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Consensus nomenclature rules for radiopharmaceutical chemistry — Setting the record straight☆,☆☆

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ABSTRACT

Over recent years, within the community of radiopharmaceutical sciences, there has been an increased incidence of incorrect usage of established scientific terms and conventions, and even the emergence of 'self-invented' terms. In order to address these concerns, an international Working Group on '*Nomenclature in Radiopharmaceutical Chemistry and related areas*' was established in 2015 to achieve clarification of terms and to generate consensus on the utilisation of a standardised nomenclature pertinent to the field.
Upon open consultation, the following consensus guidelines were agreed, which aim to:

- Provide a reference source for nomenclature good practice in the radiopharmaceutical sciences.
- Clarify the use of terms and rules concerning exclusively radiopharmaceutical terminology, i.e. nuclear- and radiochemical terms, symbols and expressions.
- Address gaps and inconsistencies in existing radiochemistry nomenclature rules.
- Provide source literature for further harmonisation beyond our immediate peer group (publishers, editors, IUPAC, pharmacopoeias, *etc.*).

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☆ This is a free access article and can also be viewed on the journal's Web site (www.nucmedbio.com). Complimentary access to this article is available until the next issue publishes online.
☆☆ *Recommended guidelines, assembled by an international and inter-society working group after extensive consultation with peers in the wider field of nuclear chemistry and radiopharmaceutical sciences.*

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1. Introduction

The primary function of nomenclature is to ensure that spoken or written scientific terms and concepts leave no ambiguity in their interpretation. The ultimate intent of generating consensus nomenclature is therefore to create common conventions for terms and definitions, enabling effective and unambiguous communication and understanding within a scientific community.

In order to achieve these goals, the international natural science community agreed to abide by and adopt the use of SI-derived units (1960) [1] and IUPAC rules for chemistry (1921) [2] (SI, International System of Units; IUPAC, International Union of Pure and Applied Chemistry). As the field of radiopharmaceutical chemistry is part of this wider community, it also behoves us to adopt these conventions: to ignore this would be impractical.

Over recent years, within the community of radiopharmaceutical sciences, there has been an increased incidence of incorrect usage of established scientific terms and conventions, and even the emergence of 'self-invented' terms. In order to address these concerns, in 2015 the 'Drug Development Committee' (DDC) of the 'European Association of Nuclear Medicine' (EANM) established an international Working Group on '*Nomenclature in Radiopharmaceutical Chemistry and related areas*' (H.H. Coenen, chair; A.D. Gee, co-chair). The scope of the Working Group was to achieve clarification of terms and to generate consensus on the utilisation of a standardised nomenclature pertinent to the field of radiopharmaceutical sciences. The members were selected on the basis of their scientific good standing and active engagement with relevant scientific societies, e.g. EANM, 'Society of Radiopharmaceutical Sciences' (SRS), 'Society of Nuclear Medicine and Molecular Imaging' (SNMMI), 'International Association of Radiopharmacology' (IAR) and respective national societies.

After conducting a worldwide survey by questionnaire, a summary of the WG's initial recommendations was produced. These were used as 'guidelines to authors' for the submission of abstracts for the 22nd International Symposium on Radiopharmaceutical Sciences (ISRS 2017). Other societies also responded positively to using this summary as guidelines for future abstract submissions at their meetings. In addition to the summary document, a full text was prepared by the WG and presented on the home page of the SRS in a wider context at the end of 2016, requesting comments from peers in the field.

Following a period of open consultation, in order to gain feedback on the proposed recommendations, all received comments and views were considered by the working group. The current guidelines, representing a consensus of the wider field of radiopharmaceutical sciences, were presented and approved at an open forum at the ISRS 2017 in Dresden (May, 2017).

The consensus guidelines presented here aim to:

- Provide a reference source for nomenclature good practice in the radiopharmaceutical sciences.
- Clarify the use of terms and rules concerning exclusively radiopharmaceutical terminology, i.e. nuclear- and radiochemical terms, symbols and expressions.
- Address gaps and inconsistencies in existing radiochemistry nomenclature rules.
- Provide source literature for further harmonisation beyond our immediate peer group (publishers, editors, IUPAC, pharmacopoeias, *etc.*).

2. Scientific concepts, definitions, IUPAC rules and SI-derived units

Below are summarised a number of terms (and descriptions thereof) of relevance to radiochemistry and related fields, which are described and already agreed upon by the wider scientific community, but are often used incorrectly in the literature. (for IUPAC see: [3] and for SI Units see: [4]).

