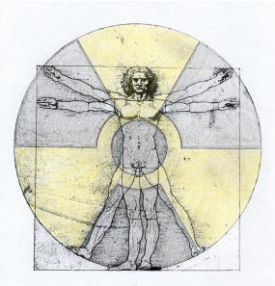


IDEA System
The Expert System for Internal Dosimetry

Newsletter No. 2/2018

Implementation of new radionuclides for Targeted Alpha Therapy (TαT)

With the overall survival benefit conferred by Ra-223 treatment and its subsequent approval for bone-predominant mCRPC (metastatic castration-resistant prostate cancer), interest in the therapeutic potential of α–emitting radionuclides is increasing. Other α-emitters being investigated in preclinical and clinical studies include Th-227, Ac-225, Bi-213, At-211, and Pb-212, as pointed out in a recently published review article [1].

Features of new radionuclides

Th-227

Thorium-227 is an α-emitter with a physical half-life of 18.7 days. The Th-227 decay scheme is initiated by its α-decay into Ra-223, which subsequently follows the decay chain of Ra-223. As Th-227 decays to stable Pb-207, 5 α-particles are released, making Th-227 an attractive candidate for TαT. Targeted Th-227 conjugates are being investigated in several preclinical and phase 1 studies across tumortypes, including prostate cancer, colorectal cancer, gastric cancer, ovarian cancer, non-Hodgkin lymphoma, and leukemia.

Ac-225

The decay of Ac-225 results in the emission of 4 α-particles, which marks Ac-225 as an attractive and potent choice for TαT. Actinium-225 has a physical half-life of 9.92 days and yields 3 daughter radionuclides that each emit an α-particle on their decay. As with Ra-223, the relatively long half-life of Ac-225 allows for centralized production, distribution, and administration of Ac-225 TαT. Another distinct advantage of Ac-225–based TαT is the emission of a 440-keV γ-ray after the decay of the Bi-213 daughter radionuclide, which can be used for imaging to determine biodistribution. An ongoing phase 1/2 trial of Ac-225–lintuzumab targeting CD33-positive myeloid leukemia cells in patients with acute myeloid leukemia has shown that treatment is safe.

Bi-213

Bismuth-213 has a short physical half-life of 45.6 minutes and is prepared for therapeutic use in an Ac-225 and Bi-213-generator. The generator produces Bi-213 that is clinically useful for 10 days. Bismuth-213 decays to stable Bi-209 through the emission of an α-particle and 2 beta particles. Bismuth-213 is readily conjugated to mAbs, peptides, and small molecules and has been investigated as a TαT in several clinical

trials. However, its short half-life and conjugation chemistry restrict the use of Bi-213 for patients. Despite these practical limitations, clinical trials have shown promising efficacy of Bi-213.

At-211

Astatine-211 has a physical half-life of 7.2 hours and decays through a branched pathway, with each decay path producing an α-particle as it decays to stable Pb-207. Astatine-211 has several attractive features for use as a TαT, including no long-lived α-particle–emitting daughter radionuclides, 18 photon emission that allows imaging, and compatibility for conjugation with several carrier molecules to allow targeted delivery. The availability of At-211 is limited by its short half-life, which makes it difficult to deliver sufficient quantities of At-211 to distant treatment centers and has limited the number of preclinical and clinical studies of this radionuclide.

Pb-212

Lead-212 is a β-particle emitter with a physical half-life of 10.2 hours; it is the immediate parental radionuclide of Bi-212. Bismuth-212 decays to stable Pb-208 through the emission of 1 α-particle and 1 β-particle.

Radiation qualities for *in vivo* monitoring

Nuclide	Radiation	Energy, keV	Abundancy, %	LLD, Bq
Th-227	γ	256,2	6,78	700
Ac-225	γ	99,7	3,5	2000
Bi-213	γ	440	27,3	200
At-211	K-α1	79,3	21,1	200
Pb-212	γ	239	44,6	100

As can be seen from the table above, the new radionuclides emit significant γ- and/or K-α-X-rays. The abundancy of the emissions, however, is too low for the application in routine monitoring, this being illustrated in the following for the examples of Th-227 and Ac-225.

