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On the Consensus Nomenclature Rules for Radiopharmaceutical Chemistry – Reconsideration of Radiochemical Conversion

Abbreviated title: Reconsideration of Radiochemical Conversion

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Abstract:

Radiochemical conversion is an important term to be included in the “Consensus nomenclature rules for radiopharmaceutical chemistry”. Radiochemical conversion should be used to define the reaction efficiency by measuring the transformation of components in a crude reaction mixture at a given time, whereas the radiochemical yield is better suited to define the efficiency of the entire reaction process including, for example, separation, isolation, filtration, and formulation steps.

Dear Editor,

We are writing to you with respect to the recent “Consensus nomenclature rules for radiopharmaceutical chemistry” [1,2]. We understand and appreciate that the intent of this initiative was to generate a consensus for terms and definitions used within the field of radiopharmaceutical chemistry. The initiative has been well adopted by the radiopharmaceutical chemistry community and is intended to ensure unambiguous communication of scientific findings and diminish misunderstandings thereof. We concur with these aims and believe that the guidelines presented are an excellent first step in this direction. However, in our opinion, the suggested definition of *radiochemical yield (RCY)* is unclear. As defined, the term RCY can be used to describe the reaction efficiency of a specific radiolabeling step but also the overall process efficiency of the entire radiosynthesis procedure [1,2]. This ambiguity can lead to major misunderstandings with respect to the achievable yield of a given radiolabeling process and isolated products.

Terms that unambiguously distinguish parameters connected to reaction and process efficiencies would prevent contradictions in the communication of scientific results and avoid misunderstandings. As such, we recommend the use of specific terms for both types of efficiencies and proposetherefore to add a new term to the consensus nomenclature rules. Mirroring synthetic organic chemistry terminology, we propose here to use distinct terms for reaction efficiency and the overall process efficiency of a given radiolabeling step, which are misrepresented with the current definition of RCY. In this respect, we propose that ***radiochemical conversion (RCC)*** is an appropriate term to define reaction efficiency.

The current consensus nomenclature rules allow the use of RCY to describe the *procedure efficiency* (in which the activity of the purified product is compared to the starting activity) as well as the *reaction efficiency* (in which chromatographic analysis is usually performed on an aliquot from a reaction solution) [2]. Consequently, RCY can drastically vary for the same reaction depending on how it is measured. For example, in the case of copper-mediated aromatic ^{18}F-fluorinations, this ambiguity becomes especially apparent: for one specific reaction, the "*reaction efficiency RCY*" based on aliquot analysis can be on the order of 75%, whereas the "*process efficiency RCY*" can be below 20% [3]. In this context, the term RCY (given its present definition) is unclear, and reaction efficiency and process efficiency can easily be confused with each other, especially for scientists outside the radiopharmaceutical sciences community. In synthetic organic chemistry, similar challenges have been addressed using distinct terms for reaction efficiencies and overall process efficiencies [4,5]. In this respect, the term *conversion* is frequently used to describe the reaction efficiency, *i.e.* the efficiency by which reactants react with each other. Conversion is typically monitored by chromatography (TLC, GC or HPLC) or NMR spectroscopy and is reported as the ratio between the concentration observed at a given time point and the maximum theoretically achievable concentration of the product. In contrast, the *yield* of a chemical reaction refers to the number of moles of the purified product in relation to the number of moles of the limiting starting material. Consequently, the yield is not only dependent on the efficiency of the reaction (*i.e.* the conversion) but also on other important factors, such as losses occurring during work-up and purification.

The authors of the "consensus nomenclature" guideline are aware of the issues that have arisen from the ambiguity of the term "radiochemical yield", as they have stated in the follow-up report [2]: "In *fact, many papers do not clearly report that the stated radiochemical yields are only based on chromatographic analyses of small aliquots from reaction solutions. The concern with this practice is that the reported product fraction only represents the activity eluted from an HPLC column, overlooking any components that are not eluted or transferred during the analysis workup procedure. This can lead to overestimation of radiochemical yields and inconsistent comparisons of the robustness and applicability of methods across laboratories*." Nevertheless, they maintain that the use of alternative terms for individual reaction processes and steps is "*neither necessary nor advantageous*".

We disagree with this conclusion. Therefore, we propose introducing the term RCC to describe reaction efficiency while keeping the term RCY to describe process efficiency. Figure 1 illustrates how the terms RCC and RCY should be used to describe reaction efficiencies and process efficiencies, respectively, for single-step or multi-step radiolabeling sequences.

