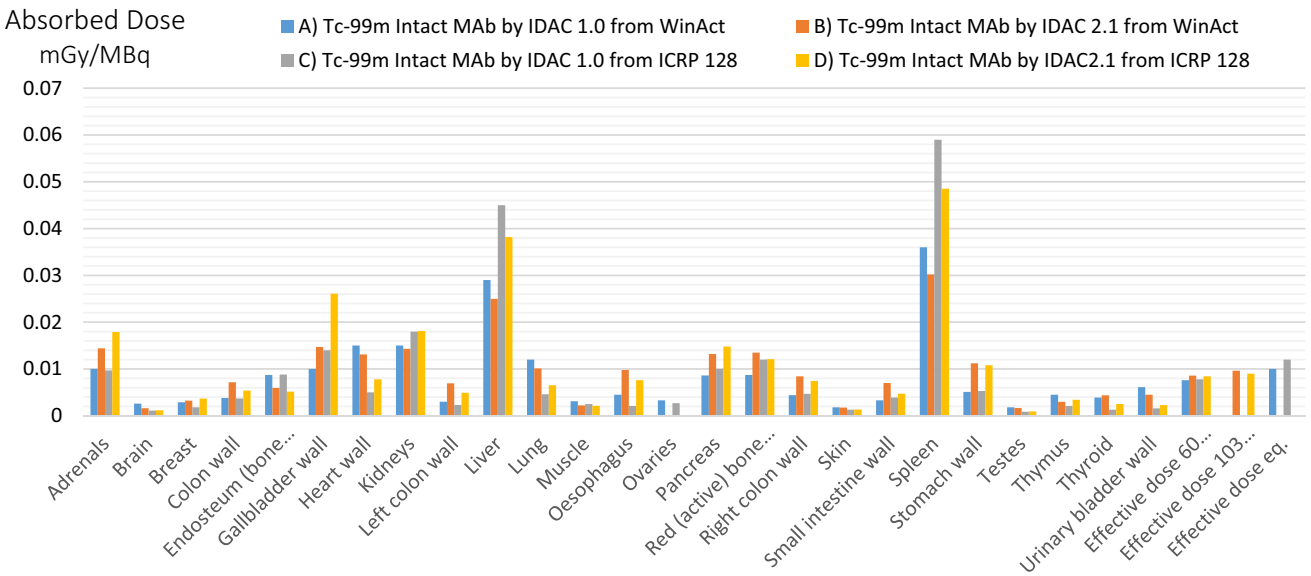


**Fig. 4** Absorbed dose comparison from the IDAC software (1.0 and 2.1) associated with intact monoclonal antibodies using cumulative activity from the WinAct program and ICRP-128 for $^{99m}$Tc