These are complemented by other terms, not described by international convention, but have been adopted within our field and have prompted discussion with a cross-section of experts within the field of nuclear and radio-chemistry in order to clarify and enhance the unambiguous communication of scientific findings and research results within the community.

2.1. Measurement of radioactive decay

The physical *phenomenon* of 'radioactivity' is a *property* of nuclides, which undergo spontaneous nuclear disintegration (radioactive decay). As such, 'radioactivity' is not a measure or quantity. 'Activity' and its SI derived *unit*, the 'Becquerel', are the agreed terms for the *measure* and *quantity* of radioactivity, respectively (cf. [5,6]). According to IUPAC [7] the definitions of these terms are:

'Radioactivity' is defined as the *property* of certain nuclei to spontaneously fragment or rearrange, resulting in the emission of radiation.
'***Activity***' is the *quantitative measure* of radioactivity: The number of nuclear decays, occurring in a given quantity of material over a certain time interval, divided by that time interval.
'***Becquerel***' (Bq) is the agreed SI derived unit for the *quantity* of activity, equal to one disintegration per second.

Pre-SI units (e.g. imperial units) (e.g. mCi, Ci) can also be used, but must be placed in parentheses after the stated SI units (see Appendix B: Table).

N.B.: In current practice, the term 'radioactivity' is often used as a synonym for 'activity' to describe the quantitative measure of radioactive decay. This practice, although strictly speaking, incorrect according to IUPAC definition, can be helpful, as 'activity' is frequently used to describe other physical processes outside of a nuclear context, e.g. 'enzyme activity', 'optical activity' 'structure activity relationship', 'activity coefficient' etc.

The use of the term 'radioactivity' as a substitute for 'activity' therefore may actually add clarity in a cross-disciplinary context. This remains an outstanding issue for discussion with IUPAC; however, the use of 'activity' is recommended until this is resolved.

Generally, the prefix 'radio' indicates a context relating to the phenomenon of radioactivity, e.g. 'radiochemistry', or in combination with analytical methods, where it also denotes the measurement of radiation in addition to other spectroscopic signals, e.g. 'radio-HPLC or radio-TLC'.

Furthermore, the correct terms 'radioactive' and 'non-radioactive' must not be replaced by the often-used lab-jargon 'hot' and 'cold',

respectively, in formal public presentations, manuscripts or official documents.

2.2. Specific activity (A_s) and molar activity (A_m)

According to SI convention, the term 'specific' refers to a physical property as a function of the mass of the material in question; e.g. the specific heat capacity is the heat capacity of an object per kg of mass. Since in chemistry the amount of material (mass) is most often denoted in moles, related chemical properties are indicated in 'molar' units; e.g. molar volume. Because of this possible source of confusion, the following terms are to be used correctly (see Appendix A):

- ***Specific activity***: the measured activity **per gram** of compound; measured in Bq/g or GBq/mg etc.; symbol: $\mathbf{A_s}$.
- ***Molar activity***: the measured radioactivity **per mole** of compound; measured in Bq/mol or GBq/μmol, etc.; symbol: $\mathbf{A_m}$.

Besides in the occasional situation, where the molecular weight cannot be determined, or in the context of radionuclide development (such as the activity of irradiated target material), the term 'specific activity' is to be used instead of the term 'molar activity'.

Due to radioactive decay, the measurement time for the specific activity or molar activity determination must be stated; e.g. 'the specific activity was 50 GBq/mg' or 'the molar activity was 50 GBq/μmol' 2 h after the end of nuclide production, at the end of synthesis, at time of administration, etc.

2.3. Apparent and effective specific and molar activity

In cases where amounts of other material are present in a radiolabelled compound preparation, the measured specific or molar activity is lower than the true value. This often happens if non-labelled materials present in the synthesis mixture are not entirely removed from the labelled product during purification.

Examples are precursor molecules (e.g. spiperone) or a complexing ligand (e.g. DOTA-TATE), which has not been fully removed during the final product purification (e.g. N-[*methyl*-^{11}C]methylspiperone or [^{177}Lu]Lu-DOTA-TATE) after methylation or complexation, respectively, but also any other chemically different impurity.

In such cases, the terms 'apparent specific activity' and 'apparent molar activity' also take into account the amounts of the labelled and non-radiolabelled impurities (using moles, or weight, respectively).

An additional term used in this context is 'effective specific or molar activity'. This addresses the chemically, biologically or pharmacologically 'active' fraction of radioactive and non-radioactive materials. The term is often used to consider other (unknown) material present in a sample prepared, competing with the labelled product in its chemical or biological reactions, for example a complexation process or the binding to a target protein. In this case, however, the 'effectivity' must be determined by an additional analytical process (e.g. receptor or enzyme binding assay, etc.), since it is not simply described by the measured 'activity per total amount (quantity or mass) of material'.