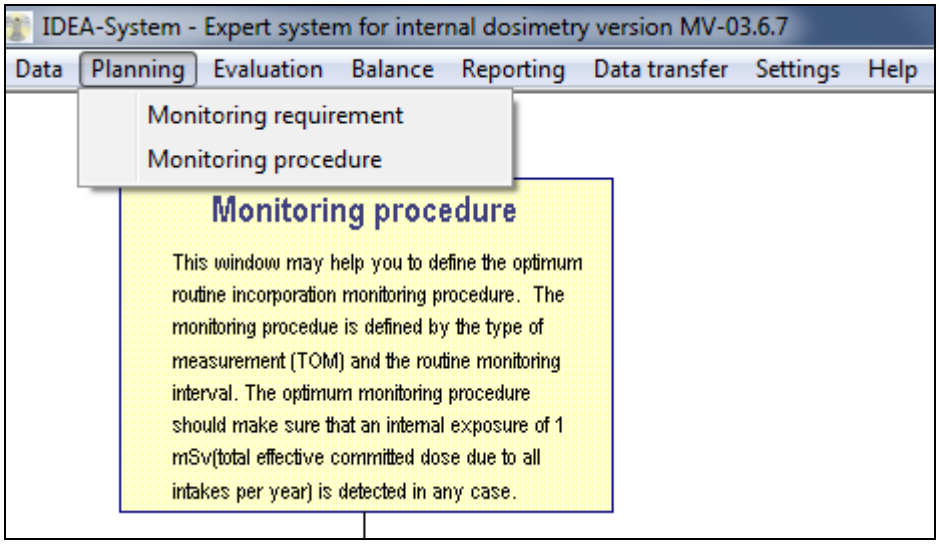
Monitoring procedures

The procedures for routine monitoring should meet the following requirements:

- The monitoring procedure should make sure to detect an internal exposure of 1 mSv per year for any exposure scenario (sensitivity criterion S).
- The monitoring intervals should make sure that the misinterpretation potential due to unknown time of intake is less than factor 3 (misinterpretation criterion M).

For most of the α-emitters there is no monitoring procedure meeting these requirements. For this reason, the German regulations recommend for most α-emitters routine room-air monitoring in combination with two urine measurements per year for control of potential long-term exposures. This monitoring procedure is adopted by IDEA System as default for the 5 new radionuclides.

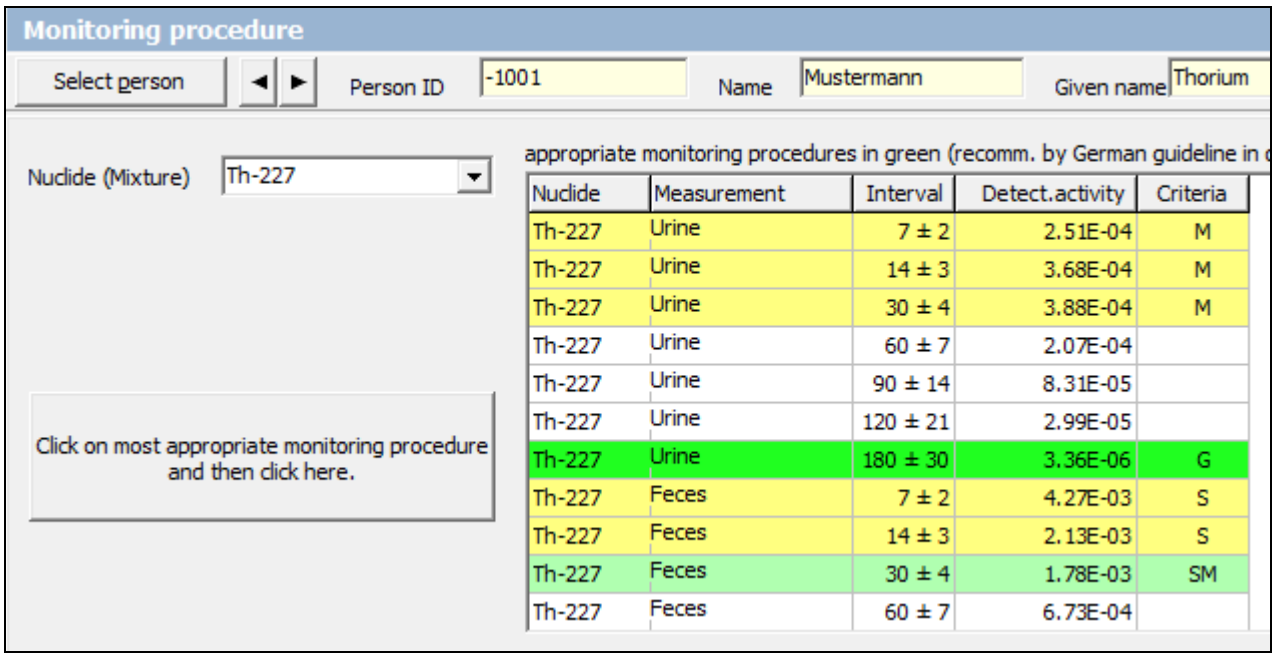
Regardless of the default setting, IDEA System provides the possibility for defining customized monitoring procedures according to the requirements as specified above using the Planning tool as shown in the following for Th-227 and Ac-225.



Th-227

The optimization procedure is illustrated by the screenshot below. In principle, intakes of Th-227 can be monitored by measurement of the Th-227-activity excreted by urine and feces. The urine measurement complies the misinterpretation criterion (M) if the monitoring interval is 30 days or less (indicated by the yellow lines). The sensitivity of the urine measurement, however, is not sufficient to meet the sensitivity criterion (S). The required LLD (lower limit of detection) is in the order of 0,4 mBq, this being reached only by few laboratories. Thus, in general the urine measurement meets only one of the two requirements for routine monitoring. The feces measurement, however, meets both requirements for the monitoring interval of 30 days, this being indicated by the light green line.