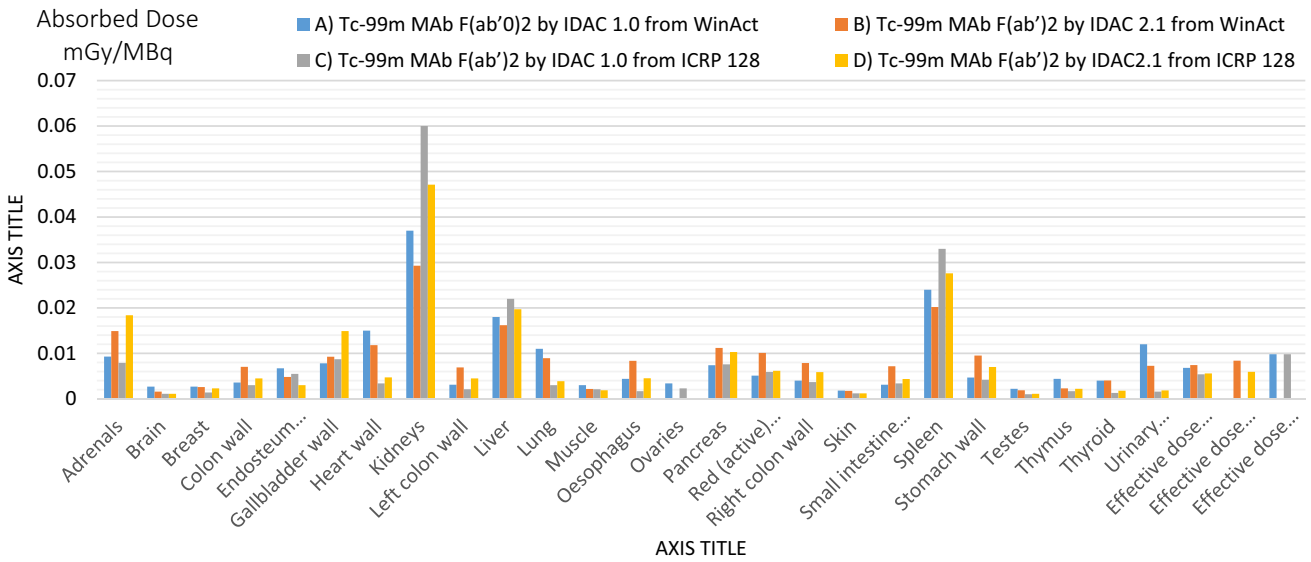


**Fig. 5** Absorbed dose comparison from the IDAC software (1.0 and 2.1) associated with fragment F (ab')$_2$ antibodies using the cumulative activity from the WinAct program and ICRP-128 for $^{99m}$Tc

## 3 Results and discussion

The comparisons of different models of intact and Mab fragments are presented in Figs. 4, 5, and 6. According to the model of each case (intact Mab (Fig. 1) and fragments (Fig. 2) [14]), the absorbed dose calculations from the IDAC software (1.0 and 2.1) using the cumulative activity from the WinAct program and ICRP-128 for $^{99m}$Tc, associated with intact and fragments of MAbs, are presented. In general, a small difference is observed between IDAC (1.0) and IDAC (2.1) owing to the different phantoms used for each version.

The results of the WinAct program calculations based on the presented biokinetic model give different fraction distributions for the absorbed dose, but the effective dose is still in good agreement with that calculated by ICRP-128. The shape of the distribution is approximately the same, but the

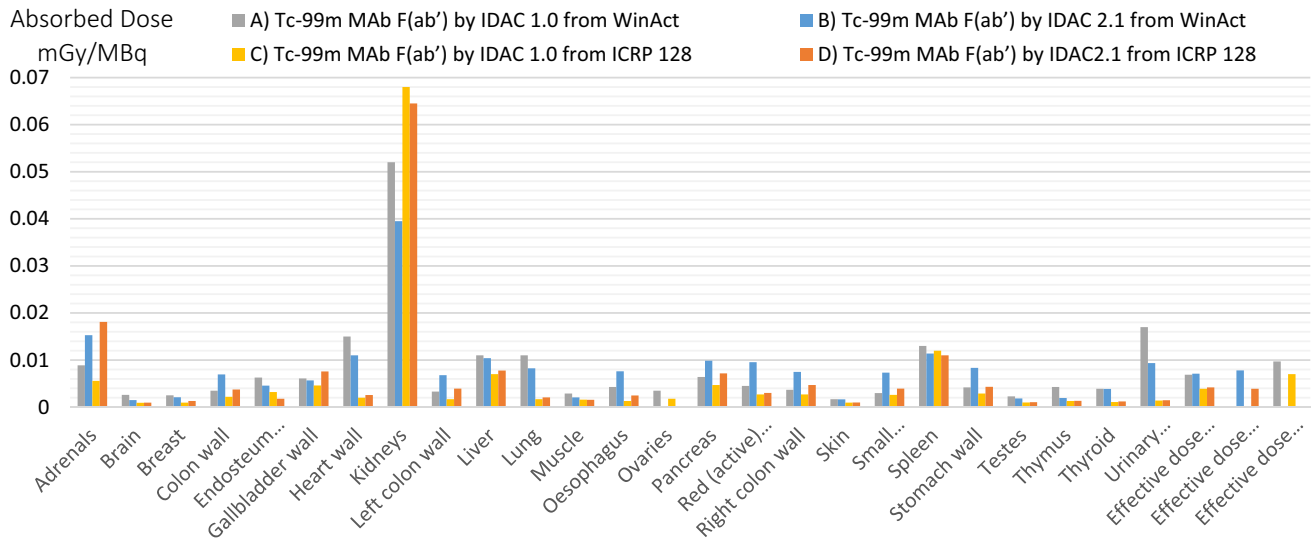


**Fig. 6** Absorbed dose comparison from the IDAC software (1.0 and 2.1) associated with fragment F (ab') antibodies using cumulative activity from the WinAct program and ICRP-128 for 99mTc

value of the absorbed fraction in the organs is higher. This is because the WinAct program gives the cumulative activity not only for the main organs, but also for other small organs. Hence, the WinAct program is recommended for calculating the cumulative activity.

When administered into the body, $^{99m}$Tc associated with the intact MAb provides a significantly higher absorbed dose in the spleen, liver, heart wall, red bone marrow, and kidneys, as shown in Fig. 4.

Figure 5 presents the absorbed dose comparison of $^{99m}$Tc associated with fragment F(ab')$_2$ (100 kDa). In this case, the fraction is ordered as follows: kidneys with a relative high fraction, followed by spleen with a fraction similar to that of kidneys, and then liver with a fraction three times smaller than that of kidneys. Moreover, the effective dose is nearly the same with the different calculation programs.

