Radiolabelling of nanoparticles for nanosafety evaluation: direct beam activation.

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Due to their small size and high surface area, metal and metal oxide nanoparticles (NPs) have interesting and unique properties that differ from bulk phase materials. Consequently, they are ubiquitously utilized as food or paint additives, in the construction and semi-conductor industries, cosmetic applications, solar cells, and in many other industrial and societal sectors. The increased use of metal and metal oxide NPs has raised many concerns about potential risks for human health. However, the investigation of the potential toxicological effects and biological fate of the NPs after incorporation into biological systems is extremely challenging because they are very difficult to detect *in vivo*. In addition, many detection methods do not rely on the identification of nanoparticulate materials, but rather on the individual chemical components present in the NPs. As a consequence, natural or background levels of such components may mistakenly be considered as a sign of NP presence.

One possibility to overcome this problem is by labelling the NPs with radionuclides that can lead to their detection in biological systems by means of ultra-sensitive *in vivo* imaging techniques such as Positron Emission Tomography (PET) or Single Photon Emission Computerized Tomography (SPECT). However, the incorporation or attachment of a radionuclide to the NPs without introducing significant modifications of the physicochemical and morphological properties of the NPs is not trivial.

NPs can be radiolabelled by a variety of methods, including: (i) chemical surface attachment of a radiotracer via a linking and/or chelating molecule; (ii) synthesis of the NPs using radiolabelled precursors; (iii) diffusion of radioisotopes into the NPs; (iv) direct neutron activation; (v) direct ion-beam activation and (vi) recoil implantation of radionuclides. The appropriate method should be selected by considering aspects such as the physicochemical and surface properties of the NPs, NP size, the detection technique to be employed and the duration of the study, among others.

In the context of nanosafety and metal or metal oxide NPs, direct beam activation methods are considered valuable strategies because they allow the activation and investigation of the industrial materials themselves without modifying (*a priori)* their bulk and surface characteristics, or their state of aggregation or agglomeration. In this presentation, a brief overview of the different methods for radiolabelling NPs using beam activation will be provided. The pros and cons of each strategy will be discussed and specific examples based on published data and personal experience will be presented. Finally, application of radiolabelled NPs for determining their biodistribution pattern in experimental animals using nuclear imaging techniques, as well as different administration routes, will be provided.