NUCLEAR MEDICINE EUROPE
the industry association

Transport Experts
Nuclear Medicine Europe working group

Nuclear Medicine Europe Position on the Proposed Revision to IAEA Safety Standard Series SSR-6 Revision 1, Regulations for the Safe Transport of Radioactive Material 2018 Edition, Table 2 A_1 & A_2 Values

Nuclear Medicine Europe represents many of the major pharmaceutical & imaging equipment companies in the field of Nuclear Medicine in Europe. The combination of radiopharmaceuticals & state-of-the-art imaging permits noninvasive visualization of organs, function & structure within the body. Nuclear medicine is used in the diagnosis, management, treatment & prognosis of diseases across a broad range of medical specialties, such as oncology, cardiovascular & neurology to name a few, and as such is an integral part of patient care.

There are currently 40 million nuclear medicine procedures performed annually worldwide. Nuclear medicine involves the injection of medical radionuclides or radiopharmaceuticals (RPs) ("drugs that rely on medical isotopes") into a patient's body for radiotherapy or for diagnostic imaging.

The transportation of medical isotopes and radiopharmaceuticals relies on an international supply chain facilitated by the International Atomic Energy Agency (IAEA) Regulations for the Safe Transport of Radioactive Material, 2018 Edition (SSR-6) which provides a consistent framework for safe transport.

Medical radionuclides and radiopharmaceuticals used in nuclear medicine are typically transported in one of the following three types of packages: Excepted package, Type A package, and Type B package. The short half-lives of most medical radionuclides and radiopharmaceuticals require hourly and daily shipments from manufactures and nuclear pharmacies to healthcare providers for patient care. These shipments are made according to stringent regulations designed to protect the public and the environment from risks, as well as accidents that may occur during shipping.

Currently, nearly all of the short-lived medical radionuclide and radiopharmaceutical shipments from manufacturers and nuclear pharmacies to healthcare providers are contained in Type A packages. In fact, Nuclear Medicine Europe member companies could not identify a single short-lived radionuclide or radiopharmaceutical product that would require to be shipped in a Type B package to a health care provider. A Type A package, and its short-lived medical radionuclide or radiopharmaceutical contents, must meet standard testing requirements designed to ensure that the package retains its containment integrity and shielding under normal transport conditions. Requirements for Type A packages have historically been proven safe and cost-

effective for industry. In addition, IAEA SSR-6 regulations establish A_1 and A_2 values with which in combination with design criteria on containment and control during transport in a Type A package will prevent overexposures to people and environment.

The IAEA is currently revising SSR-6 which includes revisions to many of the A_1 and A_2 values in Table 2, Basic Radionuclide Value. Most notably are the significant reductions in the A2 values for radionuclides that emit high energy alpha particles through radioactive decay either directly or indirectly through their short-lived progeny.

In recent years and with the further development of RPs, important research and clinical advances have been made in Targeted Alpha Therapy (TAT). TAT is a type of cancer treatment that uses alpha-emitting radionuclides such as actinium-225 (Ac-225), lead-212 (Pb-212), radium-223 (Ra-223) or astatine-211 (At-211) to selectively target and destroy cancer cells. These radionuclides are attached to molecules that specifically bind to cancer cells, delivering a high dose of radiation directly to the tumor while minimizing damage to surrounding healthy tissue. The high-energy alpha particles cause double-strand breaks in DNA, leading to effective cell killing. Clinical trials using Ac-225, Pb-212, and At-211 have shown promising results, with demand for TATs projected to grow significantly over the next decade. The development of new radiopharmaceutical therapies also includes other radionuclides, such as but not limited to, Ac-226, Bi-212, Ra-226, Th-228 and U-230. They can be directly used in TAT or may be precursors needed to produce the high-energy alpha emitting radionuclides.

The "Draft Safety Requirements: (DS543) Regulations for the Safe Transport of Radioactive Material, 20XX Edition; Revision of IAEA Safety Standards Series No. SSR-6 (2018 Edition)", as available in October 2024, includes significant revisions for the A_1 and A_2 values for all the mentioned illustrative isotopes.

The table below emphasizes the proposed changes for those radionuclides.