The term 'pseudo' specific/molar activity must not be used, since the impurity has not been intentionally added.

2.4. 'No-carrier-added', 'carrier-free' and 'carrier added'

Since labelled compounds are generally mixtures of an isotopically unmodified compound and isotopically substituted compound(s), the non-quantitative terms 'carrier-free' (c.f.), 'no-carrier-added' (n.c.a.) and 'carrier-added' (c.a.) are often used as a practical indication of specific/molar activity levels. These terms have already been adequately defined in 1981 by A.P. Wolf [8] and intensively discussed by de Goeij and Bonardi [9] and in a thus far unpublished IUPAC draft from 2014 by Bonardi et al. [10].

It is advised, however, that, the term 'carrier-free' should only be used in cases, where an analytical verification has proven this state, i.e. that the theoretical specific or molar activity (absence of all other than specified isotope) has been attained.

Molar activity values approaching the theoretical values can be attained (e.g. technetium-99m in fresh eluates), and that extremely high values have been achieved with iodine-123, fluorine-18 and carbon-11 under certain conditions [11–13]. More recently, however, Eckelman et al. [14] and Lapi and Welch [15] emphasised, that the routinely used radionuclides (e.g. ^{11}C, ^{18}F, ^{99m}Tc, ^{123}I, etc.) are never 'carrier-free'.

Thus, it is recommended to generally avoid the term 'carrier-free' altogether.

N.B.: While 'carrier-free' implies 'no-carrier-added', the reverse is not true!

It has to be pointed out, that all measures, involving the determination of amounts of material (e.g. molar activity or radiochemical purity), should be accompanied by a clear description of the method of its detection.

For example, 'Compound X was obtained with an A_M of 50 GBq/μmol in 98% radiochemical purity as determined by analytical HPLC, using UV absorption at $\lambda = 254$ nm.'

3. Radionuclide and radioisotope descriptors

The enrichment of a chemical compound with an isotope (stable or radioactive) of one or more of the elements, of which it is constituted, is indicated by the symbol of the element (E), together with its mass number (A) (as a superscript in front), within square brackets, [^{A}E], immediately preceding the compound's name or chemical formula.

Example: [^{2}H,^{14}C]benzene, or [^{2}H,^{14}C]C_6H_6, represents the compound *benzene*, enriched or labelled, with stable deuterium and radioactive carbon-14, respectively (see Appendix A).

N.B.: The symbol for isotopic enrichment [^{A}E] should be treated like a syllable, and thus only be hyphenated at the end of a line of text.

If a symbol of an element is given in a chemical formula, or in combination with the name of a chemical compound, together with a mass number '**^{A}E**', but without square brackets, this indicates an isotopically substituted compound, having a composition such that all molecules of the compound only consist of the indicated (radio)nuclide (see Appendix A). This means that the theoretical specific or molar activity of the atom or compound is attained; i.e. it is strictly 'carrier-free', a state rarely achieved in practice (see 'specific/molar activity' above).

Examples of correct and incorrect descriptions of isotopically labelled compounds:

L-[^{13}N]alanine or (S)-[^{13}N]alanine is correct.

[^{13}N]L-alanine, L-^{13}N-alanine, (S)-[^{13}N]-alanine or L-[^{13}N]-alanine is incorrect.

More detailed rules for designating labelling positions (e.g. L-[*methyl*-^{11}C]-methionine or L-[*carboxyl*-^{11}C]methionine), are described in an IUPAC document [7].

In the case of 'fluorobenzene' labelled with fluorine-18:

[^{18}F]fluorobenzene is correct, while

[^{18}F]benzene is incorrect, since benzene does not contain a fluorine atom. Likewise, for technetium-III, forming a 1:1 complex with DTPA: [^{99m}Tc]TcDTPA^{2-} is correct, while [^{99m}Tc]DTPA^{2-} or ^{99m}Tc-DTPA^{2-} is incorrect, since the chelator itself does not contain a technetium atom.

According to these conventions, isotope symbols in square brackets in combination with nouns or verbs are meaningless and are to be avoided in a published chemical text or presentation. Instead, the

element symbol together with the mass number must be used without any brackets. There is no contradiction or likelihood of confusion with the indication of a carrier-free state (see above), since nouns and verbs cannot be enriched or labelled with the indicated isotope.

