

Declaration of Financial Interests

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I have no financial interests or relationships to disclose with regard to the subject matter or interests of this presentation

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Consensus nomenclature rules for radiopharmaceutical chemistry

- Recommendations by an international working group -

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Questionnaire and Consultation Contributors – Too numerous to mention

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“...you should say what you mean,” the March hare went on.

“I do,” Alice hastily replied; -

“At least I mean what I say – that’s the same thing – you know.”

“Not the same thing a bit!” said the Hatter.

“Why, you might just as well say that ‘I see what I eat’ is the same thing as ‘I eat what I see’!

‘You might just as well say’ added the March hare, **“that ‘I like what I get’ is the same thing as ‘I get what I like!’”**

IUPAC – *International Union of Pure and Applied Chemistry* - 1921

SI – *Système international d'unités* - 1960

Review Article

Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands

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1534

JCBFM (2007) 27, 1533-1539

Consensus reached within the PET/SPECT pharmacokinetic modelling community

In vivo imaging of radioligands

RB Innis et al

The binding potential concept was embraced by the expanding field of radioligand imaging and often used as the primary outcome measure of experiments. Over several years, binding potential was defined in different ways and noted with varying abbreviations. The lack of consensus on nomenclature continues to cause significant confusion and often necessitates redundant explanations in manuscripts to clarify the specific terms used by the author. We propose a nomenclature that has broad support among experts in quantitation of *in vivo* radioligand binding.

An international group of experts in pharmacokinetic modeling recommends a consensus nomenclature to describe *in vivo* molecular imaging of reversibly binding radioligands.

Journal of Cerebral Blood Flow & Metabolism (2007) 27, 1533–1539; doi:10.1038/sj.jcbfm.9600493; published online 9 May 2007

Consensus nomenclature rules for radiopharmaceutical chemistry

Background

- 2013** - Discussions at ISRS (International Society of Radiopharmaceutical Sciences) meeting in Jeju, Korea.
- 2014** - Start of EANM Drug Development Committee initiative
 - Trial of questionnaire
 - Questionnaire distribution (email and social media)
- 2015** - Formation of geographically balanced expert Working Group (WG)
 - First working group Face-to-face WG meeting SRS Missouri
 - First draft of consensus document and feedback by WG
- 2016** - Incorporation of summary rules for 2017 SRS Dresden abstract submission
 - Consensus rules posted on SRS website and call for consultation
 - Consultation phase and feedback by peers
- 2017** - Letter to Editor of Nuclear Medicine and Biology and EANM open call
 - post-consultation revision of consensus rules on SRS website
 - Approval of post-consultation Nomenclature Guidelines (May 2017)

Consensus nomenclature rules for radiopharmaceutical chemistry

Babylonian
confusion
of tongues!



IUPAC

[Chemical Terminology \(Gold book\)](#)

[Quantities, Units and Symbols in Physical Chemistry \(Green Book\)](#)

[Nomenclature of Inorganic Chemistry \(Red Book\)](#)

[Nomenclature of Organic Chemistry \(Blue book\)](#)

[Compendium of Polymer Terminology and Nomenclature \(Purple book\)](#)

[Analytical Nomenclature \(Orange book\)*](#)

[Compendium of Terminology and Nomenclature](#)

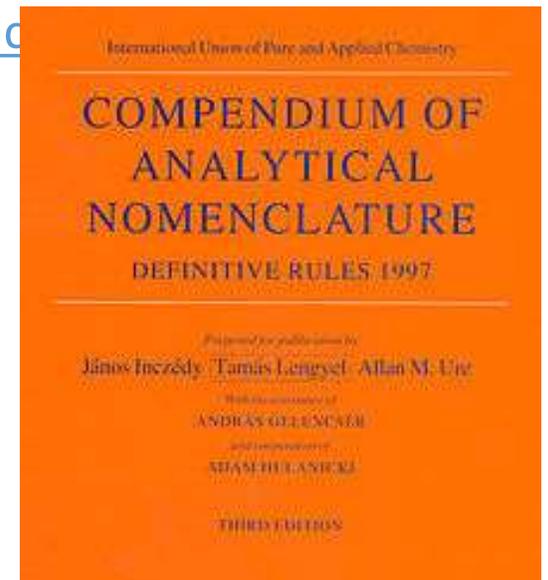
[Clinical Laboratory Sciences \(Silver book\)](#)

[Biochemical Nomenclature \(White Book\)](#)

[Principles of Chemical Nomenclature](#)

*Described as the "Definitive Rules", 3 editions (1978, 1987, 1997) published, updates coming!