Radionuclide	A_1		A_2		NEW / CURRENT	
	IAEA SSR-6	WG A_1/A_2	IAEA SSR-6	WG A_1/A_2		
	TBq	TBq	TBq	TBq	A_1	A_2
Ac-225	8,00E-01	4,00E+00	6,00E-03	7,00E-04	5	0,12
Ac-226	x	6,00E+00	x	2,00E-03	x	x
At-211	2,00E+01	2,00E+01	5,00E-01	4,00E-03	1	0,01
Bi-212	7,00E-01	5,00E-01	6,00E-01	1,00E-03	0,71	0,002
Pb-212	7,00E-01	4,00E-01	2,00E-01	9,00E-04	0,57	0,005
Ra-223	4,00E-01	2,00E+00	7,00E-03	2,00E-03	5	0,29
Ra-226	2,00E-01	6,00E-01	3,00E-03	2,00E-03	3	0,67
U-230 (slow lung absorption)	3,00E+01	1,00E+01	3,00E-03	2,00E-03	0,33	0,67

The significant reduction of A_2 values for some alpha-emitting radionuclides in the current revision to SSR-6 is due to recalculated $Q_{D,\ skin}$ values. This will present significant challenges in the development, production, and distribution of innovative medical radionuclides and radiopharmaceuticals utilizing radioisotopes such as Pb-212, Ac-225, and At-211. Manufacturers and nuclear pharmacies will potentially need to migrate to Type B packaging for supply chain shipments as well as radiopharmaceutical deliveries to healthcare providers for the short-lived isotopes like At-211 (half-life of 7.2 hours), Pb-212 (half-life 10.6 hours) and Ac-225 (half-life 10 days). Type B packaging is designed for the transport

of larger activities of radioactive materials, with more stringent regulatory requirements for shippers and recipients (such as nuclear pharmacies and hospitals), higher maintenance costs, and requirements for a Certificate of Compliance for Radioactive Material Packages from the competent authorities.

Meeting the projected increase in TATs will be challenging given the limited supply of suitable radionuclides and their precursors, (whose proposed A_2 values were also significantly reduced as a result of the recalculated $Q_{D,skin}$ values). For example, the annual production of Ac-225 can currently only support a few hundred patients per year. Overall, there are ongoing technical efforts (both in the private and public sectors) to overcome the production and supply issues associated with targeted alpha therapy radioisotopes. The limited supply coupled with the impact on the distribution of these radionuclides if the proposed A_2 values are accepted into the revision of SSR-6 will further increase the cost of production and distribution of TATs, as well as increasing regulatory burden on shipping for manufacturers, nuclear pharmacies, and healthcare providers. This ultimately will impact patient access to TATs and increase the cost of patient care.

The table below provides some figures on the impact of the new A_2 values for two specific nuclides.

Radio--nuclide	Typical patient dose at injection (Bq)	Activity to be shipped (Bq) [1]	A_2 Value (Bq)		Maximum number of patient doses per Type A shipment [2]	
			Today	Tomorrow	Today	Tomorrow
Ac-225	7,40E+06	7,95E+06	6,00E+09	7,00E+08	755	88
Pb-212	2,04E+08	9,63E+08	2,00E+11	9,00E+08	208	< 1

[1] Such activity guarantees the typical patient dose at injection after transport time and shelf life of the product (24 hours)
[2] This column represents the batch size. Ultimately a patient dose will always be one per vial, i.e. one per lead pig. For example for some products, up to 4 doses can be shipped in one type A box to the same location as long as there are 4 patients needing the treatment more or less at the same time.

Although the impact may be seen as moderate for Ac-225, the new value is likely to limit the ongoing technical efforts to overcome the production and supply issues, which requires transports in bulk quantities.

For lead-212, the impact seems obvious, whether in the supply chain process or in the direct delivery to hospitals. The estimated quantity of patient doses in a single Type A package taking into account the proposed A_2 value is likely to be less than 1, except when hospitals are close to the production facility (in case the transport time is short).

Moreover, it is reminded that the data above are for typical patient doses at injection, as in the current state-of-art. Further developments could be activity-demanding, the proposed A_2 values are therefore likely to have a negative impact on future developments.