Consequently, for example [^{11}C]compound, [^{125}I]-substitution, [^{18}F]-derivative and [^{68}Ga]conjugate, are incorrect terms, since these nouns are not names of 'chemical compounds'. These words should instead read as follows: ^{11}C-compound, ^{125}I-substitution, ^{18}F-derivative and ^{68}Ga-conjugate (note: with hyphen!), or preferably: ^{11}C-labelled compound, substitution with iodine-125, ^{18}F-tagged derivative, and ^{68}Ga-labelled conjugate. Analogously, ^{68}Ga-complex of a chelator, ^{111}In-chelate, ^{124}I-iodinated antibody, or ^{99m}Tc-labelled conjugate is to be used.

Equally, terms commonly found in literature such as [^{11}C]labelling, [^{64}Cu]-labelling, or [^{18}F]-(radio)fluorination are erroneous, because 'labelling' and 'radiofluorination' are verbs and nouns and of course do not contain 'chemical elements'. These expressions should instead read: ^{11}C-labelling, ^{64}Cu-labelling and ^{18}F-fluorination, while the prefix 'radio' is redundant here.

Correspondingly, e.g., fluorine-18, technetium-99m, etc., should be used, rather than '^{18}F' and '^{99m}Tc' (at least not without definition) as this would, strictly speaking, infer a carrier-free status for the radionuclide (see above). Generally, terms such as 18F, F18, F-18, or 99mTc, Tc99m, Tc-99m must not be used.

Likewise, '^{76}Br^{-}' (the bromine-76 anion) is more accurately described in texts by the terms [^{76}Br]bromide ion or [^{76}Br]Br^{-}, and by analogy, [^{177}Lu]Lu^{3+} is correct for the description of the [^{177}Lu]lutetium cation rather than '^{177}Lu^{3+}'.

N.B.: It is understood, however, that when used in chemical formulae, nuclide symbols or those of their ions are given without square brackets, and the latter can also be left out in graphical reaction schemes.

These rules apply equally to organic, inorganic and organometallic compounds labelled with metallic radionuclides, and for complexes, they follow the same conventions as given above for covalently labelled compounds, e.g. [^{223}Ra]$RaCl_2$, [^{99m}Tc]$NaTcO_4$, [^{99m}Tc]Tc-MDP, and [^{99m}Tc]Tc-MIBI. Examples of radiometal-labelled conjugates are: '[^{68}Ga]Ga-chelator-Z' (where 'Z' is a place holder for a molecule to which the [metal(ligand)$_n$] complex is attached to, e.g. a peptide or antibody such as in [^{68}Ga]Ga-DOTA-TATE and [^{89}Zr]Zr-DFO-trastuzumab.

It should be mentioned that square brackets are of course also used to denote metal complexes, and care should be taken to avoid confusion (see also IUPAC recommendations 'Nomenclature of Inorganic Chemistry' [16]).
Illustrative examples include [^{99m}Tc][$Tc(CO)_3(OH_2)_3$]$^{+}$, [^{111}In][In(DTPA)]$^{2-}$, [^{111}In][In(oxyquinoline)$_3$] ([^{111}In]In-oxine), or [^{64}Cu][Cu(ATSM)].

The terms '(radio)isotope' and '(radio)nuclide' are often used incorrectly in texts, e.g. erroneously inferring that 'isotope' means 'radioactive nuclide' or even 'labelled compound'.

N.B.: All (radio)isotopes are (radio)nuclides, while the reverse is not true!

For example, both the nuclear reactions ^{176}Yb(n,γ)^{177}Yb (induced by thermal neutrons) and ^{124}Xe(p,2n)^{123}Cs (induced by charged particles) produce radionuclides, but only the first one leads to a radioisotope of the starting material.

For the sake of clarification, the definitions of these terms are repeated below:

- 'Nuclide' indicates an atom, characterised by its numbers of protons (atomic number, identifying its elemental nature) and of nucleons (indicating its mass). There are isobaric, isotonic, isodiapheric, and isotopic nuclides (see chart of the nuclides), which can be stable or radioactive, e.g. ^{1}H and ^{2}H are stable, ^{3}H is radioactive.
- 'Isotopes' are nuclides of the same element (same proton number, i.e., atomic number), but having different numbers of neutrons (hence different atomic mass). Isotopic nuclides of different energy state are called isomeric nuclides, isomeric isotopes or isomers, such as technetium-99g and -99m.
- 'Isobars' are nuclides with the same mass number, such as ruthenium-100, technetium-100, molybdenum-100, etc.
- 'Isotones' are nuclides with the same number of neutrons, but different numbers of protons, such as hydrogen-2 (deuterium) and helium-3, or lithium-8, beryllium-9, boron-10, carbon-11, nitrogen-12 and oxygen-13.
- 'Isodiapheres' are nuclides with the same difference of neutrons and protons, such as boron-10, carbon-12, nitrogen-14, oxygen-16, fluorine-18, neon-20, etc. (difference: zero), or titanium-49, vanadium-51, chromium-53, manganese-55, iron-57, etc. (difference: five excess neutrons).