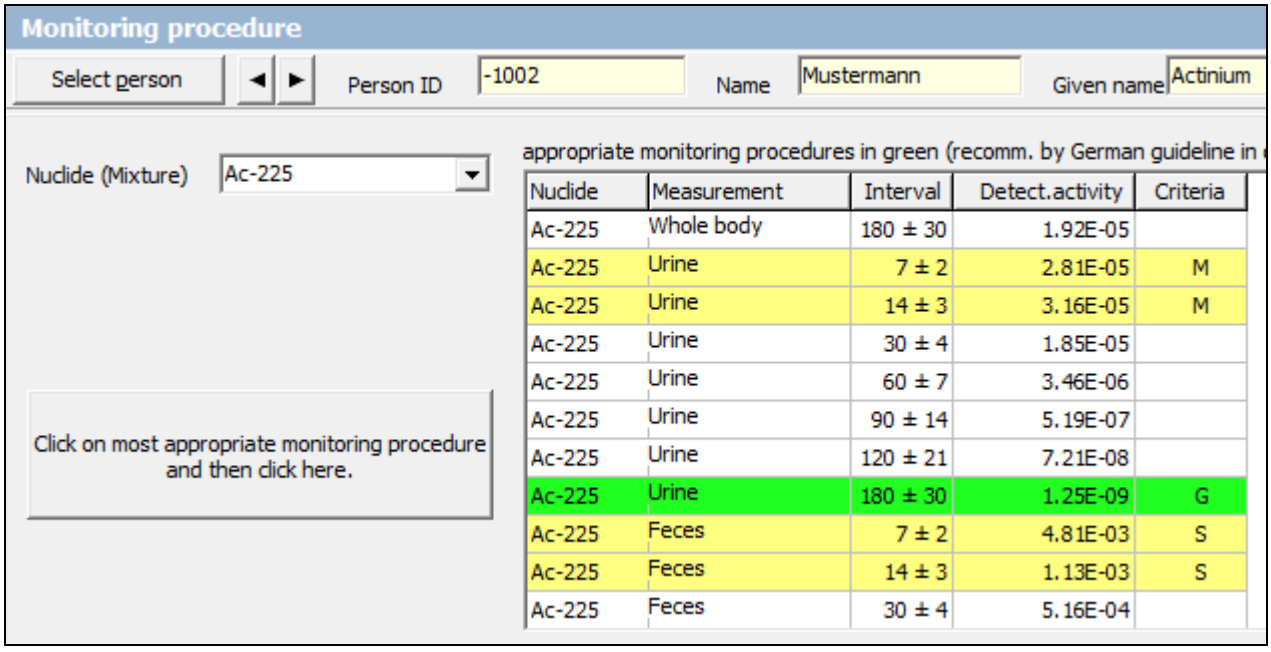
Thus, optimum individual monitoring for Th-227 would consist in the collection of one feces and one urine sample at the end of each 30 days monitoring interval. The feces sample would then be evaluated in order to check whether there has been an intake. If so, the urine sample would be evaluated in order to determine the time of intake.



Nuclide	Measurement	Interval	Detect.activity	Criteria
Th-227	Urine	7 ± 2	2.51E-04	M
Th-227	Urine	14 ± 3	3.68E-04	M
Th-227	Urine	30 ± 4	3.88E-04	M
Th-227	Urine	60 ± 7	2.07E-04	
Th-227	Urine	90 ± 14	8.31E-05	
Th-227	Urine	120 ± 21	2.99E-05	
Th-227	Urine	180 ± 30	3.36E-06	G
Th-227	Feces	7 ± 2	4.27E-03	S
Th-227	Feces	14 ± 3	2.13E-03	S
Th-227	Feces	30 ± 4	1.78E-03	SM
Th-227	Feces	60 ± 7	6.73E-04	