When the fragments consist of *F* (ab') (50 kDa), as shown in Fig. 6, the main absorbed dose is located in the kidneys. The sum of the absorbed dose fractions in the spleen and liver is less than three times that of the absorbed dose fraction absorbed in the kidneys.

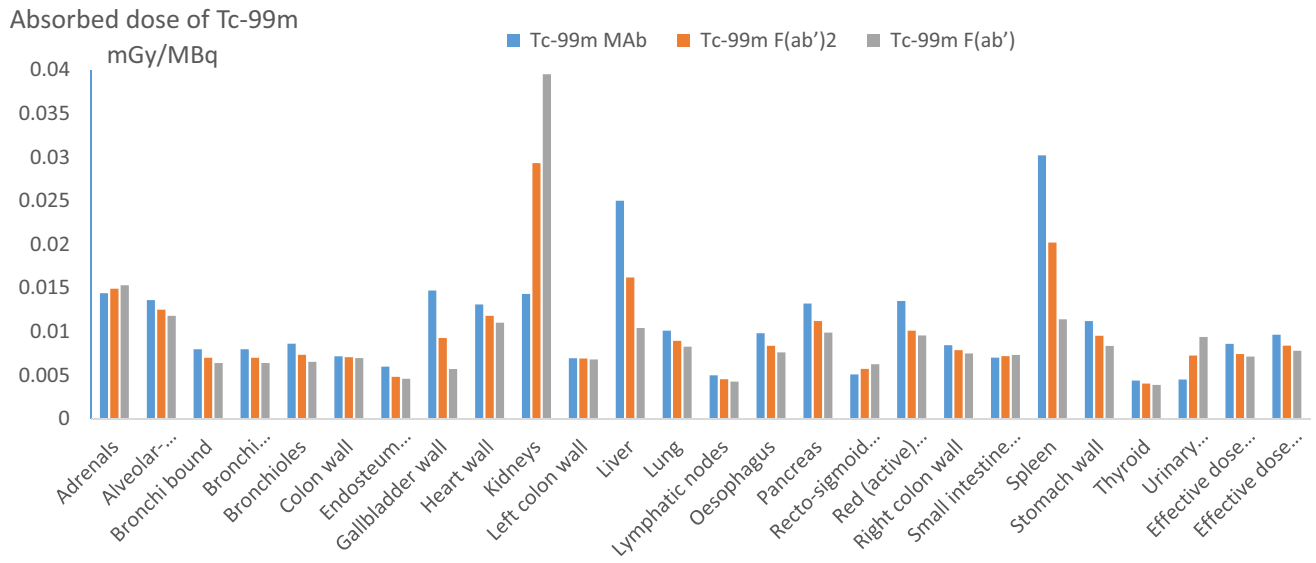


**Fig. 7** Absorbed dose comparison from the IDAC software (2.1) associated with the intact molecule (150 kDa) and as fragments F (ab')$_2$ (100 kDa) and F (ab') (50 kDa) using cumulative activity from the WinAct program for $^{99m}$Tc

The WinAct program and IDAC software (2.1) confirm that the removal of fragments through the kidneys is higher compared to the intact MAbs. The highest activity is seen in the spleen, liver, bone marrow, and kidneys for intact monoclonal antibodies. For the fragments, the main dose fraction is in the kidneys, as explained in Fig. 7. Although the effective dose is similar in the three cases, the dose fraction distribution in the organs is completely different between the intact MAb and the MAb fragments.

Figures 8 and 9 present the fractional activity of urine and fecal excretion with time, respectively, for the radiopharmaceutical case of $^{99m}$Tc associated with MAb. It is clear that the principal amount of the fractional activity excreted is through urine. Fecal excretion is small compared to urine excretion (by nearly 2000 times). Figure 8 shows the dependence of urine excretion on the type of MAb. The highest fraction for *F* (ab') is three times higher than that of the intact molecule and two times higher than that of F (ab')$_2$. This is because the kidneys accumulate the main part of activity compared to other organs in the case of F (ab'). Unlike urine excretion, fecal excretion does not depend on the type of Mab, as shown in Fig. 9.