N.B.: These terms are also defined in the IUPAC Gold Book [7].

4. Radiochemical yield (RCY)

Prior to a discussion of radiochemical yields, two facts should be considered:

- Synthetic chemistry is the science of combining elements and molecules to form compounds in proportion to their components; i.e. in relation to their masses. Since it is the number of atoms/molecules that are generally referred to, amounts of materials are usually expressed in moles.

(Example: 1 mole of carbon is combusted with 1 mole of oxygen gas to form 1 mole of carbon dioxide; $C + O_2 \rightarrow CO_2$.)

- Radiochemistry is the chemistry of radioactive materials (elements, atoms, molecules). With the exception of the field of 'hot-atom-chemistry', the standard laws and conventions of chemistry still apply, with the exception of accounting for radioactive decay.

The correction for the decay of two (or more) radioactive samples to an identical point in time enables the law of relative masses to be employed; i.e. the application of established chemistry concepts, definitions and terms.

'Radiochemical yield', calculated using decay-corrected radioactivity values for products and starting compounds, is identical to the concept of 'chemical yield'.

Logically, the reference time for correction of decay must be identical to describe a particular reaction, irrespective of whether it is chosen to be the end of the radio-nuclide production, the end of bombardment, the start of synthesis, the end of synthesis, or any other convenient reference time point.

4.1. Definition of radiochemical yield (RCY)

Radiochemical yield is the amount of activity in the product expressed as the percentage (%) of starting activity used in the considered process (e.g. synthesis, separation, etc.). The **quantity of both must relate to the same radionuclide and be decay corrected to the same point in time** before the calculation is made (see also Appendix A).

It should be understood, that under this definition, the radiochemical yield is only related to the considered radionuclide, and it does not include compounds labelled with all radionuclides that may undergo the same reaction as the radionuclide of interest (e.g. Ge-68 in Ga-68 preparations).

N.B.: Sometimes the amount of activity produced at the end of a nuclide production cannot be (or is not) determined, for example with gaseous compounds such as [^{11}C]CO. However, it is recommended to measure the activity of resultant product or to determine the 'trapping efficiency' of the labelled starting material and use this to correct the RCY calculation.

If it is accepted that **radiochemical yields are always decay corrected** (as is general convention in the wider nuclear and

radiochemistry fields), it makes 'newly created' terms to describe yields with radioactive materials superfluous. However, it enables an approach that is consistent with mainstream chemistry nomenclature, and it simplifies the understanding of our scientific findings and concepts within and outside the field of radiochemistry.

Furthermore, it is good practise to report, if the radiochemical yield refers to an isolated or non-isolated product.

Consider the following example. 'The (radio)synthesis of compound Y':

The first step of reaction of A and B formed compound C, which was converted into D, oxidised to E and finally hydrolysed to product Y and then isolated by preparative HPLC.

Description of chemical yields: The overall yield of product 'Y' was 40 %. While the yield of C after the first step was 90 %, the yield of the conversion of C to D amounted only to 50 %; but the yield of oxidation and hydrolysis were almost quantitative.

Description of radiochemical yields: The radiochemical yield of product 'Y' was 40 %. While the radiochemical yield of C after the first step was 90 %, the radiochemical yield of the conversion to D amounted only to 50 %; but the radiochemical yield of oxidation and hydrolysis were almost quantitative.

If it is understood that radiochemical yield is identical to chemical yield, the sentences are identical and easily comprehended. If non-decay corrected yields were used, the 'yields' would be totally different to the standard chemical description of yields.

By comparison, colloquial terms for 'radio-yield' found in literature are neither necessary nor helpful: e.g. expressions such as 'radiochemical conversion', 'analytical radiochemical yield', or 'radio-HPLC yield' must not be used as a surrogate for the accepted terms 'radiochemical yield' or 'radiochemical purity'. If these terms were to be used, the previous example would be even more nonsensical.

Also, a term such as 'radiochemical conversion yield' might give the impression that there is a nuclear change. Furthermore, other expressions such as 'radioincorporation', 'radio-oxidation', 'radiohydrolytic' yield etc. would have the same justification.

Equally, 'analytical radiochemical yield' or 'radio-HPLC yield' should not be used as a surrogate for the accepted term radiochemical purity (RCP).

The following are examples of good practice when describing radiochemical yields:

"The radiochemical yield of 'Y' was 67 % (based on HPLC analysis of the crude product)."