Ac-225

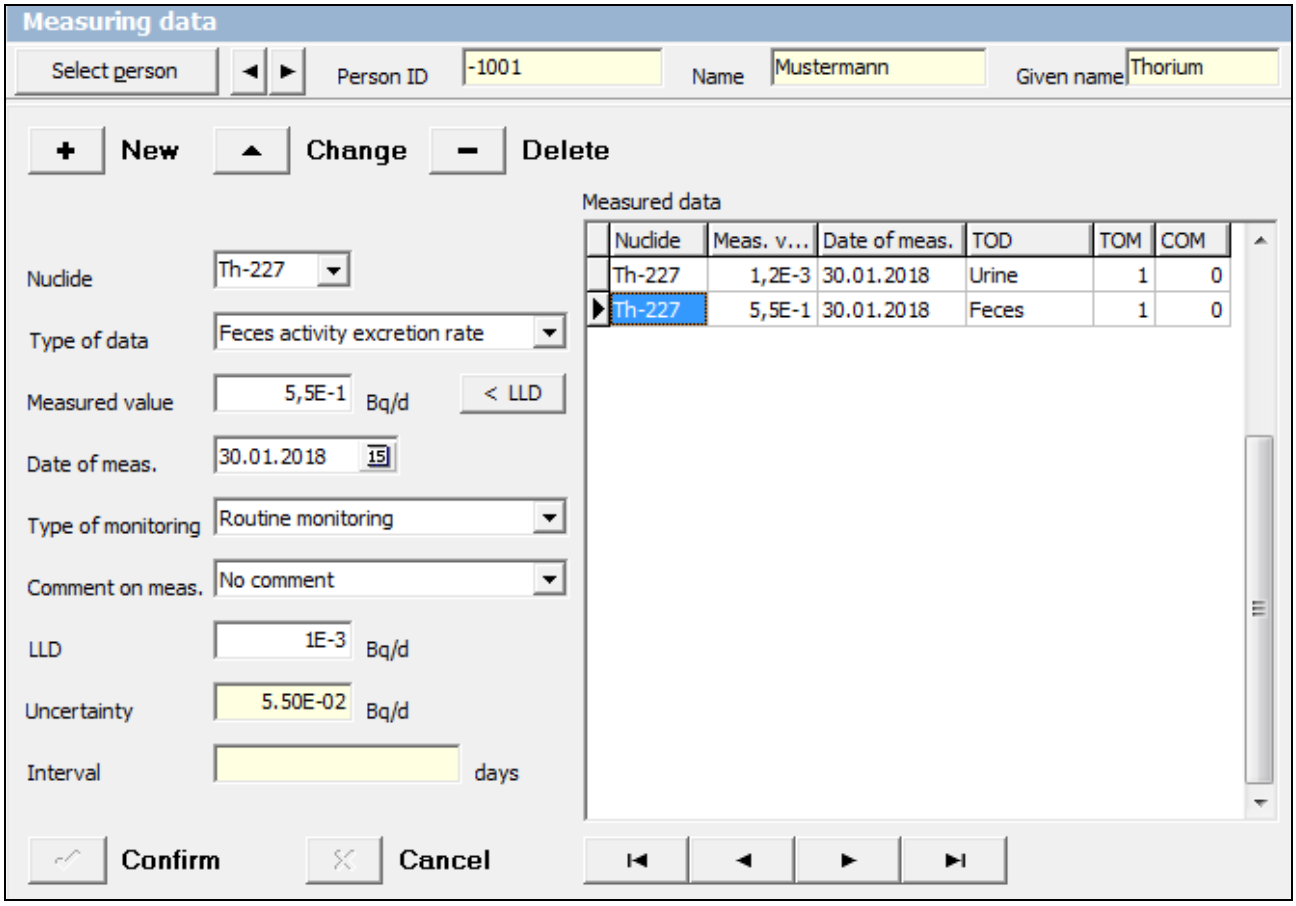
In the case of Ac-225 individual routine monitoring is possible but because of the shorter physical halflife of Ac-225 the optimum monitoring interval is only 14 days. Moreover, individual monitoring should be done by measurement of both urine and feces, because the urine measurement complies only with the misinterpretation criterion whereas the feces measurement complies only the sensitivity criterion.