## 4 Conclusions

In this study, we consider the dynamics of behavior of a radiopharmaceutical based on $^{99m}$Tc-labeled antibodies within the body, and a biokinetic model has been constructed. The WinAct program is used to calculate the cumulative activity and to compare the results obtained from ICRP. The absorbed dose fraction for the organs is calculated and compared with two versions of the IDAC (1.0 and 2.1) software. The calculation of absorbed dose fraction with IDAC 2.1

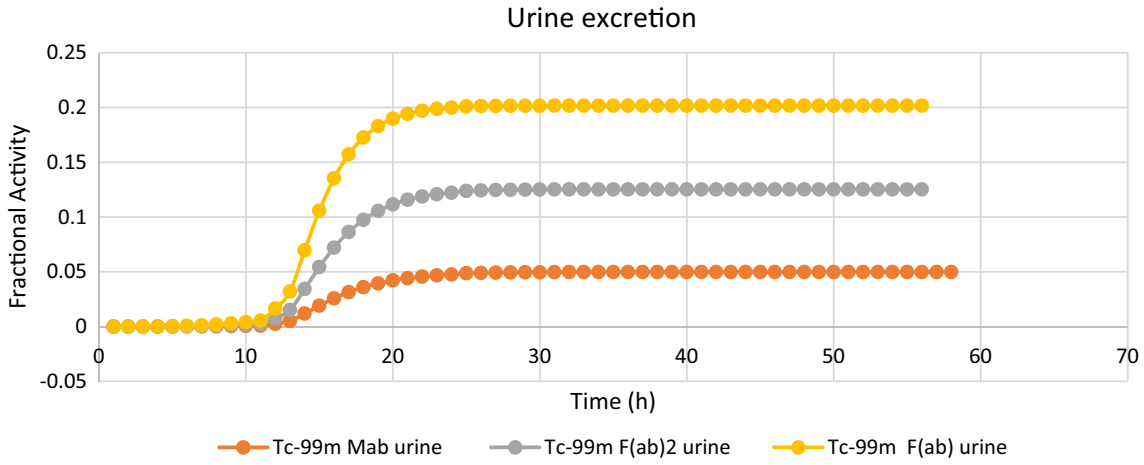


**Fig. 8** Urinary excretion fraction as a function of time (h)

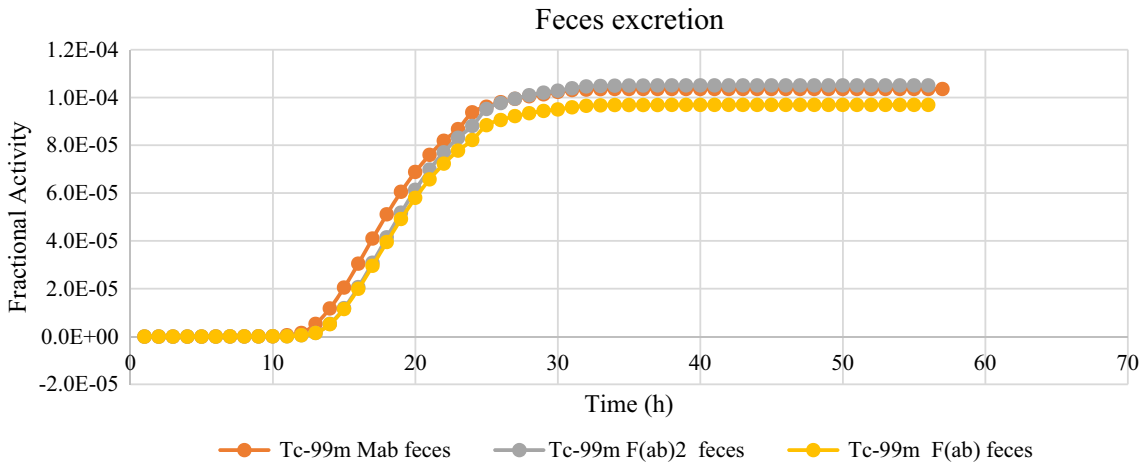


**Fig. 9** Fecal excretion fraction as a function of time (h)

software is more accurate, and the use of the WinAct program to calculate the cumulative activity is recommended. For the organs that have been exposed maximally, the dose coefficients of the activity of the injected antibodies are calculated. The results show that for the $^{99m}$Tc-labeled monoclonal antibodies, the organs that are the most exposed are the spleen, liver, kidneys, red bone marrow, and gallbladder wall. In addition, the results show that fecal excretion does not depend on the type of Mab, and the quantity of fractional activity is very small compared to excretion in urine (factor difference of 2000).

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## Compliance with ethical standards

**Conflict of interest** Mostafa Y.A. Mostafa has received research grants from Act 211 of the Government of the Russian Federation (contract no 02. A03.21.0006) and the Centre of Excellence: Radiation and Nuclear Technologies. Hesham M.H. Zakaly declares that he has no conflict of interest. Michael Zhukovsky declares that he has no conflict of interest.

**Ethical approval** This article does not contain any studies on human participants or animals.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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