"The radiochemical yield* of 'Y' was 67 %", with the following as a footnote:

*'determined by radio-HPLC analysis of the crude product', or

*'non-isolated, estimated by radio-HPLC',

or, in the general experimental section: 'All radiochemical yields were determined by radio-HPLC analysis of the crude product, unless stated otherwise.',

or alternatively use: 'The radiochemical purity of the crude product was 67 %.',

or: "The radiochemical yield of 'Y' determined from an aliquot of the reaction solution amounted to 67 %.",

or: "The radiochemical yield of crude 'Y' was 67% based on the amount of activity eluted from the HPLC column".

Expressions such as 'conversion' or 'incorporation', however, may be used in a semantic sense and are indispensable in context of mechanistic discussions to avoid over-repetition of the same phrase in a text. For example: 'The 'conversion' (or 'incorporation') proceeded with 50% yield. Here it is clear from the context, that the radiochemical yield of the conversion or incorporation is intended. In this case, the prefix 'radio' is to be avoided.

4.2. Definition of activity yield (AY)

Activity yield is the amount of radioactive product expressed in Bq (MBq, GBq), which is obtained from a starting amount of activity (e.g. produced from a cyclotron) and is **not corrected for decay**.

This term is useful, or necessary to indicate the amount of radioactive product obtained from a starting amount of radioactivity. If this is expressed as a 'non-decay-corrected radiochemical yield' in %, it is significantly dependent on losses due to the technical manipulations used, and on their duration, in addition to the yield of the labelling reaction.

Thus, if an 'activity yield' is stated, e.g. to demonstrate the (economic) efficiency of a production process, the time required for all production steps should be carefully described in order to make results comparable! A rigorous scientific report or publication will indicate the length of reaction times used in addition to the time required for other technical manipulations. Only in this case, can starting activity levels be calculated from reported activity yields.

In an experimental section it should also state, if a yield is estimated using the measured radioactivity of the isolated product, or if it was estimated, for example, by HPLC analysis of a sample of the crude product.

It is further recommended to specify how radioactivity, specific activity, etc. are analysed and measured; e.g. determined by HPLC. Although normally reported in the experimental section of publications, it may also be useful to include these clarifications in footnotes on slides and electronic presentations.

5. Definitions of purity

Chemical purity

Chemical purity is the absence of other chemical compounds/species.

N.B.: 1. Chemically pure samples may contain isotopically labelled material!

2. In the context of radiotracers, if chemical purity is described as ratio of the mass of carrier to the mass of other impurities this leads to a nonsensical result, i.e. that as the level of carrier decreases (and molar activity increases) the chemical purity would decrease! It is strongly discouraged, to report chemical purity in this manner. Furthermore, the determination of the chemical purity of radiopharmaceutical preparations containing 'unknown materials', using HPLC and UV detection, is a non-quantitative assessment. This issue requires careful consideration and further discussion. For further reading, see a compilation of criteria for quality assurance and control for radiopharmaceuticals in the chapter by G.-J. Meyer et al. of the monograph by Stöcklin and Pike [17].

Radiochemical purity

Radiochemical purity is the absence of other radiochemical compounds/species.

N.B.: Radiochemically pure samples may contain other non-radioactive chemicals.

Radionuclidic purity

Radionuclidic purity is the absence of other radionuclides.

Radioisotopic purity

Radioisotopic purity is the absence of other radioisotopes. This refers to radioisotopes of the same element, but not to radionuclides of other elements!

N.B.: Here the 'property' of all these purities are defined. In practice, the 'degree of purity', i.e. its measure, is expressed as a percentage or fraction. For example, the 'radionuclidic purity' is given as the percentage of the activity of the radio-nuclide with respect to the total activity of all radionuclides in the material.

Examples:

i) If a sample of acetyl-salicylic acid consists of a mixture of ^{11}C-carbonyl labelled autologous compounds (some labelled in the acetyl-position and some in the benzoyl-position), this material is chemically, radionuclidically, and radioisotopically pure, but not radiochemically.
ii) Iodine-123 labelled para-iodo-bromo-benzene is chemically and radioisotopically pure (i.e., containing no other radioiodine isotopes),

but it may accidentally also contain bromine-77. This compound would neither be radionuclidically nor radiochemically pure.

6. Physical units

Attention must be paid to the correct use of physical units, such as using the correct term for a given unit (see above molar activity for Bq/mole).

For example, in figures, such as radio-chromatograms, the y-axis indicating activity might generally be denoted by 'Activity (arbitrary units)', since quantities are generally not exactly measured.

