Iraqi Journal of Industrial Research, Vol. 10, No. 3 (2023)

Open Access

Iraqi Journal of Industrial Research (IJOIR)

Journal homepage: http://ijoir.gov.iq

Human – Environment QSAR Studies of Radioactive Chemicals by Online Prediction Websites

Kafa Khalaf Hammud*

Iraqi Atomic Energy Commission – Iraq

Article information

Article history:
Received: August, 20, 2023
Accepted: September, 24, 2023
Available online: December, 14, 2023

Keywords:
Radioactive complex,
Online websites,
Toxicity,
Prediction

Corresponding Author:
Kafa Khalaf Hammud
kafaakhalaf@gmail.com

DOI:
https://doi.org/10.53523/ijoirVol10I3ID367

Abstract

Diagnosis, therapy, and research – development are main targets in radioactive materials issues that took huge places in medical sector of radio-molecular imaging and nuclear medicine where adsorbed radionuclide by the target(s) with high selectivity and minimum duration management compared to chemotherapy. In this study, three online websites created by various scientific groups in Baker Institute, university of Queensland, and School of Computing and Information Systems, University of Melbourne as a computed base to predict toxicity of various radiopharmaceuticals having Sm-153; Ga-68; F-18; Hg-197; I-131; I-123; Tc-99m: In-111, or Se-75. Prediction of forty – five radio-chemicals targeted embryo, cardio-: Arrhythmia, heart block, Cardiac Failure, hERG, Myocardial Infarction, and hypertension. Herbicidal activity and environmental safety represented by Honey Bee, Avian, *Minnow*, as well as human toxicity that include Ames, rat acute (LD_{50}) and chronic (LOAEL) toxicities were additionally evaluated by these three online websites. Here first Iraqi attempt showed that these tested materials had a toxic site to one or more of human (embryo or pregnant mother), cardio- (Arrhythmia, Cardiac Failure, Heart Block, hERG, Hypertension, or Myocardial Infarction) or rat acute (LD_{50}) – chronic (LOAEL), as well as environment (honey, avian, *Minnow*) characters. Samarium-153 Lexidronam gave a safe in Silico toxicological response to embryo (and pregnant mother), all tested cardio-, honey, and avian. Also, it showed a low number towards *Minnow* and rat chronic (LOAEL) toxicities. In the same manner, Selenomethionine - 75Se derivative was highly unsafe to embryo (and mother) beside toxic effect in Arrhythmia case. In comparison to Sm-153, Se-75, as a corresponding radio – compound of the naturally amino acid found in soybeans and nuts, had lower *Minnow* and rat chronic toxicological values but not LD_{50}. So, both radiopharmaceuticals were structurally toxic especially in high concentration and repeated uptake by human or other species.

1. Introduction

Diagnosis, therapy, and research – development are main targets in radioactive materials issues that took huge places in published scientific sources especially in medical sector named as radio-molecular imaging and nuclear

medicine [1]. In the part of radio-chemicals therapies, early starts were begin in 20th centenary after Becquerel and Curie discoveries in the subject followed limited experiments done by Danlos, Bloch, Proescher, and Bell testing radium effect on skin lesion, tumor, and other diseases. Huge expansion in radionuclide therapy was noticed via delivering adsorbed dose to the target(s) with high selectivity and minimum duration management compared to chemotherapy (see Table 1) [2, 3, 4].

From these beginnings, nuclear medicine become a functionalized branch in molecular imaging by utilizing radiopharmaceutical as a visualizing biomaterial enabling highly accurate metabolic, chemical, biological, and functional characterizations. These characterizations may be achieved at molecular – cellular levels to measure and treat living systems depending upon defined linkage between radioactive atom(s) and organic carrier (Table 1, Figures 1, 2, & 3) that directly reacts with human body after intravenous step [5, 6,7, 8]. So, molecular imaging in diagnosis, therapy, and research fields mainly based upon radioactive atom decay as diagnostic tool that transforms detected radioactive pharmaceutical to visualized image as well as enabling characterization and measurement of the particle emission (Tables 1 and 2) [8, 9].

Table (1). Several Radioactive pharmaceutical examples and their target cancer disease(s).

Radioactive pharmaceutical	Trade name	Cancer
^{90}Y-ibritumomab tiuxetan	Zevalin®	anti-CD20 antibody complex, non-Hodgkin's Lymphoma (NHL)
^{90}Y-Epratuzumab	Lymphocide®	anti-CD20 antibody complex, non-Hodgkin's Lymphoma (NHL), chronic lymphocytic Leukemia (CLL)
^{131}I-Tositumomabor	Bexxar®	anti-CD20 antibody complex, non-Hodgkin's Lymphoma (NHL)
^{131}I-Lym-1	Oncolym®	Anti-HLADR10 antibody complex, non-Hodgkin's Lymphoma (NHL), chronic lymphocytic Leukemia (CLL)

Table (2). β - Decay of several nuclides for therapy [3].