**Unambiguous and concerted
nomenclature in science!**



Overview of Nomenclature Good Practice Recommendations

see updated version on SRS website: www.srsweb.org

Activity vs. Radioactivity

Specific Activity A_s (activity per gram)

Molar Activity A_m (activity per mole)

Apparent Activity

Effective Activity

Carrier Free

No Carrier Added

The use of square brackets and $\frac{A}{N}E^n$

Radiochemical Yield (decay corrected)

Activity yield (not decay corrected)

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- Presentation and annotations/comments/explanations -

Types and symbols of (radio)nuclides

IUPAC Red Book: *The mass, charge and atomic number of a nuclide are indicated by means of three indexes placed around the element symbol, with left superscript, left subscript and right superscript, respectively:*



‘Radioactivity’ is defined as property of nuclides showing radioactive decay, as such it is not a quantity or measure (Pure Appl. Chem. 1982 and 1994).

‘Activity’ is the quantity for the measurement of radioactive decay, and its SI-derived unit defined as the ‘Bequerel’ [Bq]. (Values in [Ci] may be added.)

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Specific and molar (radio)activity*

Specific activity - the measured activity **per total amount in gram** of compound present; measured in Bq/g or GBq/mg etc.; symbol: A_s .

Molar activity - the measured radioactivity **per total amount in mole** of compound; measured in Bq/mol or GBq/ μ mol, etc.; symbol: A_m .

An IUPAC task group (Bonardi[†] et al., 2014) defines terms equally and uses same symbols, but a proposal for the new version of the IUPAC Orange Book suggests different symbols:

=> specific activity: $a = A/m$ and => molar activity: $A_m = A/M$

**"Radioactivity" may be used as measure, if it clearly refers to the decay of a radionuclide!*

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Apparent and effective specific and molar (radio)activity

The terms “**apparent specific or molar (radio)activity**” take into account all amounts (weight or mole, resp.) of materials present in a sample, i.e., also all labelled and non-radiolabelled impurities.

The “**effective specific or molar (radio)activity**” addresses the chemically, biologically or pharmacologically ‘active’ fraction of radioactive and non-radioactive materials, considering other (unknown) materials present in a sample, which compete with the labelled product in its chemical or biological reactions, for example in a complexation process or in 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.).

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Status of carrier

The terms carrier-free (c.f.), no-carrier-added (n.c.a.) and carrier-added (c.a.) are practical terms, indicating only roughly the level of specific/molar activity. Besides in case of c.f., n.c.a. and c.a. are **not quantitative measures of the A_s or A_m** - why the latter must be determined in published reports.

“c.f.” indicates the theoretically attainable state that is never reached with radio-nuclides typically used in radiopharmaceutical chemistry, and should be avoided.

IUPAC Orange Book proposal:

Carrier-free: “A radioactive nuclide, which is measurably 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.”

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Types of labelled compounds (IUPAC Red Book):

*An **isotopically substituted compound** has a composition such that **all the molecules of the compound only contain the indicated nuclide(s)** at each designated position.**

**Substituted nuclides are indicated by insertion of the mass numbers as left superscripts preceding the appropriate atom symbols in the normal formula, e.g., $H_2^{18}O$*

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

- It is called a **specifically labelled** compound when a unique isotopically substituted compound is formally added to the analogous isotopically unmodified compound.*
- It is called a **selectively labelled** compound if it is a mixture of specifically labelled compounds.*

***Indicated by the insertion of the mass numbers as left superscripts preceding the respective element symbols, that are put in square brackets, directly in front of a chemical formula or name. e.g. $[^{18}F]FDG$*

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The use of square brackets and of hyphens exemplified:

correct

L-[¹³N]alanine, l-[¹³N]alanine

[¹⁸F]fluorobenzene

[^{99m}Tc]TcDTPA²⁻

¹¹C-labelling, ⁶⁴Cu-labelling,
¹⁸F-fluorination (**with hyphen!**)