Another example that is frequently cited incorrectly in reports on nuclide production, is the erroneous use of 'MBq/μAh' to represent the amount of activity produced per μA beam current during a 1-h irradiation, unless this is clearly stated (or the exact time of bombardment is indicated). In fact, the yield of activity should actually relate to the activity produced per current or per number of charged particles applied.

Thus, it is strongly encouraged to report either physical yields in units activity per charge (Becquerel per Coulomb, MBq/C) or saturation yields as activity per current (Becquerel per Ampere, MBq/μA), since all relevant information can be calculated from these parameters.

This issue has been discussed for many years. In some instances, 'measures' of produced activity, using alternative units, may also be justified. If this is the case, however, definitions must be properly given. Such terms and their utility are explained in an IAEA document [18]. The topic was also recently dealt with in detail by Otuka and Takacs [19].

7. Summary and outlook

One only has to read, for example, a few lines of one of the works of Shakespeare to appreciate that language always changes with the passing of time. This is also true for the language of science. The advancement and refinement of concepts, new scientific findings and developments necessitate the creative extension and adaptation or revision of existing terminology. Scientific communication with its sublime goal for exactness and precision also requires international standardisation to ensure unambiguous description and dissemination of findings. The frequent revisions of the 'so-called' IUPAC 'colour books' on chemical nomenclature are an eloquent testimonial to the continued development of scientific language in the chemical sciences. 50 years of rapid advancements in the field of radiopharmaceutical science has also produced a plethora of new terms and conventions, necessitating the review and international harmonisation of the nomenclature discussed within this article. A comparison with an earlier guideline for authors (and editors) is worth reading, as it discusses additional relevant items and provides a compilation of physical units [20].

The urgency and timeliness of the current initiative were affirmed by the considerable amount of positive feedback from our colleagues in supporting the compilation of the guidelines, and the expeditious unanimity reached upon worldwide consultation. Nevertheless, the assembled consensus guidelines should be regarded as exemplars of 'best practice', rather than strict rules or laws 'written in stone'. The widespread adoption of these guidelines will ultimately be the arbiter of their utility and acceptance within the community. This will include their congruity with nomenclature rules from other areas of chemistry, not dealing with radioactivity, which are not the subject of the current initiative. To this end, it is anticipated that further revisions of these guidelines will be necessary at some point in the future. However, the resonance generated during the consultation phase and the broad interest received from journal editors already indicate this as a timely and worthwhile initiative.

As pointed out above, existing international conventions are the basis of agreed nomenclature rules. Nevertheless, it is reasonable to anticipate future revisions aiming to aid clarity in scientific communication and in response to new findings and concepts. Although we generally recommended adhering to the current IUPAC guidance, several discrepancies and differences in IUPAC rules have been highlighted in this manuscript, for which we recommend alternatives agreed by consensus. These include for example: the definition of radiochemical yield (decay corrected vs. uncorrected); definitions of purity; and symbols for specific and molar activity (IUPAC nomenclature is not self-consistent). Furthermore, the wider community judged that 'activity' is too general an expression to unambiguously describe the measure of radioactivity, and should be an issue for further discussion. Until this is resolved, we recommend retaining the use of 'activity', unless the context dictates that ambiguity may result. Further examination and discussion of these differences with IUPAC are in progress, in anticipation of a revision of some radiochemistry-relevant terms in the near future.

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Appendix A. Some definitions from IUPAC nomenclature documents

For completeness and comparison, several extracts of IUPAC Books are given:

The convention for naming radioactive matter is concisely described in 'Nomenclature of Inorganic Chemistry, IUPAC Recommendations 2005': (www.**iupac**.org/fileadmin/user_upload/databases/Red_Book_2005.pdf).

A more detailed treatment of these conventions are provided in chapter II-2 of 'Nomenclature of Inorganic Chemistry II, IUPAC Recommendations 2000' (Red Book II), and in the IUPAC Nomenclature of Organic Chemistry (Blue Book) prepared by Advanced Chemistry Development; found on the ACD website: http://acdlabs.com/iupac/nomenclature. The corresponding 'Compendium on Analytical Nomenclature' (Orange Book) is under revision. The 1988 online version is found via: https://www.iupac.org/home/publications/technical-reports/guidelines-for-drafting-reports/references.html.

As mentioned above, a new draft IUPAC document on 'Terminology on carrier, specific activity, and purities in nuclear and radio-chemistry, radio-analytical and radiopharmaceutical chemistry' by Bonardi et al. [10] is currently under discussion.

Indication of mass, charge and atomic number using indexes (Red Book)

The mass, charge and atomic number of a nuclide are indicated by means of three indexes (subscripts and superscripts) placed around the element symbol.