Radioactive emission	Radionuclide therapy
^{88}Sr (n, γ) ^{89}Sr **^{152}Sm (n, γ) ^{153}Sm** **^{185}Re (n, γ) ^{186}Re**	Bone metastasis
^{31}P (n, γ) ^{32}P **^{165}Ho (p, n) ^{165}Er** **^{176}Yb (n, γ, β−) ^{177}Lu**	Synovitis
^{89}Y (n, γ) ^{90}Y	Hepatic metastasis

For more understanding of radiopharmaceutical therapy, several characters determine this medical section efficiency such as half – life, energy, purity, decay mode (α, β, or γ), concentration, chemical structure, bio-target specification, toxicity, stability, stability in the bio-target, delivery, metabolism, excretion, clearance, cost, and others..

In this study, three online websites created by various scientific groups in Baker Institute, University of Queensland and School of Computing and Information Systems, University of Melbourne as a computed base to predict various radiopharmaceuticals.

Prediction of forty – five radio-chemicals targeted embryo, cardio-: Arrhythmia, heart block, Cardiac Failure, hERG, Myocardial Infarction, and hypertension. Herbicidal activity and environmental safety represented by Honey Bee, Avian, *Minnow*, as well as human toxicity that includes Ames, rat acute (LD_{50}) and chronic (LOAEL) toxicities.

2. Experimental Procedure

2.1. Chemicals under Testing

Studied radioactive chemicals were tested via three online websites [10, 11, 12]. Studied toxicological properties were embryo, cardio-: Arrhythmia, heart block, Cardiac Failure, hERG Toxicity, Myocardial Infarction, and hypertension. Herbicidal activity and environmental safety represented by Honey Bee, Avian, *Minnow*, as well as human toxicity that includes Ames, rat acute (LD_{50}) and chronic (LOAEL) toxicological characters. Each radiopharmaceutical symbolizes as Code: Name.

These radioactives were **Sm-153** : Samarium-153 Lexidronam; **Ga-68**: Ga-68 Dotatoc; **F-18**: Fludeoxyglucose F -18; **F1-18**: F-18 Fluorocholine: **Hg-197**: Merisoprol Hg-197; **I-131**: Tolpovidone ^{131}I; **I1-131**: o - Iodohippurate Sodium ^{131}I labeled; **I-123**: Iofetamine ^{123}I; **I1-123**: o - Iodohippurate Sodium ^{123}I labeled; **Tc-99m**: Technetium - 99m Bicisate; **Tc1-99m**: Technetium - 99m Mertiatide; **Tc2-99m**: Technetium - 99m Sestamibi; **Tc3-99m**:Oxidronic Acid -^{99m}Tc derivative; **Tc4-99m**: Tetrofosmin -^{99m}Tc complex; **Tc5-99m**: Technetium ^{99m}Tc Pentetate; **Tc6-99m**: Technetium ^{99m}Tc Exametazime; **Tc7-99m**: ^{99m}Tc-CCMSH; **Tc8-99m**: Technetium-99 Tin(4+,2+) complex; **Tc9-99m**: ^{99m}Tc –α-MSH; **Tc10-99m**: ^{99m}Tc- (V) DMSA; **Tc11-99m**: ^{99m}Tc TRODAT; **Tc12-99m**: ^{99m}Tc –DG; **Tc13-99m**: ^{99m}Tc- EDDA/HYNIC-C(RGDyK); **Tc14-99m**: ^{99m}Tc-Hypericin; **Tc15-99m**: Technetium ^{99m}Tc Bicisate; **Tc16-99m**: Technetium ^{99m}Tc- Apcitide; **Tc17-99m**: ^{99m}Tc- DTPA-TOR; **Tc18-99m**: ^{99m}Tc-PrDP; **Tc19-99m**: ^{99m}Tc-MDP; **Tc20-99m**: EC-DG-^{99m}Tc; **Tc21-99m**: Technetium ^{99m}Tc glucoheptonate; **Tc22-99m**: ^{99m}Tc- DO3A-Folate; **Tc23-99m**: ^{99m}Tc-HYNIC-EGF; **Tc24-99m**: ^{99m}Tc-MIP-1404; **Tc25-99m**: ^{99m}Tc-Hl91; **Tc26-99m**: EMIDP^{99m}Tc; **Tc27-99m**: MAG3-HBP^{99m}Tc; **Tc28-99m**: EC20^{99m}Tc; **Tc29-99m**: ^{99m}Tc -Rp128; **Tc30-99m**: Technetium (^{99m}Tc) Etrarfolatide; **Tc31-99m**: Technetium ^{99m}Tc Tetrofosmin; **Tc32-99m**: Technetium ^{99m}Tc Disofenin; **Tc33-99m**: Technetium Tc-99m TMPDA; **In-111**: Pentetreotide ^{111}In chelate; and **Se-75**: Selenomethionine - ^{75}Se derivative. Each tested radioactive material was inserted in the online website under evaluation through SMILES as Simplified Molecular Input Line Entry System coding of the tested material.

For example, SMILES code of Samarium-153 Lexidronam is C(CN(CP(=O)([O-])[O-])CP(=O)([O-])[O-])N(CP(=O)([O-])[O-])CP(=O)([O-])[O-].[Na+].[Na+].[Na+].[Na+].[Na+].[153Sm+3]. This isomeric or canonical SMILES with copy-paste in any online website that mentioned in [10, 11, or 12] article present the full accurate molecular structure of the molecule under test then pressing predict to get the needed information.