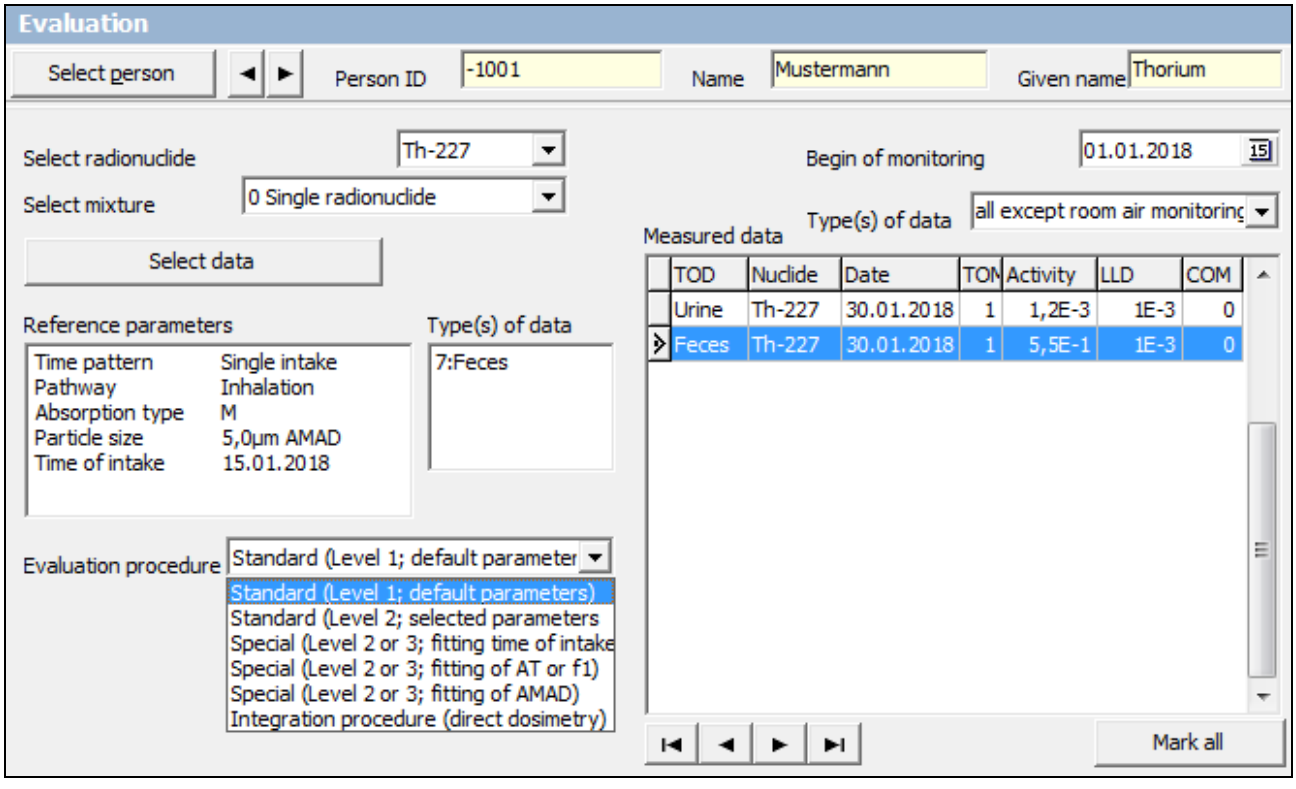


Nuclide	Measurement	Interval	Detect.activity	Criteria
Ac-225	Whole body	180 ± 30	1.92E-05	
Ac-225	Urine	7 ± 2	2.81E-05	M
Ac-225	Urine	14 ± 3	3.16E-05	M
Ac-225	Urine	30 ± 4	1.85E-05	
Ac-225	Urine	60 ± 7	3.46E-06	
Ac-225	Urine	90 ± 14	5.19E-07	
Ac-225	Urine	120 ± 21	7.21E-08	
Ac-225	Urine	180 ± 30	1.25E-09	G
Ac-225	Feces	7 ± 2	4.81E-03	S
Ac-225	Feces	14 ± 3	1.13E-03	S
Ac-225	Feces	30 ± 4	5.16E-04	

Evaluation procedures (Example Th-227)

The evaluation procedure is illustrated by the following example, assuming the evaluation of the first routine fecal sample to result in an activity of 550 mBq Th-227.





For evaluation of this value the standard procedure is applied using the reference parameters (single intake by inhalation in the middle of the monitoring interval assuming absorption type M and 5 µm AMAD particle size). This procedure results in an intake of 1,7 kBq Th-227 with the corresponding effective dose being 10,5 mSv. Thus, the dose estimate is above the investigation level and further steps are necessary to evaluate the dose.

Results

The dose is above 6 mSv or 30 % of the dose limits, respectively;
the measuring values are allocated to "Level 3"
according to the IDEAS General Guidelines.

