Current activities in the ICRP concerning estimation of radiation doses to patients from radiopharmaceuticals for diagnostic use

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Abstract. A Task Group within the ICRP Committees 2 and 3 is continuously working to improve absorbed dose estimates to patients investigated with radiopharmaceuticals. The work deals with reviews of the literature, initiation of new or complementary studies of the biokinetics of a compound and dose estimates. Absorbed dose calculations for organs and tissues have up to now been carried out using the MIRD formalism. There is still a lack of necessary biokinetic data from measurements in humans. More time series obtained by nuclear medicine imaging techniques such as whole-body planar gamma-camera imaging, SPECT or PET are highly desirable for this purpose. In 2008, a new addendum to ICRP Publication 53 was published under the name of ICRP Publication 106 containing biokinetic data and absorbed dose information to organs and tissues of patients of various ages for radiopharmaceuticals in common use. That report also covers a number of generic models and realistic maximum models covering other large groups of substances (e.g. $^{123}$I–brain receptor substances$^\text{a}$). Together with ICRP Publication 80, most radiopharmaceuticals in clinical use at the time of publication were covered except the radioiodine labeled compounds for which the ICRP dose estimates are still found in Publication 53. There is an increasing use of new radiopharmaceuticals, especially PET-tracers and the TG has recently finished its work with biokinetic and dosimetric data for $^{18}$F-FET, $^{18}$F-FLT and $^{18}$F-choline. The work continues now with new data for $^{11}$C-raclopride, $^{11}$C-PiB and $^{123}$I-ioflupan as well as re-evaluation of published data for $^{82}$Rb-chloride, $^{18}$F-fluoride and radioiodide. This paper summarises published ICRP-information on dose to patients from radiopharmaceuticals and gives some preliminary data for substances under review.
1. Introduction
As early as in 1968, Professor R. E. Ellis was asked by the ICRP to prepare a report on the protection of the patient in radionuclide investigations. The report describes the basic principles for minimising the dose to patients receiving radiopharmaceuticals, and also presents a compilation of the absorbed doses resulting from the administration of the more commonly used compounds in nuclear medicine at that time (ICRP Publication 17, [1]). In view of the growing importance of nuclear medicine and the need for more detailed absorbed dose estimates, a group was appointed early in the 1980s as a Task Group of ICRP Committee 2 and later converted to a Joint Task Group with Committee 3 to:

- provide biokinetic models for current and new radiopharmaceuticals which have come into use since Publication 17,
- supply estimated absorbed doses and effective dose equivalents (later effective doses) to patients, including the range of variation to be expected in pathological states, for adults, children, the embryo and foetus.

As a result of the work of the Task Group, ICRP published in 1987 a report entitled ‘Radiation dose to patients from radiopharmaceuticals’ (Publication 53) [2]. This report contained calculations of absorbed doses and effective dose equivalents per unit activity administered for some 120 radiopharmaceuticals in regular diagnostic use at the time. A first addendum to Publication 53 was included in ICRP Publication 62 [3], where also an age related bladder voiding model was introduced. Publication 62 contained biokinetic and dosimetric (absorbed doses and effective doses) data for six new radiopharmaceuticals, and a table of effective doses per unit administered activity for those radiopharmaceuticals that had been covered in Publication 53. In a second addendum to Publication 53 (ICRP Publication 80) [4], the Task Group presented biokinetic and dosimetric data on 10 new radiopharmaceuticals, and recalculations of dose data for 19 of the most frequently used radiopharmaceuticals in Publication 53 as well as an updated effective dose table. In 2008, a third printed addendum to ICRP Publication 53 was published under the name of ICRP Publication 106 [5] containing biokinetic data and absorbed dose information to organs and tissues of patients of various ages for 25 individual radiopharmaceuticals or groups of radiopharmaceuticals in common use. That report also covers a number of generic models and realistic maximum models covering large groups of substances (e.g. “123I–brain receptor substances”). Together with ICRP Publication 80, most radiopharmaceuticals in clinical use at the time of publication were covered except the radioiodine labeled compounds for which the ICRP dose estimates are still those found in Publication 53. ICRP Publication 106 also includes recommendations related to breast-feeding for mothers who have undergone nuclear medicine investigations.