3. Results and Discussion

Various radiopharmaceuticals were studied in this paper where their actual actions according to the mentioned references in introduction section, https://pubchem.ncbi.nlm.nih.gov/ website with its cited references beside recent references related to cancers are limited as Antineoplastic, Radio-conjugate in somatostatin receptor imaging in conjunction with Positron Emission Tomography (PET), Radioactive Imaging Agent or Diagnostic aid in (renal function, hypoalbuminemia, or Lung scintigraphy), Radiotracer, Probe for primary and metastatic melanoma imaging or as a diagnosis agent in malignant Melanoma, Parkinson' disease detector, and labeled form as a tumor-targeting agent [13, 14, 15, 16] . These radiopharmaceuticals contains radioactive elements or ions of Sm-153; Ga-68; F-18; Hg-197; I-131; I-123; Tc-99m: In-111, and Se-75.

Here, a new toxicological evaluation was done with in Silico prediction via various online websites to evaluate different toxicity of each radio-compound against embro-, cardio, and environmental: avian, honey bee, *Minnow* fish, Ames, rat, and herbicidal as shown in Tables (3 & 4, Figure 4).

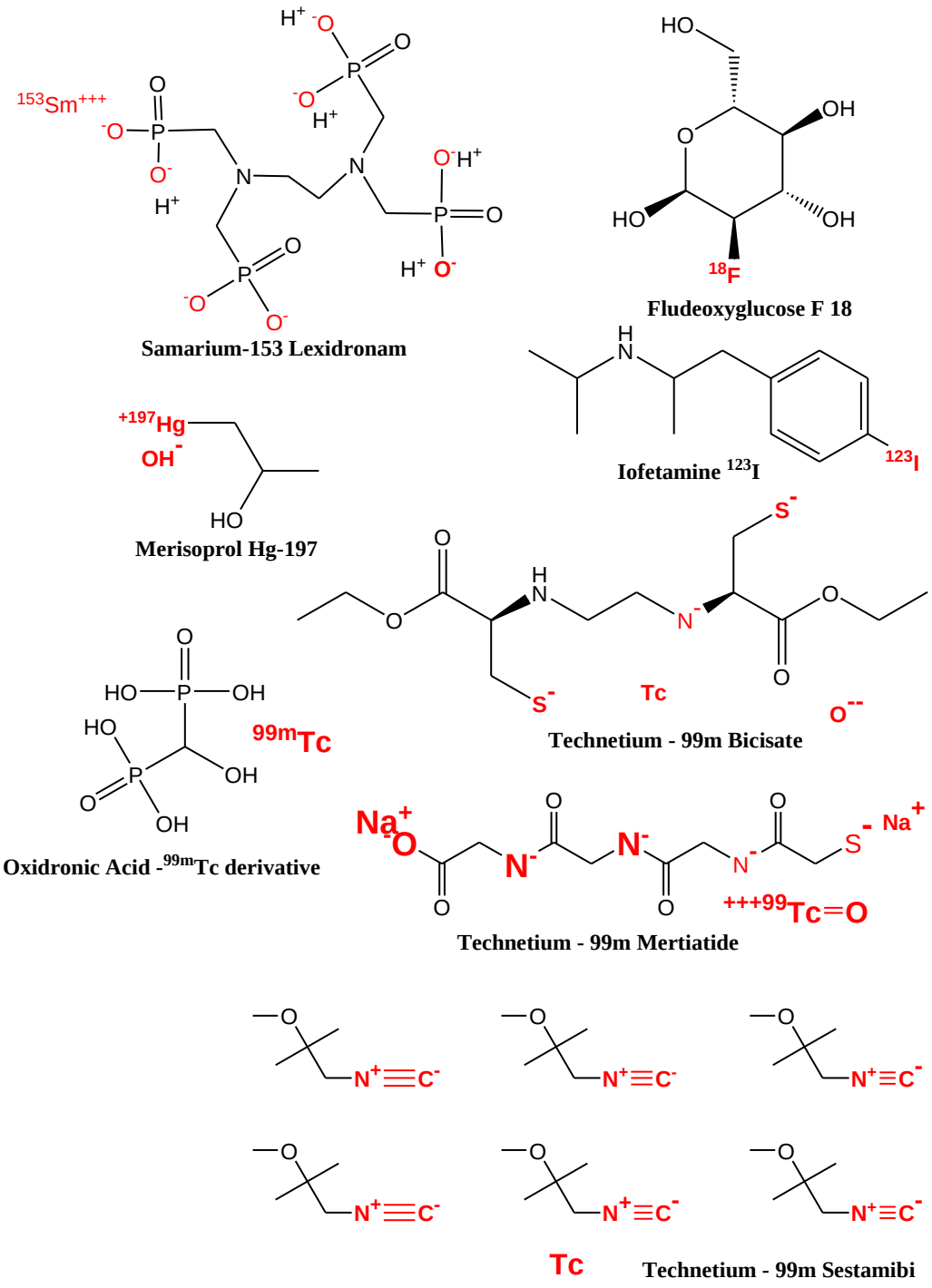

Figure (1). Chemical structures of several radioactive materials.