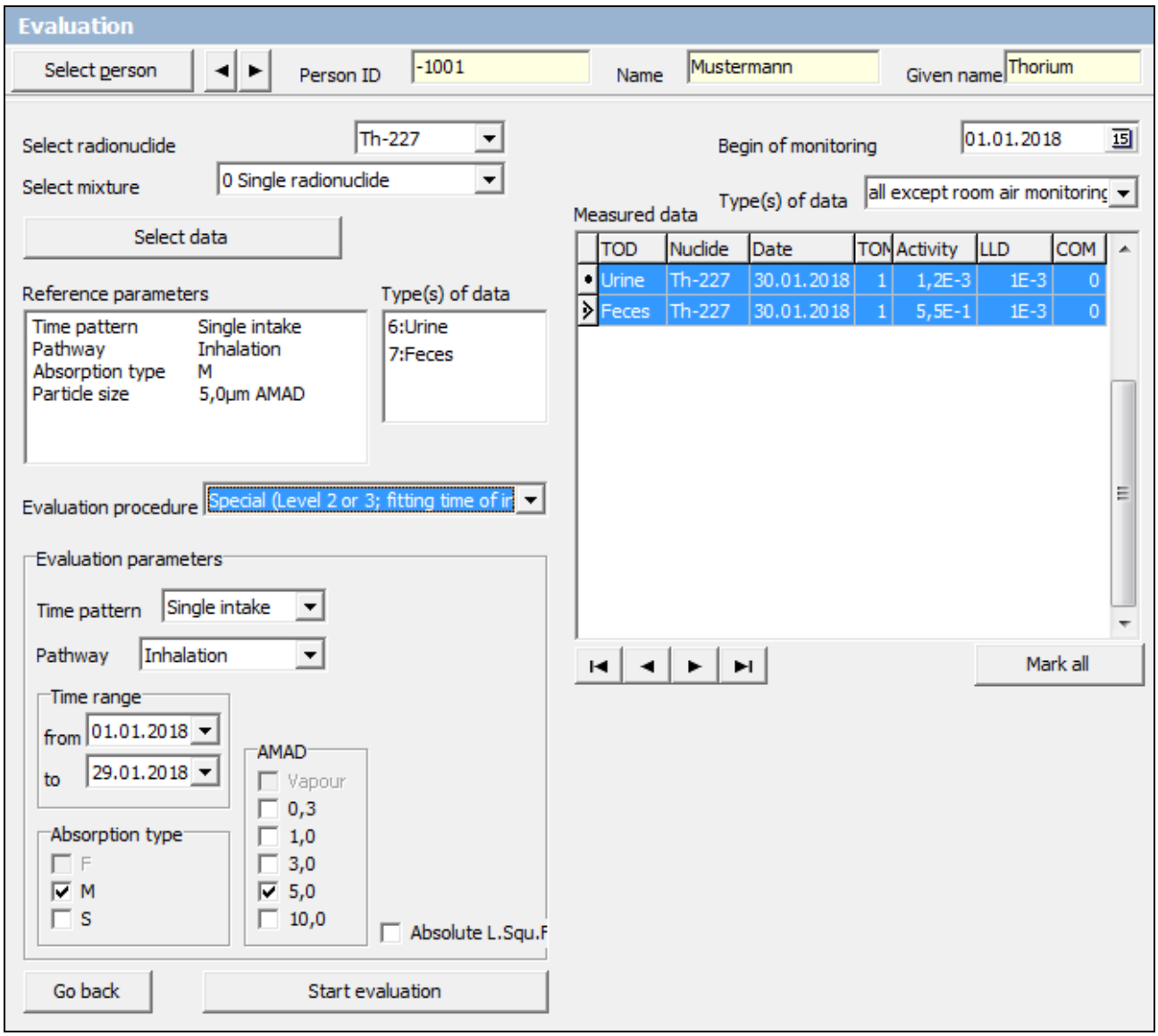
Evaluation procedure	Standard (Level 1; default p
Nuclide	Th-227
Intake	1.70E+03 Bq
Time pattern	Single intake
Pathway	Inhalation
Time of intake	15.01.2018
Absorption type	M
Particle size	5,0µm AMAD
Effective dose	1.05E-02 Sv
Critical organ	Lungs
with organ dose	8.66E-02 Sv
Potential error (SF)	1,1