There is an increasing use of new radiopharmaceuticals, especially substances for PET- and SPECT-investigations and the TG has recently finished its work with biokinetic and dosimetric data for O-(2-[18F]fluorethyl)-L-tyrosine (18F-FET), 3'-deoxy-[18F]-3'-fluorothymidine (18F-FLT) and 18F-choline. The work continues now with new data for 11C-raclopride, 11C-PiB and 123I-ioflupan as well as re-evaluation of published data for 82Rb-chloride, 18F-fluoride and radioiodide. The aim of this paper is to describe the current and planned work within the Task Group with the intention to encourage feed-back and input from the nuclear medicine, medical physics and radiation protection communities.

2. Materials and methods
In the reports [2-5], data on each substance are presented in three subsections: biokinetic model, biokinetic data, and table of absorbed dose per unit of activity administered. Unless otherwise stated, the model refers to intravenous administration.

2.1. Biokinetic and dosimetric data
The calculations are based on biokinetic models and best estimates of biokinetic data for individual radiopharmaceuticals. Furthermore for consistency, standardised biokinetic or dosimetric models are used for the dose calculations. For the bladder, a voiding period of 3.5 hours is used. For the
gastrointestinal (GI) tract, the former ICRP G-I tract model [6] has hitherto been applied. A kinetic model for substances excreted via the liver and gallbladder has been introduced and used. For activity distributed in circulating blood, the fractional blood volume, or, for short-lived radionuclides, the fractional cardiac output is considered for assessing the distribution of the radioactive source in the body [7].

The rates of the biological processes, for example uptake, metabolism, and excretion, are usually given as the half-time of the corresponding exponential function. If the process is assumed to be multi-exponential, the fraction \( a \) of the organ content belonging to each exponential component is given in brackets immediately after the half-time figure. When rates were reported in the cited publications as fractions per time unit \( k \), they are transformed into half-times; \( T = 0.693/k \).

The tables sometimes contain empty spaces under the headings \( T \) and \( a \), usually because the kinetics are described by a complex exponential, or non-exponential, expressions, which cannot easily be defined in the table. This is the case, for example, for activity in the gastrointestinal tract, the gallbladder, and the urinary bladder. In these cases, the tables present only the cumulated activities together with the fractional distributions.

The relative cumulated activities are presented in hours (h). Average organ or tissue absorbed doses are given as milligray (mGy) per megabecquerel (MBq). The effective dose is given as millisievert (mSv) per MBq.

Dose calculations have been performed for adults and 15-, 10-, 5-, and 1-year-old children. The organs (or tissues) are presented in alphabetical order except ‘Remaining organs’, which is placed at the end. The dose to organs or tissues not mentioned in the table can usually be approximated with the value given for ‘Remaining organs’.

For the dose calculations, the MIRD method has been used based on the mathematical phantom and hence \( S \)-values from MIRD Pamphlet 11 [8]. For children, absorbed fractions from Cristy and Eckerman [9] were utilised for the dose calculations. For bone tissue dosimetry, a refined model from Eckerman and Stabin [10] was used.

2.2. Effective dose from various radiopharmaceuticals

The quantity ‘effective dose’ [11, 12] can be of practical value for comparing the relative doses related to stochastic effects from: different diagnostic examinations and interventional procedures; the use of similar technologies and procedures in different hospitals and countries; and the use of different technologies for the same medical examination provided that the representative patients or patient populations for which the effective doses are derived are similar with regard to age and gender. However, comparisons of effective doses are inappropriate when there are significant dissimilarities between the age and gender distributions of the representative patients or patient populations being compared (e.g. children, all females, elderly populations) and the Commission’s reference distribution of both genders and all ages. This is a consequence of the fact that the magnitudes of risk for stochastic effects are dependent on age and gender. Risk assessment for medical uses of ionising radiation is best evaluated using appropriate risk values for the individual tissues at risk, and for the age and gender distribution of the population groups undergoing the medical procedures.