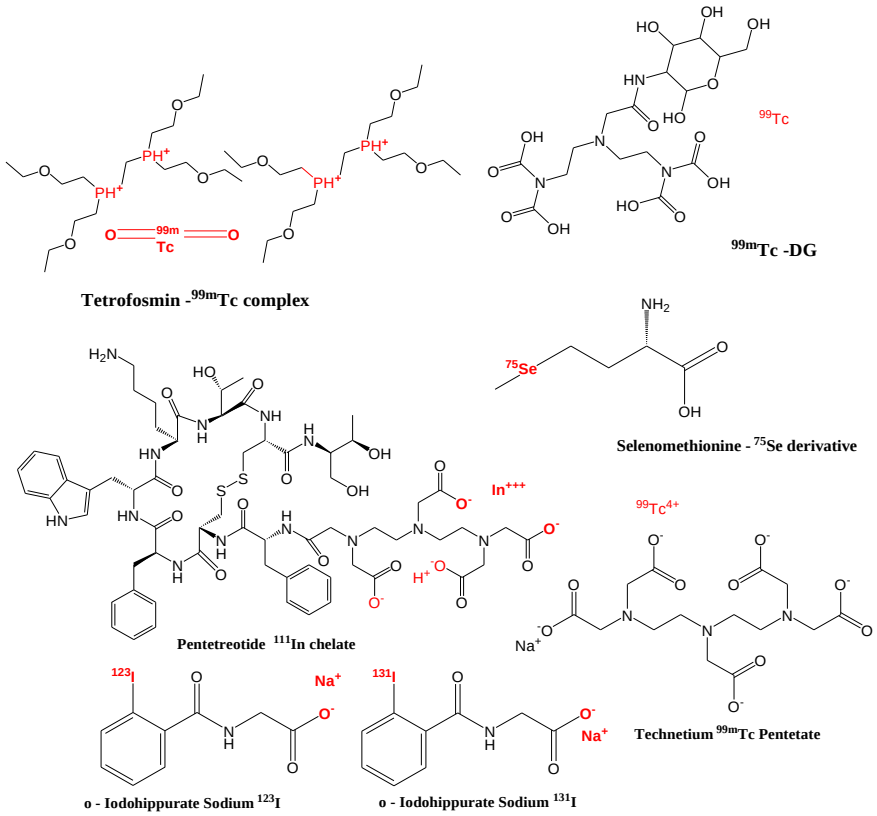

Figure (2). Chemical structures of other radioactive materials.

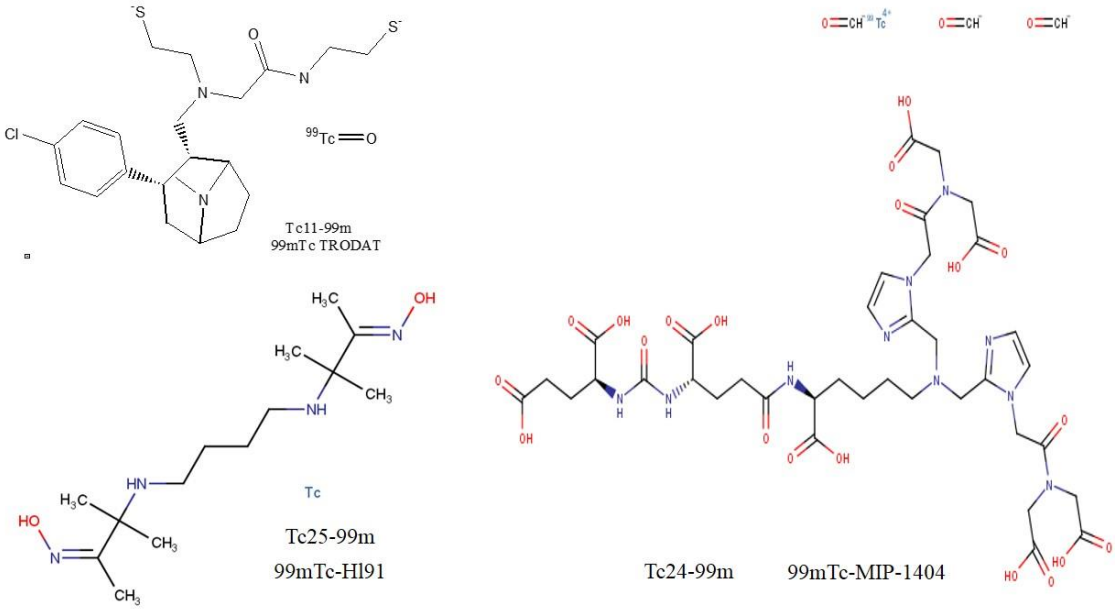

Figure (3). Chemical structures of Tc11-99m, Tc24-99m, and Tc25 -99m radioactive materials.

