CHAIRMAN Resource

From:	Carol Marcus <csmarcus@ucla.edu>
Sent:	Friday, May 31, 2019 5:31 PM
To:	Jamerson, Kellee; Cmr. Stephen G. Burns; CMRBARAN Resource; CHAIRMAN Resource; CMRCaputo Resource; CMRWright Resource
Subject:	[External_Sender] Comments for June 10th ACMUI Meeting
Attachments:	NRC-comments to ACMUI for draft RG 8.39 05-30-19.docx; NRC-Siegel-Marcus Stabin HP paper 12-07.pdf

May 31, 2019

Dear Ms. Jamerson:

Attached are my comments for the June 10 ACMUI meeting regarding draft Regulatory Guide 8.39. I wish to make comments at the meeting. I am also attaching the reference mentioned in my comments.

Thank you for your attention and consideration.

Sincerely,

Carol S. Marcus, Ph.D., M.D.

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May 30, 2019

Christopher J. Palestro, M.D.
Zucker School of Medicine at Hofstra/Northwell
131 Grotke Road
Spring Valley, NY 10977

Re: Comments pertaining to draft of NRC Regulatory Guide 8.39

Dear Dr. Palestro:

I have grave concerns about this draft Regulatory Guide (RG) 8.39. I ask that you forward my comments to your committee, at least the subcommittee studying this, and I ask to speak at the June 10, 2019 meeting.

This document fails to repair the mistakes in its predecessor regulatory guide, NUREG-1556 Appendix U. Despite several telephone calls and e-mails and a few letters requesting correction of erroneous material in Appendix U and its predecessor versions, no corrections have ever been made. Finally, in frustration, I, Jeffry Siegel, and Michael Stabin published a paper in Health Physics delineating the errors (this paper did not address the errors in the breastfeeding portion of this RG). The reference is Siegel JS, Marcus CS, and Stabin MG: Licensee over-reliance on conservatisms in NRC guidance regarding the release of patients treated with I-131. Health Phys 93(6):667-677, 2007, and a copy is included with this e-mail. I urge you to read it carefully. Copies were sent to the NRC after publication, but still no corrections were made.

The Health Physics paper addresses the four most flagrant apparently purposeful misrepresentations in the RG. They are (1) assumption of the patient as a point source, with no reduction of exposure to others based upon patient self-absorption, (2) a non-void period for the first 8 hours after I-131 NaI administration, (3) a presumption of an occupancy factor of 0.75 for the non-void period, and (4) a presumption of internal contamination of 10^{-5}. Assumption (1) introduces an overestimate of about 100%, because there are high quality data measuring patient self-absorption. Assumption (2) is ludicrous, as patients are well hydrated before I-131 NaI administration and strongly encouraged to consume copious amounts of fluids. This assumption erroneously raises the calculated exposure to others, as the renal half-time for clearance of the non-thyroidal fraction is about 8 hours. The patients urinate very shortly after I-131 NaI administration and frequently thereafter. Assumption (3) is a completely unsubstantiated

misrepresentation of the occupancy factor and introduces an exposure overestimate of 300%. There is no reason to change the occupancy factor from 0.25 to 0.75. Assumption (4) ignores all the literature and introduces an exposure overestimate of 1000%. All the literature finds that 10^{-6} is an appropriate factor. The present draft RG repairs none of these misrepresentations and also fails to cite literature references which are important and may be found in the Health Physics paper. The NRC appears to be hugely and purposefully overestimating absorbed dose to others in order to dissuade licensees from using the 500 mrem patient discharge rule. There were NRC staff members who fought this rule change for nearly seven years until it was accepted. They still haven't given up.

The draft RG cautions against releasing patients when there are pregnant women or young children at home. This is inappropriate. The radiation limit of 500 millirem is so low that young children and pregnant women may safely receive it. In fact, NRC's limit to the fetus of a declared pregnant woman is 500 mrem, which NRC considers to be safe. The rule does not state this, and neither should this draft RG.