Up to now, the Task Group has calculated effective doses according to ICRP Publication 60 [12]. For the exposure of young children, the risk would be higher, perhaps by a factor of two or three [12]. For many common types of diagnostic examinations, the higher risk will be offset by the reduction in administered activity relative to that to an adult. For an age at exposure of approximately 60 years, the risk would be lower, perhaps by a factor of three and will decrease somewhat thereafter [12]. As indicated above, the specific demographics of the medically exposed population raise issues related to the application of the concept of effective dose as a tool for comparing doses from medical irradiation with other sources of exposure to humans. Nonetheless, the quantity continues to be calculated for diagnostic pharmaceuticals and its use for summarizing and comparing dose between radiopharmaceuticals and other procedures involving ionising radiation has been widely accepted in the clinical community.
3. Results and discussion

Table 1 gives examples of effective doses per unit administered activity (E/A₀) for adults for some commonly used radiopharmaceuticals [2, 4, 5]. To give the reader an idea about the effective dose per investigation, these values have been multiplied with “typical” activities (A₀) used for investigations of adults.

For substances labelled with radionuclides of short physical half-life, the variation of E/A₀ is limited after an i.v. injection. For ¹¹C-substances, E/A₀ varies between 0.0027 and 0.0084 mSv/MBq (around a factor of 3). A “realistic maximum model” [5] for ¹¹C, which could be used for those ¹¹C-substances for which there are not yet better estimates, is defined and gives 0.011 mSv/MBq, or about 1.3 to 3 times the effective doses predicted by the compound-specific ¹¹C models.

For ¹⁸F-labelled substances, E/A₀ varies between 0.016 and 0.028 mSv/MBq (less than a factor of 2), where the higher value itself is a conservative estimate for a group of brain receptor substances.

Also for ⁹⁰ᵐTc-labelled substances, the range of E/A₀-values is limited. Values between 0.0047 and 0.017 mSv/MBq are found.

### Table 1. Effective dose per unit administered activity (E/A₀) for adults and the “typical” activities (A₀) used for adults investigations with the corresponding effective dose (E), for some commonly used radiopharmaceuticals.