The positions are occupied as follows:

- *left upper index mass number*
- *left lower index atomic number*
- *right upper index charge*

A charge placed on an atom of symbol A is indicated as A^{n+} *or* A^{n-}*, not as* A^{+n} *or* A^{-n}*.*

For example: $^{1632}S^{2+}$ *represents a doubly ionised sulphur atom of atomic number 16 and mass number 32.*

Hydrogen is an exception in that the three isotopes ^{1}H, ^{2}H and ^{3}H can have the alternative names protium, deuterium and tritium, respectively, and the symbols D and T may be used for deuterium and tritium. However, ^{2}H and ^{3}H are preferred, because D and T can disturb the alphabetical ordering in formulae. These names give rise to the names proton, deuteron, and triton for the cations $^{1}H^{+}$, $^{2}H^{+}$ and $^{3}H^{+}$, respectively. Because the word 'proton' is often used in contradictory senses, i.e., for isotopically pure $^{1}H^{+}$ ions on the one hand, and for the naturally occurring undifferentiated isotope mixture on the other, it is recommended that the undifferentiated mixture be designated by the name hydron, derived from hydrogen.

It has to be pointed out, that the lower-case characters p, d, t and the symbol α are also valid descriptors for the ions of hydrogen and helium, respectively, and are generally used when describing nuclear reactions, e.g., $^{14}N(p,\alpha)^{11}C$, or isotopically substituted solvents, such as DMSO-d_6 in NMR-spectroscopy.

Specifically and selectively labelled compounds (Red Book)

An **isotopically substituted compound** *has a composition such that all the molecules of the compound have only the indicated nuclide(s) at each designated position. The substituted nuclides are indicated by insertion of the mass numbers as left superscripts preceding the appropriate atom symbols in the normal formula.*

An **isotopically labelled compound** *may be considered formally as a mixture of an isotopically unmodified compound and one or more analogous isotopically substituted compounds.*

An isotopically labelled compound is called a **specifically labelled** *compound when a unique isotopically substituted compound is added formally to the analogous isotopically unmodified compound.*

A **selectively labelled** *compound may be considered as a mixture of specifically labelled compounds.*

Specific activity and molar activity (Orange Book proposal)

Specific Activity*: 'The activity (A) of a specified radionuclide, or of a mixture of radioisotopes, in an amount of substance divided by the mass (m) of the total number of atoms present in it. Symbol: $a = A/m$.*

Molar Activity*: 'For a specified isotope, the activity (A) of a molecule incorporating the radionuclide divided by its molecular weight (M) expressed in moles. Symbol: $A_m = A/M$.'*

Status of carrier (Orange Book proposal):

Carrier-free*: 'A radioactive nuclide, which is measurable free from stable isotopes of the corresponding element.'*

No-carrier-added: '*A preparation of radioactive nuclide which is essentially free from stable isotopes of the corresponding element.*

Radiochemical Yield (Gold Book and Orange Book proposal)

'The ratio of the activity of a specified radionuclide of a specified element after its radiochemical separation and its activity originally present in the substance undergoing the radiochemical separation.'

Radiochemical purity **and** ***r*****adioactive purity** (Orange Book proposal)

Radiochemical purity*: 'Ratio of the activity of a radionuclide in a stated chemical species in a material over the total activity of all species containing that radionuclide in this material.'*

Radioactive Purity*: 'Ratio of the activity of a stated radionuclide over the total activity of all radionuclides present in a material.'*

Appendix B. Definitions and units of radiological measures

Measure	Definition	SI-Unit[a]	Older Unit	Conversion Factor
Activity (Decay rate)	Number of radioactive disintegrations per time	Becquerel 1 Bq = 1 s^{-1}	Curie 1 Ci = 3.7 10^{10} s^{-1}	1 Ci = $3.7 \cdot 10^{10}$ Bq 1 Bq = $2.7 \cdot 10^{-11}$ Ci
Energy dose	Total absorbed radiation energy per mass	Gray 1 Gy = 1 J/kg	Rad 1 rad = 10^{-2} J/kg	1 rad = 10^{-2} Gy 1 Gy = 100·rad
Equivalent dose	Energy dose quality factor of type of radiation	Sievert 1 Sv = 1 J/kg	Rem 1 rem = 10^{-2} J/kg	1 rem = 10^{-2} Sv 1 Sv = 100 rem
Ion dose	Electrical charge of ions produced in 1 kg air by radiation	Coulomb/kg	Röntgen R	1 R = $2.58 \cdot 10^{-4}$ C/kg 1 C/kg = $3.876 \cdot 10^{3}$ R

[a] SI Units = International System of Units.

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