The draft RG amazingly does not reference the Radiation Absorbed Dose Assessment Resource (RADAR) web site, with its excellent tutorial on how to perform these dose calculations and an online exposure calculator for individual patients. The site is free and this past year received 66,000 hits. Unlike this draft RG, RADAR is scientifically solid and uses reliable data for its calculations. Competent nuclear medicine professionals are voting with their mice. They want RADAR, not NRC junk.

The information about breastfeeding patients was always misleading. The original calculations were "take out" calculations using the highest values for breast milk uptake, milk intake, and infant thyroid uptake. No infant ever received these doses, but the idea was that if the administered activity of the radiopharmaceutical in question was less than that which was in the table, it was impossible for the infant to get 100 mrem and no dose calculation needed to be carried out by the licensee. The explanation of the original calculation was in a footnote to the table but was taken out many years ago by Donna-Beth Howe to "save space". What this means is that these are not actual dose calculations but are overestimates by at least 1000%. New calculations were recently performed by Pat Zanzonico, who was formerly on the ACMUI, and were given to the NRC. Dr. Zanzonico's calculations were for infant doses of 100 mrem and 500 mrem. What happened to them? They were supposed to be in this draft RG. In addition, the old RG had calculations for suggested interruption of breast feeding, and often had multiple suggested times for single radiopharmaceuticals based upon administered activity. The lower times for lower administered activities were removed from this draft RG. In addition, this RG only addresses doses of 100 mrem, not the regulatory limit of 500 mrem. They are therefore overestimated by 500 %. So, these values in the RG are *at least* 1500 % overestimates.

The writer of this document opines that she/he is only being "conservative". That is not true. She/he is committing purposeful lying fraud.

In Table 3, NRC lists "Ga-67 and Zr-80 labeled" and doesn't finish the drug. It also lists "C-11, N-13, O-15, Rb-82 labeled" and doesn't finish the drugs. It lists "F-18 labeled" and does not list the drugs. It lists "Lu-177 diagnostic" but Lu-177 labeled compounds are all therapeutic. It lists "Ra-223 and all alpha emitters" and recommends complete cessation of breastfeeding for that infant but there are no calculations and that doesn't make sense. Do the calculation and justify the RBE. Infants are exposed to alpha emitters at least from birth when they are exposed to Rn-222. It doesn't seem to hurt them. Anyway, Ra-223 dichloride is only approved for the treatment of castration-resistant prostate cancer with no known metastases other than bone. It is ridiculously expensive and insurance companies will only reimburse for the FDA approved indication. It is therefore not used off-label, and men don't breast-feed. NRC lists "Ga-55 labeled" but doesn't finish the drug and there is no such radionuclide as Ga-55. Under "Notes" the NRC is behind the times. It certainly does regulate accelerator-produced radioactive material and changed the definition of "byproduct material" to include it. This same erroneous message is in "Notes" in Table 2.

There are many examples of added paperwork requirements that are not in the actual rule and that were not in previous versions of this mess. This is completely inappropriate.

All in all, I find this draft RG, and its predecessors, to be without scientific value and to be grossly dishonest and suggest that the ACMUI recommends that they be trashed. We do not need any NRC "guidance". The NRC only needs to suggest that licensees use RADAR instead.

Thank you for your attention and consideration.

Sincerely,

Carol S. Marcus, Ph.D., M.D.