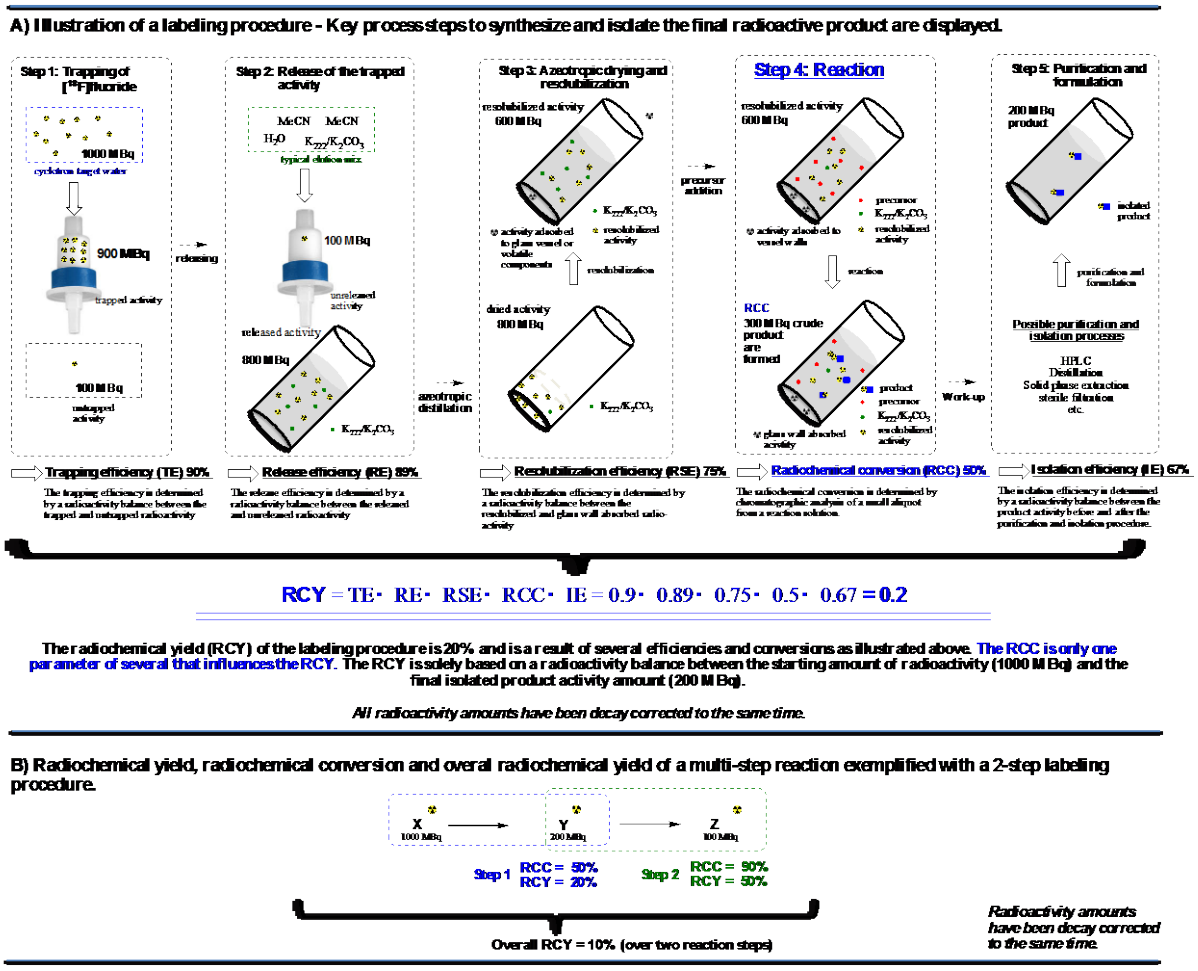

Figure 1: The difference between RCC and RCY as exemplified using a standard ^{18}F-labeling procedure. (**A**) A radiolabeling process is depicted. The labeling process efficiency is described with the term RCY and is dependent on a number of factors, including the reaction efficiency, which is defined by the RCC of the reaction. (**B**) The use of RCC, RCY, and overall RCY illustrated for a two-step reaction.

Glossary:

Reaction efficiency describes the efficiency of the transformation of components in a chemical reaction. In organic chemistry, the reaction efficiency is described with the term conversion [4,5].

Proposed term: Radiochemical conversion (RCC) is a measure to determine the reaction efficiency of a radiochemical reaction. It is based on the reaction of an available radioactive nuclide or synthon with a starting material (decay-corrected). RCC is typically determined by chromatographic analyses (e.g. by radio-TLC or radio-HPLC) of a small aliquot from a reaction solution. Losses during the measurements that could arise from reactant or product volatility, or from retention of a radioactive reaction component within the stationary phase should be accounted for. RCC should not be confused with radiochemical purity (RCP), even though the methodology to determine RCC and RCP is the same. RCP refers to the purity of the isolated product, while RCC describes the content of a product in a crude or semi-purified reaction mixture before isolation and formulation [6].

Process efficiency is a measure of the efficiencies of all sub-processes and/or steps of a specific procedure. If the process in question is a chemical synthesis, the process efficiency can be described using the term "yield" [7].

Radiochemical yield (RCY) is a measure of the process efficiency of a radioactive labeling procedure and refers only to the isolated, purified, and formulated radiochemical products. It is defined as "The amount of radioactivity in the isolated product expressed as the percentage of related starting radioactivity used in the corresponding synthesis (step)" [2]. Both quantities must be decay-corrected to the same time point. The overall RCY for a multi-step synthesis is based on the RCYs for each synthetic step in said process.

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