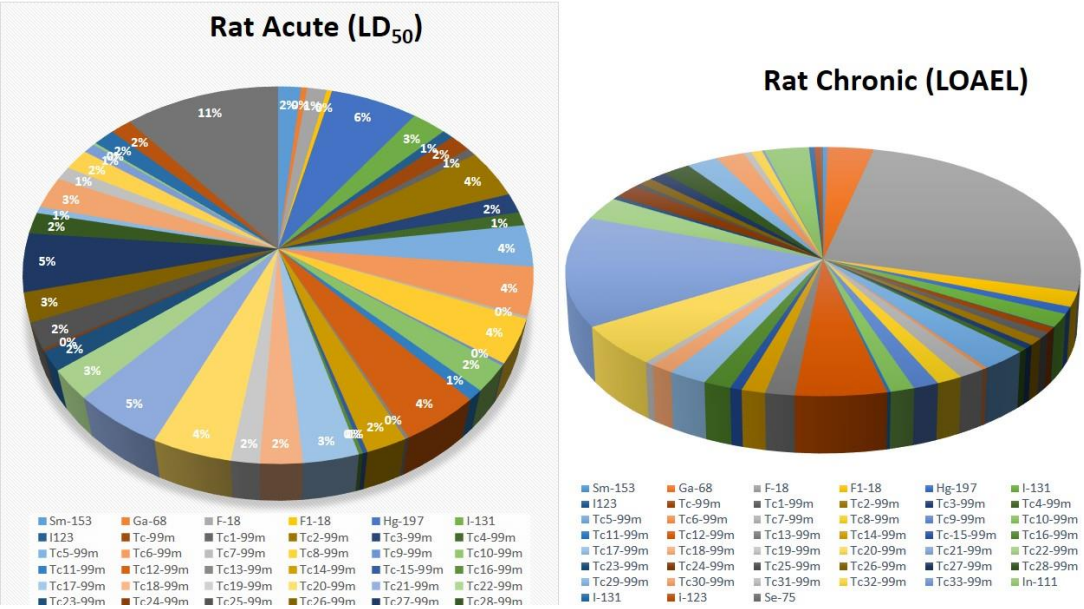

Figure (4). Rat Acute (LD_{50}) and Rat Chronic (LOAEL) toxicities of all tested radiopharmaceuticals

In medical section, irregular heartbeat (Arrhythmia) during any physical activity by human categories into brady – and tachy- arrhythmia according to heart rate (too quick, too slow, or irregular rhythm). In brady- type, heart rate is lower than 60 beats / minute (bpm) while beating excesses than 180 bpm classifies as tach- type. Deviation in rate may be resulted by many factors including toxic material(s) that may led to sudden death. Also, structural defect can cause heart failure especially in foetus then intrauterine death with absence of transplacental controlling or anti-arrhythmic drug treatment [17, 18].

Before proceeding in discussion section, one example of in Silico testing capability to give accurate results is 99mTc Sestamibi (Tc2-99m). Generally, this radiopharmaceutical is usually "taken up by intravenous injection or the myocardium, parathyroid, and/or breast tissue indicated for detecting coronary artery disease by localizing myocardial ischemia (reversible defects) and infarction (non-reversible defects); and estimating myocardial function". Also, adverse reactions (> 0.5% of patients taken Tc2-99m) have been stated signs of "seizure after administration, transient arthritis; angioedema, arrhythmia, dizziness, syncope, abdominal pain, vomiting". In this study, Tc2-99m was safe in all embro-, cardio- beside some of environmental and human toxicities in this in Silico testing. In rat acute (LD_{50}) (Figure 4) as an indicator to human toxicity, a higher value was obtained meaning high safety but not with *Minnow* and rat chronic (LOAEL) (Figure 4) which were low signifying a serious hazard effect in these issues. Here, computerized –aided prediction study showed:

- Thirty-one radiopharmaceuticals (from forty- five) were **unsafe**: Ga-68, F-18, Tc-99m, Tc1-99m, Tc3-99m, Tc5-99m, Tc7-99m, Tc8-99m, Tc9-99m, Tc10-99m, Tc11-99m, Tc12-99m, Tc13-99m, Tc14-99m, Tc15-99m, Tc17-99m, Tc18-99m, Tc19-99m, Tc20-99m, Tc21-99m, Tc22-99m, Tc23-99m, Tc24-99m, Tc26-99m, Tc27-99m, Tc28-99m, Tc29-99m, Tc30-99m, Tc32-99m, In-111, Se-75. This means **68.89%** of the tested radio-compounds were hazard effect.
- In cardio-toxicity subject, Sm-153, F-18, I-131, Tc1-99m, Tc2-99m, Tc3-99m, Tc6-99m, Tc7-99m, Tc18-99m, Tc19-99m, Tc20-99m, Tc21-99m, Tc23-99m, Tc27-99m, Tc28-99m, Tc30-99m, Tc33-99m were **safe in all tested cardio-issues**. So, **37.78%** of them were safe or **62.22%** of them were **unsafe to the heart functions.**
- In Arrhythmia case, F1-18, Tc11-99m, Tc16-99m, Tc17-99m, Tc25-99m, Tc29-99m, Tc32-99m, In-111, Se -75 were **toxic** to the **heart** (**22.22%** as a toxic percentage).
- Also, Tc4-99m, Tc31-99m, I-131, and I-123 may cause **cardiac failure** (**8.89%** as toxic in this health issue).