| Radiopharmaceutical                                                      | E/A₀ (mSv/MBq) | ICRP Publ. | A₀ᵃ (MBq) | E (mSv) |
|-------------------------------------------------------------------------|----------------|------------|-----------|---------|
| ³H-neutral fat, free fatty acids                                        | 0.22           | 80         | 0.1       | 0.022   |
| ¹¹C-acetate                                                             | 0.0035         | 106        | 500-1000  | 1.8-3.5 |
| ¹¹C-amino acids (generic model)                                         | 0.0056         | 106        | 200-400   | 1.1-2.2 |
| ¹¹C-choline                                                             | 0.0047         | TG         | 400       | 1.9     |
| ¹¹C-brain receptor substances (generic model)                          | 0.0043         | 106        | 400       | 1.7     |
| ¹¹C-methionine                                                          | 0.0084         | 106        | 200-400   | 1.7-3.4 |
| ¹¹C-thymidine [methyl-¹¹C]thymidine                                      | 0.0035         | 80         | 400       | 1.4     |
| ¹¹C-thymidine [²⁻¹¹C]thymidine                                          | 0.0027         | 80         | 400       | 1.1     |
| ¹¹C (realistic maximum model)                                           | 0.011          | 106        | 400       | 4.4     |
| ¹⁴C-neutral fat, free fatty acids                                       | 2.1            | 80         | 0.1       | 0.21    |
| ¹⁴C-urea (normal/¹⁴C-Helicobacter pos.)                                   | 0.031/0.081    | 80         | 0.1-0.2   | 0.003-0.016 |
| ¹⁵O-water                                                               | 0.0011         | 106        | 400       | 0.44    |
| ¹⁸F-amino acids (generic model)                                         | 0.023          | 106        | 400       | 9.2     |
| ¹⁸F-brain receptor substances (generic model)                          | 0.028          | 106        | 400       | 11      |
| ¹⁸F-choline                                                             | 0.019          | TG         | 400       | 7.6     |
| ¹⁸F-FDG                                                                 | 0.019          | 106        | 250-400   | 4.8-7.6 |
| ¹⁸F-FET                                                                 | 0.017          | TG         | 400       | 6.8     |
| ¹⁸F-fluoride                                                            | 0.024          | 53/80      | 400       | 9.6     |
| ¹⁸F-L-dopa                                                              | 0.025          | 106        | 400       | 10      |
| ¹⁸F-FLT                                                                  | 0.016          | TG         | 400       | 6.4     |
| ⁵¹Cr-EDTA                                                              | 0.0020         | 80         | 3-4       | 0.006-0.008 |
| ⁶⁷Ga-citrate                                                            | 0.10           | 80         | 150       | 15      |
| ⁷⁵Se-HCAT                                                               | 0.69           | 80         | 0.02; 0.4  | 0.01; 0.28 |
| ⁸²Rb-chloride                                                           | 0.0017³        | TG         | 2000      | 3.4     |
| ⁹⁹ᵐTc-apticide                                                          | 0.0047         | 106        | 750       | 3.5     |
| ⁹⁹ᵐTc-colloids (large)                                                  | 0.0094         | 80         | 80-500    | 0.75-4.7 |
| ⁹⁹ᵐTc-colloids (small), intratum. inj.                                   | 0.0012         | 106        | 20-100    | 0.024-0.12 |
| ⁹⁹ᵐTc-DMSA                                                              | 0.0088         | 80         | 100       | 0.88    |
| ⁹⁹ᵐTc-DTPA                                                              | 0.0049         | 80         | 300       | 1.5     |
| Radiopharmaceutical | Activity (mCi) | Injection Activity (mCi) | Injected Activity (mCi) | Imaging Activity (mCi) | Imaging Time (min) | Imaging Interval (min) | Imaging Duration (min) |
|---------------------|----------------|-------------------------|------------------------|------------------------|-------------------|------------------------|------------------------|
| $^{99m}$Tc-EC       | 0.0063         | 106                     | 100-1000               | 0.63-6.3               |                   |                        |                        |
| $^{99m}$Tc-ECD      | 0.0077         | 106                     | 100-1000               | 0.77-7.7               |                   |                        |                        |
| $^{99m}$Tc-furifosmin (rest/exercise) | 0.010/0.0089 | 106                     | 300-900                | 2.7-9.0               |                   |                        |                        |
| $^{99m}$Tc-HM-PAO   | 0.0093         | 80                      | 500-1000               | 4.7-9.3                |                   |                        |                        |
| $^{99m}$Tc-IDA derivatives | 0.017     | 80                      | 150                    | 2.6                   |                   |                        |                        |
| $^{99m}$Tc-MAA      | 0.011          | 80                      | 100-200                | 1.1-2.2                |                   |                        |                        |
| $^{99m}$Tc-MAG3     | 0.0070         | 80                      | 70-200                 | 0.49-1.4               |                   |                        |                        |
| $^{99m}$Tc-markers, non-absorbable (fluids/solids) per os | 0.019/0.024 | 80                      | 10-40                  | 0.19-0.96              |                   |                        |                        |
| $^{99m}$Tc-MIBI (rest/exercise) | 0.0090/0.0079 | 80                      | 300-900                | 2.4-8.1                |                   |                        |                        |
| $^{99m}$Tc-IDA derivatives: | 0.0098/0.0097/ |                      |                        |                        |                   |                        |                        |
| Intact ab/F(ab')2-fragm/F(ab')-fragm | 0.011      | 106                     | 750                    | 7.3-8.3                |                   |                        |                        |
| $^{99m}$Tc-pertechnetate, without blocking | 0.013     | 80                      | 100-800                | 1.3-10                 |                   |                        |                        |
| $^{99m}$Tc-pertechnetate, with blocking | 0.0042 | 80                      | 100-800                | 0.42-3.4               |                   |                        |                        |
| $^{99m}$Tc-phosphates and phosphonates | 0.0057 | 80                      | 600                    | 3.4                   |                   |                        |                        |
| $^{99m}$Tc-RBC      | 0.0070         | 80                      | 800                    | 5.6                   |                   |                        |                        |
| $^{99m}$Tc-pertechnegas/-Technegas | 0.012-0.015 | 80                      | 30                     | 0.36-0.45              |                   |                        |                        |
| $^{99m}$Tc-tetrofosmin (rest/exercise) | 0.0080/0.0069 | 106                     | 600                    | 4.1-4.8                |                   |                        |                        |
| $^{99m}$Tc-WBC      | 0.011          | 80                      | 200                    | 2.2                   |                   |                        |                        |
| $^{111}$In-monoclonal antibodies: | 0.22/0.20/0.20 | 106                     | 200                    | 40-44                  |                   |                        |                        |
| Intact ab/F(ab')2-fragm/F(ab')-fragm | 0.054      | 106                     | 170                    | 9.2                   |                   |                        |                        |
| $^{111}$In-octreotide | 0.022 | 53/80                    | 2-20                   | 0.44-4.4               |                   |                        |                        |
| $^{111}$I-iodide, 35% thyroid uptake | 0.02      | 53                      | 200-400                | 4-8                   |                   |                        |                        |
| $^{111}$I-iodide, after ablation, 1% thyroid uptake | 0.016 | 106                     | 150                    | 2.4                   |                   |                        |                        |
| $^{123}$I-fatty acids (BMIPP/IPPA) | 0.050 | 106                     | 180                    | 9.0                   |                   |                        |                        |
| $^{123}$I-brain receptor substances (generic model) | 0.013 | 80                      | 400                    | 5.2                   |                   |                        |                        |
| $^{123}$I-MIBG      | 0.013          | 80                      | 400                    | 5.2                   |                   |                        |                        |
| $^{123}$I-monoclonal antibodies: | 0.262/0.019/0.017 | 106                     | 200                    | 3.4-5.2               |                   |                        |                        |
| Intact ab/F(ab')2-fragm/F(ab')-fragm | 0.024 | 53/80                    | 0.2                    | 4.8                   |                   |                        |                        |
| $^{123}$I-iodide, 35% thyroid uptake | 0.052 | 80                      | 0.2                    | 0.010                 |                   |                        |                        |
| $^{123}$I-iodide, after ablation, 1% thyroid uptake | 0.005 | 80                      | 40                     | 20                    |                   |                        |                        |
| $^{131}$I-iodo hippurate | 0.042 | 106                     | 200                    | 22-84                 |                   |                        |                        |
| $^{201}$Tl-chloride | 0.14          | 106                     | 80                     | 11                    |                   |                        |                        |