¹¹C-compound, ¹²⁵I-substitution,
¹⁸F-derivative, ⁶⁸Ga-conjugate

incorrect

~~[¹³N]L-alanine, L-¹³N-alanine or L-[¹³N]-alanine~~

~~[¹⁸F]benzene (no fluorine atom in benzene)~~

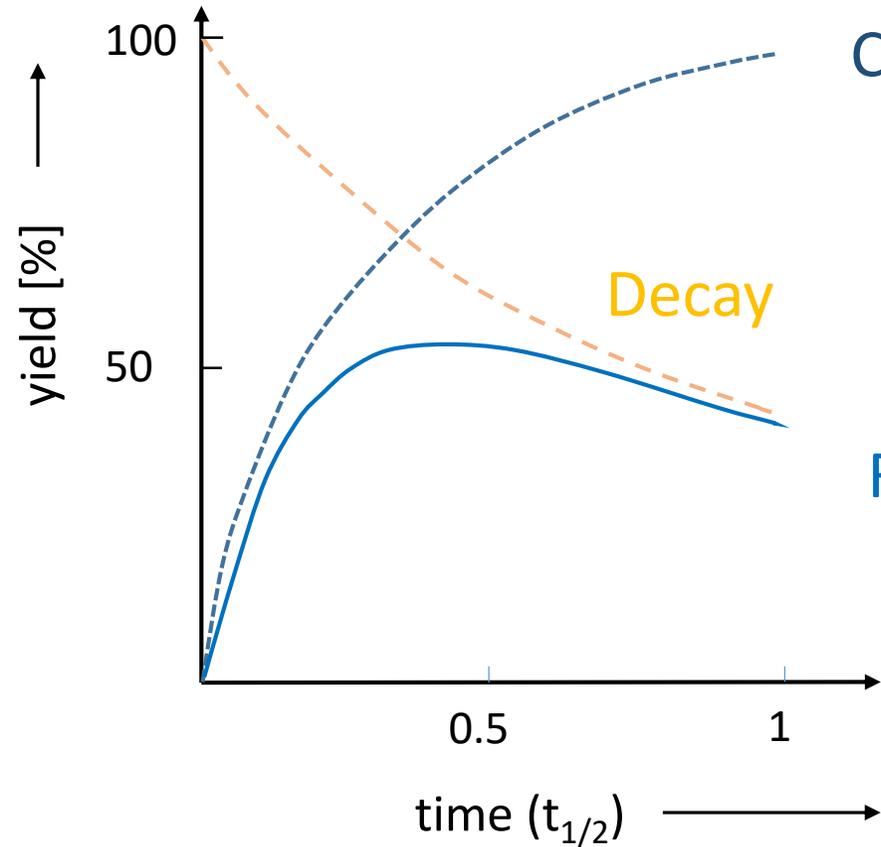
~~[^{99m}Tc]DTPA²⁻ (no Tc in chelator)~~

~~[¹¹C]labelling, [⁶⁴Cu]-labelling, [¹⁸F]-(radio)-
fluorination (**no chemical compound names**)~~

~~[¹¹C]compound, [¹²⁵I]-substitution,
[¹⁸F]-derivative, [⁶⁸Ga]conjugate (**no compounds**)~~

Best practice: ¹¹C-labelled compound, substitution with iodine-125, ¹⁸F-tagged derivative, and ⁶⁸Ga-labelled conjugate. Analogously: ⁶⁸Ga-complex of a chelator, ¹¹¹In-chelate, ¹²⁴I-iodinated antibody, or ^{99m}Tc-labelled conjugate.

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Chemical yield \Rightarrow Radiochemical yield
(a virtual yield!)

Real yield \Rightarrow Activity yield

Reaction sequence:

Always indicate conditions and reference time-point!



Consensus nomenclature rules for radiopharmaceutical chemistry

Radiochemical yield (RCY) is the amount of activity in the product expressed as the percentage (%) of starting activity used in the corresponding process.

The **quantity of both must be decay corrected to the same point in time** before the calculation is made.

- Under this definition it should be understood, that the radiochemical yield is only related to the considered radionuclide.
- It is good practise to report, if the radiochemical yield refers to an isolated or non-isolated product, how it was determined and to which step it is related.

=> Fancy terms for “yields” under different conditions become obsolete!

This contrasts to the definition in IUPAC Gold Book and Orange Book proposal!

Radiochemical Yield : “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.”

Consensus nomenclature rules for radiopharmaceutical chemistry

Definition of activity yield (AY) [alt.: (Radioactivity yield (RAY))]

Activity yield is the amount of radioactive product (**unit: Bq**), which is obtained from a starting amount of radioactivity and is **not corrected for decay**.

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 will indicate the duration of all manipulations and reactions.

Definitions of purity

(Chemical) Purity is the absence of other materials (chemical compounds).

(Indicated in pharmacopoeias as degree of purity; i.e., fraction or ratio in %.)

IUPAC Orange Book proposal

As bare number of ratio, or in % ?

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.”

Consensus nomenclature rules for radiopharmaceutical chemistry

Discrepancies of recommended suggestions with IUPAC rules and definitions:

- Measure: radioactivity vs. activity
- Radiochemical yield: decay corrected vs. uncorrected
 - (Radio)activity yield
- Symbols for spec. and molar (radio)activity
 - Definition of purities

Many concerted efforts with convincing arguments are still necessary to achieve consensus and harmonised rules!

Consensus nomenclature rules for radiopharmaceutical chemistry

Outstanding Issues and Future Prospects:

- continued collection of comments and suggestions
- extension to rules for graphs and (reaction) schemes
 - harmonisation with IUPAC
 - publication in relevant journal(s)
 - convincing of journals (**role of editors!**)
 - revision and adaptation in 2 to 4 years

“Nomenclature is subject of change like all living language!”