- This prediction showed that Tc5-99m, Tc10 -99m, Tc12-99m, Tc24-99m, Tc26-99m, Tc29-99m, and Tc32-99m **were toxic in heart block** issue (**15.56%** were toxic).
- **Myocardio- infraction** prediction found in Hg-197, I-123, Tc5-99m, Tc8-99m, Tc9-99m, Tc11-99m, Tc13-99m, and Tc29-99m (as **17.78%** Myocardio- infraction in tested radiopharmaceuticals).
- It can be noticed that **Tc29-99m** was **unsafe** in three cardio- toxicological subjects: Arrhythmia, heart block, and Myocardio- infraction. This toxic radiopharmaceutical may cause birth defects such as disruption, malformation, deformation, dysplasia, delayed mental development, growth, or other disorders as a result of its embryo – toxicity.
- While **Tc32-99m** may cause Arrhythmia, heart block, and hypertension beside embryo toxicological effects.
- Table (3) presented **Tc12-99m** and **Tc29-99m** had the same toxicological actions to embryo as well as Arrhythmia and heart block. Also, **Tc17-99m** and **In111** may cause Embryo, Arrhythmia and hERG.
- Table (4) shows attractive results about Honey Bee, Avian, *Minnow*, as well as human toxicity that includes rat acute (LD_{50}) and chronic (LOAEL) toxicological characters (Figure 4) where only **Tc11-99m** and **Tc25-99m** (Figure 3) had a serious toxicological effect on honey bee.
- Also, Table (4) showed that **Tc11-99m** had an additional toxicological effect on avian beside honey bee that mentioned above.
- *Minnow* fish that is used as toxicological indicator may be influences by these radiopharmaceuticals under prediction with a toxicity range (-1.567 to 4.071) while rat acute (LD_{50}) and chronic (LOAEL) ranges (Table 4, Figure 4) were (111.9 to 6603.9) and (5.2 to 1629.3) respectively.
- Ames test was with **No response** to all radio – chemicals under prediction.
- Table (4) showed that **Tc12-99m** the lowest value but most dangerous effect on *Minnow* fish (-1.567) between all tested materials. This toxic influence may be related to the presence of poly-ol and poly (N-COOH) in its molecular structure (Figure 2)
- Also, **Tc24- 99** (Figure 3) had a highly toxic with the lowest LD_{50} as a rat acute toxicity indication (Figure 4).
- Presence of **Iodine – 123** in the chemical structure of the secondary amine (I123) radio- substance (Figure 1) showed a dark image in this prediction study with the lowest rat chronic dose.

For more understanding of prediction efficiency, **Tc11-99m** (Figure 3) which is [2[[2-[[[3-(4-chlorophenyl)-8-methyl-8-azabicyclo[3,2,1]-oct-2-yl]-methyl] (2-mercaptoethyl) amino] ethyl]amino] ethanethiolato (3-)-N2,N2 ,S2,S2] oxo-[1R-exo-exo)])-[99mTc] technetium and abbreviated as **^{99m}Tc TRODAT** gave noticeable prediction characters. It had a toxicological fetal property beside toxic effect may cause Arrhythmia and Myocardial Infarction.

Heart attack or Myocardial Infarction is a silent - serious medical situation caused by depriving of blood flow to myocardium as a catastrophic occurrence. This may drive to death after hemodynamic deterioration [19]. For example, Tc11-99m may impulse irreversible cardiac damage of the muscular fibers or intense stress that induced spasms in the vessel walls and shorten blood supply to the smooth muscle. Also, this radioactive material is in Silico considered safe from being sick with cardiac failure, heart failure, hypertension, or hERG medical issue.

Table (3). Embryo- and cardio- toxicological prediction results.

Code	Embro-toxicity Confidence level	Cardio-toxicity					
		Arrhythmia	Cardiac Failure	Heart Block	hERG Toxicity	Hypertension	Myocardial Infarction
Sm-153	Safe Medium	Safe					
Ga-68	Unsafe High	Safe			Toxic	Safe	
F-18	Unsafe High	Safe					

Code	Embro-toxicity Confidence level	Cardio-toxicity					
		Arrhythmia	Cardiac Failure	Heart Block	hERG Toxicity	Hypertension	Myocardial Infarction
F1-18	Safe Low	Toxic	Safe				
Hg-197	Safe Low	Safe					Toxic
I-131	Safe Low	Safe					
I-123	Safe medium	Safe				Toxic	
Tc-99m	Unsafe Medium	Safe				Toxic	Safe
Tc1-99m	Unsafe medium	Safe					
Tc2-99m	Safe Medium	Safe					
Tc3-99m	Unsafe High	Safe					
Tc4-99m	Safe Low	Safe	Toxic	Safe			
Tc5-99m	Unsafe Low	Safe		Toxic	Safe		Toxic
Tc6-99m	Safe Medium	Safe					
Tc7-99m	Unsafe medium	Safe					
Tc8-99m	Unsafe High	Safe				Toxic	
Tc9-99m	Unsafe Low	Safe			Toxic	Safe	Toxic
Tc10-99m	Unsafe High	Safe		Toxic	Safe		
Tc11-99m	Unsafe Medium	Toxic	Safe				Toxic
Tc12-99m	Unsafe High	Toxic	Safe	Toxic	Safe		
Tc13-99m	Unsafe High	Safe					Toxic
Tc14-99m	Unsafe High	Safe			Toxic	Safe	
Tc15-99m	Unsafe Medium	Safe				Toxic	Safe
Tc16-99m	Safe Low	Toxic	Safe				
Tc17-99m	Unsafe Medium	Toxic	Safe		Toxic	Safe	
Tc18-99m	Unsafe Medium	Safe					
Tc19-99m	Unsafe High	Safe					