Activities currently used in some places and they should not be interpreted as a recommendation of the optimal activity to be administered. The ranges of “typical” activities used are in some cases explained by different indications for the investigations.

TG means preliminary estimate by the Task Group.

Measured with whole-body counter and gamma camera, respectively.

Interim value based on [14] and [15].

For radiopharmaceuticals where the radionuclide has a longer physical half-life, the differences between various substances are larger and more dependent on the biokinetic behaviour of the substances.

For $^{82}$Rb-chloride, now frequently used for myocardial perfusion imaging using PET/CT-technology, a re-evaluation of the “worst-case” dosimetry given in Publication 53 and repeated in Publication 80 is under way. ICRP Publication 53 assumes a model based on relative blood flow to...
various tissues as a proportion of cardiac output. More recent work within the Task Group has been based on the blood volume and blood flow models developed by Leggett et al. [14] and some direct measurements in humans [15].

For $^{123,124,125,131}$I-iodide there is an urgent need to re-evaluate existing biokinetic and dosimetric models. This will be done in parallel to the ICRP-work related to occupational exposure by the different radioiodine isotopes. As soon as new S-values for the new ICRP reference voxel phantoms for adults [13] and for children of various ages are available, the Task Group will use them for improved organ/tissue dose estimates. The new human alimentary tract (HAT) model [16] will also be used. Effective doses now calculated according to ICRP Publication 60 will then also be given according to ICRP Publication 103 [11].

Preliminary work suggests that the implementation of the new ICRP phantoms and of the HAT-model into the dose calculations will not change most organ and effective doses profoundly, but some differences will occur due to the closer proximity of organs and the more explicit treatment of electron transport implicit in the new ICRP phantoms.

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