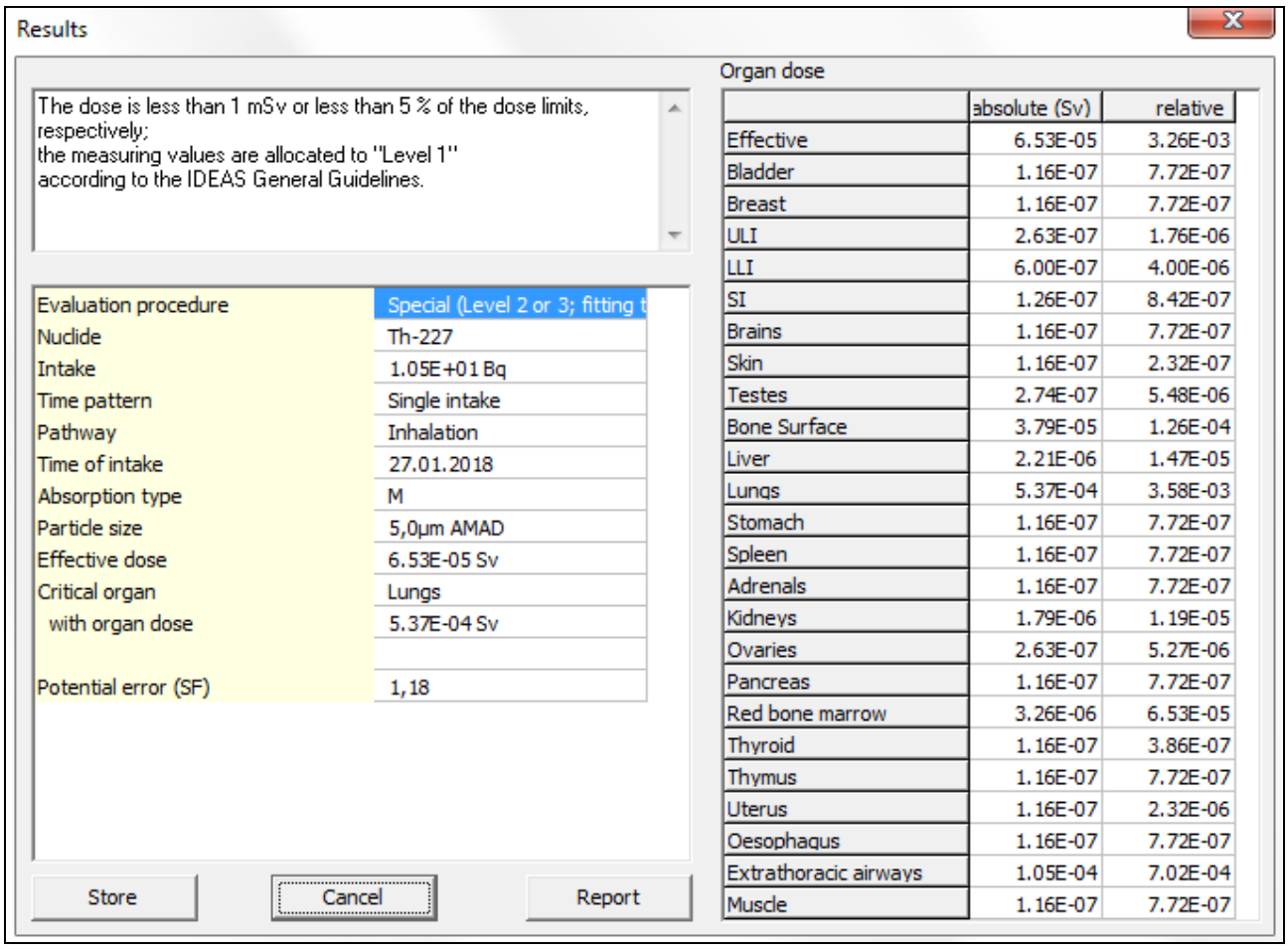
Store | Cancel | Report

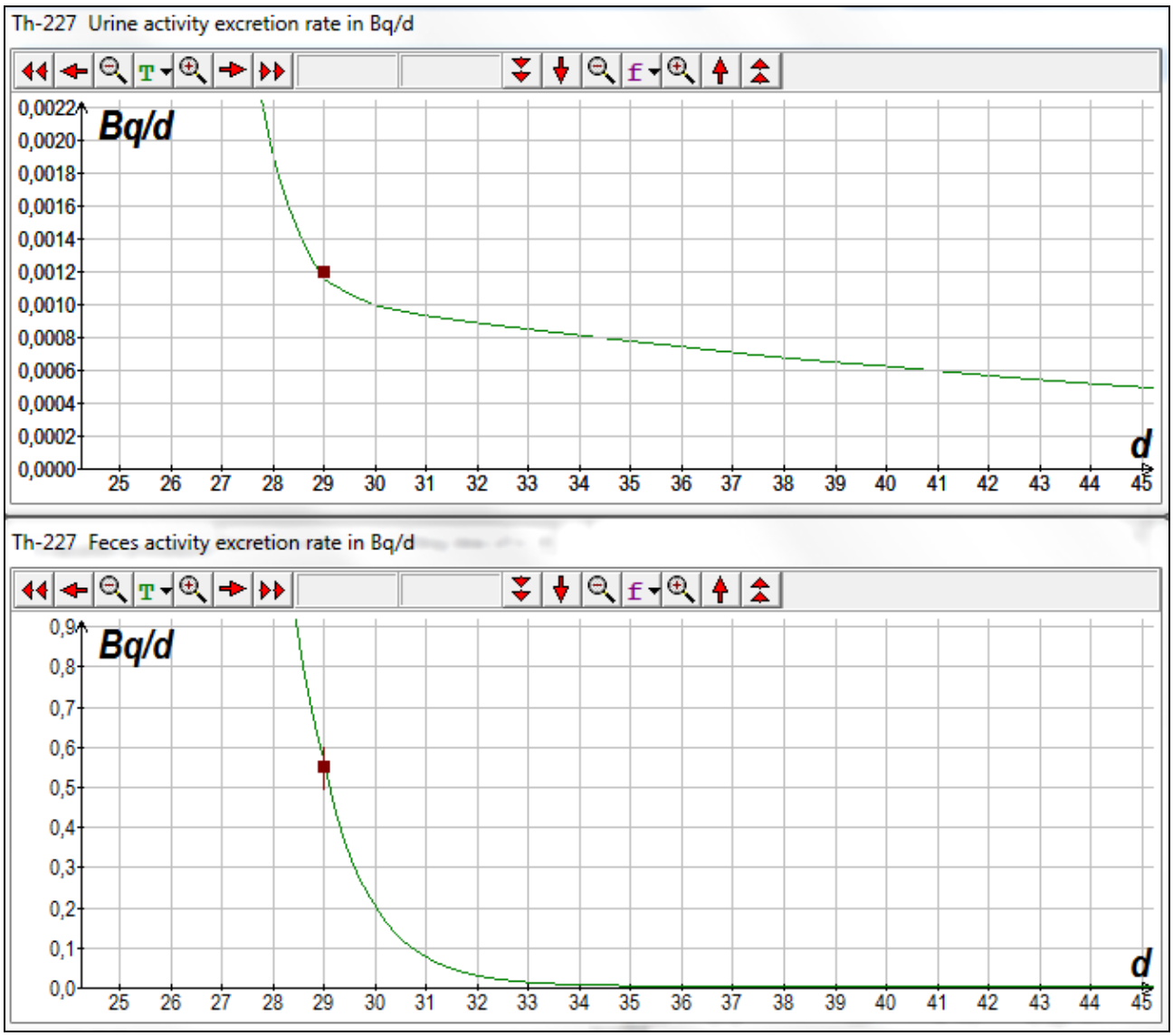
Organ dose

	absolute (Sv)	relative
Effective	1.05E-02	5.26E-01
Bladder	1.87E-05	1.24E-04
Breast	1.87E-05	1.24E-04
ULI	4.24E-05	2.83E-04
LLI	9.68E-05	6.45E-04
SI	2.04E-05	1.36E-04
Brains	1.87E-05	1.24E-04
Skin	1.87E-05	3.73E-05
Testes	4.41E-05	8.83E-04
Bone Surface	6.11E-03	2.04E-02
Liver	3.56E-04	2.38E-03
Lungs	8.66E-02	5.77E-01
Stomach	1.87E-05	1.24E-04
Spleen	1.87E-05	1.24E-04
Adrenals	1.87E-05	1.24E-04
Kidneys	2.89E-04	1.92E-03
Ovaries	4.24E-05	8.49E-04
Pancreas	1.87E-05	1.24E-04
Red bone marrow	5.26E-04	1.05E-02
Thyroid	1.87E-05	6.22E-05
Thymus	1.87E-05	1.24E-04
Uterus	1.87E-05	3.73E-04
Oesophagus	1.87E-05	1.24E-04
Extrathoracic airways	1.70E-02	1.13E-01
Muscle	1.87E-05	1.24E-04

In this example the next step would be the simultaneous evaluation of the urine sample and the fecal sample in order to determine the most likely time of intake. This evaluation reveals the most likely time of intake was just 3 days before the collection of the samples. So the intake was actually only 10,5 Bq Th-227 with the effective dose being only 65 µSv.


Evaluation
Select person
Person ID
-1001
Name
Mustermann
Given name
Thorium
Select radionuclide
Th-227
Select mixture
0 Single radionuclide
Select data
Reference parameters
Time pattern Single intake
Pathway Inhalation
Absorption type M
Particle size 5,0µm AMAD
Type(s) of data
6:Urine
7:Feces
Evaluation procedure
Special (Level 2 or 3; fitting time of ir
Evaluation parameters
Time pattern
Single intake
Pathway
Inhalation
Time range
from
01.01.2018
to
29.01.2018
Absorption type
F
M
S
AMAD
Vapour
0,3
1,0
3,0
5,0