Code	Embro-toxicity Confidence level	Cardio-toxicity					
		Arrhythmia	Cardiac Failure	Heart Block	hERG Toxicity	Hypertension	Myocardial Infarction
Tc20-99m	Unsafe High	Safe					
Tc21-99m	Unsafe High	Safe					
Tc22-99m	Unsafe Medium	Safe			Toxic	Safe	
Tc23-99m	Unsafe high	Safe					
Tc24-99m	Unsafe Medium	Safe		Toxic	Safe		
Tc25-99m	Safe Medium	Toxic	Safe				
Tc26-99m	Unsafe High	Safe		Toxic	Safe		
Tc27-99m	Unsafe High	Safe					
Tc28-99m	Unsafe High	Safe					
Tc29-99m	Unsafe High	Toxic	Safe	Toxic	Safe		Toxic
Tc30-99m	Unsafe High	Safe					
Tc31-99m	Safe Low	Safe	Toxic	Safe			
Tc32-99m	Unsafe high	Toxic	Safe	Toxic	Safe	Toxic	Safe
Tc33-99m	Safe Low	Safe					
In-111	Unsafe High	Toxic	Safe		Toxic	Safe	
I-131	Safe Low	Safe	Toxic	Safe			
I-123	Safe Low	Safe	Toxic	Safe			Safe
Se-75	Unsafe High	Toxic	Safe				

Table (4). Herbicidal activity, environmental and human toxicity prediction of the studied radiopharmaceuticals.

Code	Environmental Toxicity			Human Toxicity	
	Honey Bee	***Avian***	***Minnow***	***Rat Acute (LD_{50})***	***Rat Chronic (LOAEL)***
Sm-153	No	No	3.113	975.6	19.8
Ga-68	No	No	1.14	251.0	202.0
F-18	No	No	3.629	832.5	1629.3
F1-18	No	No	3.1	222.2	121.4
Hg-197	No	No	3.065	3714.4	58.3
I-131	No	No	1.999	1468.5	110.4
I123	No	No	-0.211	474.5	5.2
Tc-99m	No	No	1.549	913.3	43.5
Tc1-99m	No	No	2.736	386.7	54.7
Tc2-99m	No	No	0.416	2487.6	57.4
Tc3-99m	No	No	3.558	1002.6	34.2
Tc4-99m	No	No	-0.834	698.9	33.8
Tc5-99m	No	No	4.071	2107.1	170.5
Tc6-99m	No	No	0.379	2423.6	17.9
Tc7-99m	No	No	1.197	121.9	97.8
Tc8-99m	No	No	1.006	2222.7	94.3
Tc9-99m	No	No	1.33	113.2	93.2
Tc10-99m	No	No	2.813	1347.8	87.8
Tc11-99m	Yes	Yes	-0.054	530.9	12.0
Tc12-99m	No	No	3.184	2630.1	332.4

Code	Environmental Toxicity			Human Toxicity	
	Honey Bee	***Avian***	***Minnow***	***Rat Acute (LD_{50})***	***Rat Chronic (LOAEL)***
Tc13-99m	No	No	1.482	122.6	106.9
Tc14-99m	No	No	-1.567	1340.1	86.2
Tc-15-99m	No	No	1.549	156.9	43.7
Tc16-99m	No	No	1.289	133.3	100.4
Tc17-99m	No	No	-0.826	1821.1	141.9
Tc18-99m	No	No	2.269	1375.0	84.5
Tc19-99m	No	No	2.536	933.9	33.6
Tc20-99m	No	No	1.866	2598.1	335.2
Tc21-99m	No	No	3.407	2985.0	907.9
Tc22-99m	No	No	1.54	1513.3	189.5
Tc23-99m	No	No	2.539	981.5	30.0
Tc24-99m	No	No	2.494	111.9	112.3
Tc25-99m	Yes	No	1.317	1322.6	30.0
Tc26-99m	No	No	2.019	1466.7	61.7
Tc27-99m	No	No	2.404	2939.7	73.7
Tc28-99m	No	No	2.207	1075.3	123.7
Tc29-99m	No	No	2.306	342.8	137.0
Tc30-99m	No	No	2.107	1619.0	125.2
Tc31-99m	No	No	-0.834	698.9	33.8
Tc32-99m	No	No	0.442	1082.1	48.7
Tc33-99m	No	No	1.241	506.2	10.5

Code	Environmental Toxicity			Human Toxicity	
	Honey Bee	***Avian***	***Minnow***	***Rat Acute (LD_{50})***	***Rat Chronic (LOAEL)***
In-111	No	No	1.146	127.5	195.4
I-131	No	No	2.92	909.8	24.7
i-123	No	No	2.92	887.8	24.7
Se-75	No	No	2.957	6603.9	12.0

4. Conclusions

First Iraqi attempt to evaluate various in Silico toxicological characters of forty five radiopharmaceuticals was done with using online websites. This attempt showed that these tested materials had a toxic site to one or more of human (embryo or pregnant mother), cardio- (Arrhythmia, Cardiac Failure, Heart Block, hERG, Hypertension, or Myocardial Infarction) or rat acute (LD_{50}) – chronic (LOAEL), as well as environment (honey, avian, *Minnow*) characters. For example, Sm-153 : Samarium-153 Lexidronam gave a safe in Silico toxicological response to embryo and pregnant mother, all tested cardio-, honey, avian. Also, it showed a lower value towards *Minnow* and rat chronic (LOAEL) toxicities. Another example is related to selenium that has synthetic isotope (75Se) with approximately 120 days as a half- life. This micronutrient (Selenium) is essential to animal and human but can be accumulated in plant from soil. Even with selenium importance for nutrition and as enzymatic cofactor, Selenomethionine - 75Se derivative (Se-75) was highly unsafe to embryo and his mother beside toxic effect in Arrhythmia case. In comparison to Sm-153, Se-75, as a corresponding radio –compound of the naturally amino acid in soybeans and nuts, had lower *Minnow* and rat chronic toxicological values but not LD_{50}. So, both radiopharmaceuticals were structurally toxic especially in high concentration and repeated uptake by human or environmental species.