The A_1/A_2 values in the revisions to SSR-6 were derived from the "Q system" (where "Q" stands for "Quantity") radiological model, based on 5 different exposure scenarios (including Q_C internal exposure from inhalation and QD exposure to the skin). Nuclear Medicine Europe members do not question the technical aspects of the work and fully support the use

of updated ICRP data in the calculations of the Q-values. We also understand that the scope of the working group did not include reassessing the five exposure scenarios considered in the Q-system.

The exposure scenario for Q_D considers the skin dose via contamination and subsequent ingestion resulting from a damaged Type A package. The Q_D model assumes that 1% of the package contents is spread uniformly over an area of 1 m^2 and that through the handling of the debris results in contamination of the hands to 10% of this level. It is further assumed that the person is not wearing gloves but would recognize the possibility of contamination and would wash their hands within a period of 5 hours. The equivalent dose to the skin in this scenario is set at 500 mSv. Consideration of alpha particles in the skin dose calculation results in the $Q_{D,skin}$ value being more restrictive than the Q_C value derived from the inhalation exposure scenario, and thus drives the A_2 value for radionuclides associated with TATs. We believe these assumptions made in this model for the determination of the QD values are unrealistic. It is difficult to understand why a transport worker, emergency responder, or a member of the public would handle a damaged Type A package without wearing gloves, and then, not wash their hands for a period of five hours after the exposure.

As a consequence, although Nuclear Medicine Europe members do not question the technical aspects of the revision of A_1 and A_2 values and understand the fact that scenarios are not meant to be requestioned at that time, we wish to highlight the fact that margins could be found:

- it could be considered that the 5 hours period is unlikely in this case,
- for some radionuclides like lead-212 their short period has an impact (the risk is reduced, not taken into account) in the calculations,
- there are discrepancies in the Monte Carlo calculations and the maximal dose coefficients instead of the mean ones were used (as can be seen in the document “Update of the Q system to derive the A1/A2 basic values of the IAEA transport regulations No. SSR-6 – Report of the WG A1/A2 for the 2021/2024 SSR-6 review and revision cycles”, Version 1.1a July 2024, paragraph 5.2).

Once again, the reduction in the A_2 values for radioisotopes associated with TATs is not trivial and will have a negative impact on patient access to life saving care. Consider a Ra-224/Pb-212 generator currently transported in a Type A package; the generator would either require transport in a Type B package or need to be loaded with just 4% of the maximum activity the generator could contain under the current A_2 value. In either case, the cost and operational challenges associated with transport will increase dramatically, either by requiring 25 times more generators and subsequent Type A packages or from the cost of licensing, procuring, and maintaining a fleet of Type B packages, additional to the costs required to adjust manufacturing and hospital

facilities to handle Type B packages. This significant increase in the number of generators required to produce the same quantity of Pb-212 will increase the number of packages in transit and the radiation dose received by nuclear pharmacists eluting these generators by 25 times as a result of the proposed A_2 values.

A 10-year transition period has been included in the revision. This is a welcomed information, as it should give industry time to develop new packages or develop new approaches. However, Nuclear Medicine Europe members also think that this only delays the inevitable increase in operating and capital costs which will ultimately affect patient access and the cost of patient care.

Nuclear Medicine Europe's mission is to advocate for public policies that impact health care, transportation safety, homeland security, and manufacturing to expand access to safe and affordable health care treatments for all. Our member companies prioritize the health and safety of their employees and members of the public and conduct their operations under robust safety cultures. However, Nuclear Medicine Europe members do not support these revisions to the A_2 values that will have a genuine negative impact on patient access to TATs. The reduction in risk to the transport worker, emergency responder, or member of the public needs to be balanced against the lifesaving benefits that these radioisotopes bring to patient care.

Nuclear Medicine Europe strongly recommends that current A_2 values remain unchanged in the current revision cycle of SSR-6 unless it can be demonstrated that the perceived reduction in risk to a hypothetical individual outweighs the genuine negative impact on patient care. These proposed A_2 values have the potential to discourage the development of this lifesaving TAT technology by unnecessarily making it more difficult to get these alpha emitting medical isotopes into the hands of physicians for use with their patients.

If this recommendation is not taken into account and A_2 values are changed in the Regulations for the Safe Transport of Radioactive Material, Nuclear Medicine Europe recommends that those A_2 values benefit from the margins in the $Q_{D,skin}$ calculations, by multiplying those values by 2.