10,0
Absolute L.Squ.F
Go back
Start evaluation
Begin of monitoring
01.01.2018
Type(s) of data
all except room air monitoring
Measured data
TOD
Nuclide
Date
TON
Activity
LLD
COM
Urine
Th-227
30.01.2018
1
1,2E-3
1E-3
0
Feces
Th-227
30.01.2018
1
5,5E-1
1E-3
0
Mark all


Results
The dose is less than 1 mSv or less than 5 % of the dose limits, respectively;
the measuring values are allocated to "Level 1"
according to the IDEAS General Guidelines.
Evaluation procedure
Special (Level 2 or 3; fitting t
Nuclide
Th-227
Intake
1.05E+01 Bq
Time pattern
Single intake
Pathway
Inhalation
Time of intake
27.01.2018
Absorption type
M
Particle size
5,0µm AMAD
Effective dose
6.53E-05 Sv
Critical organ
Lungs
with organ dose
5.37E-04 Sv
Potential error (SF)
1,18
Store
Cancel
Report
Organ dose
absolute (Sv)
relative
Effective 6.53E-05 3.26E-03
Bladder 1.16E-07 7.72E-07
Breast 1.16E-07 7.72E-07
ULI 2.63E-07 1.76E-06
LLI 6.00E-07 4.00E-06
SI 1.26E-07 8.42E-07
Brains 1.16E-07 7.72E-07
Skin 1.16E-07 2.32E-07
Testes 2.74E-07 5.48E-06
Bone Surface 3.79E-05 1.26E-04
Liver 2.21E-06 1.47E-05
Lungs 5.37E-04 3.58E-03
Stomach 1.16E-07 7.72E-07
Spleen 1.16E-07 7.72E-07
Adrenals 1.16E-07 7.72E-07
Kidneys 1.79E-06 1.19E-05
Ovaries 2.63E-07 5.27E-06
Pancreas 1.16E-07 7.72E-07
Red bone marrow 3.26E-06 6.53E-05
Thyroid 1.16E-07 3.86E-07
Thymus 1.16E-07 7.72E-07
Uterus 1.16E-07 2.32E-06
Oesophagus 1.16E-07 7.72E-07
Extrathoracic airways 1.05E-04 7.02E-04
Muscle 1.16E-07 7.72E-07



[1] Targeted Alpha Therapy, an Emerging Class of Cancer Agents – A Review, JAMA Oncology, Published online September 20, 2018, © 2018 American Medical Association

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