Conflict of Interest: The authors declare that there are no conflicts of interest associated with this research project. We have no financial or personal relationships that could potentially bias our work or influence the interpretation of the results.

References

[1] S. Mattissom, L. Johansson, S. Svegborn, J. Liniecki, D. Nobke, K. Riklund, M. Stabin, D. Taylor, W. Bolch, S. Carlosson, K. Exkerman, A. Giussani, L. Sőderberg, and S. Valind, "Radiation dose to patients from radiopharmaceuticals: a compendium of current information related to frequently used substances," Annals ICRP publication 128, published by SAGE, 2015.

[2] A. Dash, F. Knapp, F. Knapp, and M. Pillai, "Target radionuclide therapy – an overview," *Current Radiopharmaceuticals*, vol. 6, no. 3, pp. 152 -180, 2013.

[3] C. Yeong, M. Cheng, and K. Hoong, "Therapeutic radionuclides in nuclear medicine: current and future prospects," *Journal of Zhejiang University – Science B (Biomedicine & Biotechnology)*, vol. 15, no. 10, 845 - 863, 2014.

[4] D. Milenic, E. Brady, and M. Brechbiel, "Antibody targeted radiation cancer therapy," *Nature Reviews, Drug Discovery*, vol. 3, no. 6, pp. 488 -499, 2004.

[5] F. Mottaghy, "Current and future aspects of molecular imaging methods," *Methods*, vol. 10, pp. 12, 2009.

[6] M. Pysz, S. Gamnhir, and J. Willmann, "Molecular Imaging: current status and emerging strategies," *Clinical Radiology*, vol. 65, pp. 500-516, 2010.

[7] S. Qaim and I. Spahn, "Development of novel radionuclides for medical applications," *Journal of Labeled Compounds and Radiopharmaceuticals*, vol. 61, pp. 126 -140, 2018.
[8] A. Boschi, L. Uccelli, and P. Martini, "A picture of modern Tc-99m radiopharmaceuticals: production, chemistry, and applications in molecular imaging," *Applied Sciences*, vol. 9, pp. 2526 (16 pages), 2019.
[9] I. Velikyan, "Molecular imaging and radiotherapy: theranostic for personalized patient management," *Theranostics*, vol. 2, no. 5, pp. 424 – 426, 2012.
[10] D. Pires, K. Stubbs, J. Mylne, and D. Ascher, "cropCSM: designing safe and potent herbicides with graph – based signatures," *Briefings in Bioinformatics*, vol. 23, no. 2, pp. 1-9, 2022.
[11] R. Aljarf, S. Tang, D. Pires, and D. Ascher, ‘’ embryoTox: Using Graph-Based Signatures to Predict the Teratogenicity of Small Molecules,’’ *Journal of Chemical Information and Modeling*, vol. 63, no. 2, pp. 432–441, 2023.
[12] S. Iftkhar, A. de Sá, J. Velloso, R. Aljarf, D. Pires, and D. Ascher, " cardioToxCSM: A Web Server for Predicting Cardiotoxicity of Small Molecules, *Journal of Chemical Information and Modeling*, vol. 62, no. 20, pp. 4827–4836, 2022.
[13] C. Yeong, M. Cheng, and K. Ng. (2014). "Therapeutic radionuclides in nuclear medicine: current and future prospects, " *Journal of Zhejiang University. Science. B*, vol. 15, no. 10, pp. 845–863.
[14] K. Chakraborty, J. Mondal, J. An, J. Park, and Y. Lee, (2023). "Advances in Radionuclides and Radiolabelled Peptides for Cancer Therapeutics," *Pharmaceutics*, vol. 15, no. 3, pp. 971.
[15] S. Salih, A. Alkatheeri, W. Alomaim, and A. Elliyanti. (2022). "Radiopharmaceutical Treatments for Cancer Therapy, Radionuclides Characteristics, Applications, and Challenges," *Molecules (Basel, Switzerland)*, vol. 27, no. 16, pp. 5231.
[16] S. Goldsmith (2020). "Targeted Radionuclide Therapy: A Historical and Personal Review," *Seminars in Nuclear Medicine*, vol. 50, pp. 87–97.
[17] D. Desai and S. Hajouli, Arrhythmias. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558923/.
[18] A. Veduta, A. Panaitescu, A. Ciobanu, D. Neculcea, M. Popescu, G. Peltecu, and P. Cavoretto, ‘’Treatment of Fetal Arrhythmias,’’ *Journal of Clinical Medicine*, vol. 10, no. 11, pp. 2510, 2021.
[19] C. Gopalan and E. Kirk, ‘’Biology of cardiovascular and metabolic diseases,’’ Chapter 6- Coronary artery disease, Elsevier Inc., USA, pp. 103-122, 2022.