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Paper

LICENSEE OVER-RELIANCE ON CONSERVATISMS IN NRC GUIDANCE REGARDING THE RELEASE OF PATIENTS TREATED WITH ^{131}I

Jeffry A. Siegel,* Carol S. Marcus,† and Michael G. Stabin‡

Abstract—**Medical licensees are required to comply with U.S. Nuclear Regulatory Commission (NRC) regulations pertaining to the release of patients administered radioactive material. However, use of the associated NRC guidance expressed in NUREG-1556, Volume 9, is completely optional and has been shown to be overly conservative. Rigid adherence to the guidance recommendations has placed an undue burden on nuclear medicine therapy patients and their families, as well as licensees responsible for ensuring compliance with NRC requirements. More realistic guidance has been published by other responsible professional societies and will be presented in this work. These more realistic calculations allow for higher releasable activity levels than the widely adopted NUREG levels, particularly for thyroid cancer patients. The guidance-suggested releasable activity limit is similar to our calculational result for hyperthyroid patients, 2.1 GBq (57 mCi) compared to 2.3 GBq (62 mCi), but is significantly lower for thyroid cancer patients, 6.6 GBq (179 mCi) vs. 16.9 GBq (457 mCi) using the regulatory definition of the total effective dose equivalent (TEDE). Higher limits are both possible and reasonable, if the permissible extra-regulatory definition of the TEDE is used in which the effective dose equivalent (EDE), rather than the deep-dose equivalent (DDE), is determined. We maintain that professionals evaluating compliance with the NRC requirements for patient release, pursuant to 10 CFR 35.75, should use the procedures presented here and not rely automatically on the NUREG.**

Health Phys. 93(6):667–677; 2007

Key words: nuclear medicine; dosimetry; safety standards; medical radiation

INTRODUCTION

U.S. NUCLEAR Regulatory Commission (NRC) regulations for the release of patients administered radioactive material, pursuant to 10 CFR 35.75, authorize patient release according to a dose-based limit, i.e., the dose to other individuals exposed to the patient (U.S. NRC 1997). The dose-based limit, which replaced the activity- or dose-rate-based release limit, <1,110 MBq (30 mCi) or <0.05 mSv h^{-1} (5 mrem h^{-1}) at 1 m in 1997, better expresses the NRC's primary concern for the public's health and safety and makes good scientific sense. A licensee may release patients, regardless of administered activity, if it can be demonstrated that the total effective dose equivalent (TEDE) to another individual from exposure to a released patient is not likely to exceed 5 mSv (0.5 rem).

Individuals exposed to released radionuclide therapy patients can potentially receive radiation doses by two distinct sources: external exposure and internal intake. The TEDE concept makes it possible to combine these dose components in assessing the overall risk to the health of an individual. The TEDE, pursuant to 10 CFR 20.1003, is equal to the sum of the deep-dose equivalent (DDE), due to external exposure, and the committed effective dose equivalent (CEDE), due to internal intake. Thus, TEDE = DDE + CEDE.

U.S. NRC regulations, pursuant to 10 CFR 20.1101, require that applicants and licensees develop, document, and implement operating policies and procedures as part of an overall radiation protection program that will ensure compliance and the security and safe use of licensed materials. These radiation protection policies and procedures for their implementation are neither detailed in the regulations nor required to be submitted as part of the license application (Siegel 2004). Some practitioners have developed their own radiation protection programs, but most have relied on model procedures published by the NRC in guidance documents. There is no question that licensees must comply with NRC regulations, but doing so by adopting regulatory guidance is not necessary. The NRC will accept alternative approaches, but a large number of licensees know that use and adoption of NRC-proposed guidance will clearly provide an acceptable approach to the NRC and many licensees are not able to devote the time or resources

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necessary to establish their own alternative implementing procedures and policies. Although guidance documents do not contain regulatory requirements, if licensees commit to following these procedures they will become conditions of their licenses.

We do not take issue here with the NRC regulations related to patient release. We do, however, note that the associated NRC guidance for licensee compliance with 10 CFR 35.75 as promulgated in NUREG-1556, Vol. 9, Rev.1, Appendix U, *Model Procedure for Release of Patients or Human Research Subjects Administered Radioactive Materials*, has been shown to be overly conservative and places a high burden on nuclear medicine therapy patients and their families, as well as on licensees who adopt the guidance. A series of published studies and guidelines issued by other responsible professional societies has provided guidance in compliance with the applicable NRC requirements at a clearly lower burden to all parties involved. Substitution of these approaches for those in the NUREG will provide a clear benefit to patients and their families, and will make the job of licensees easier as well. We will confine our arguments to the release of patients who have received oral $Na^{131}I$ for the treatment of thyroid cancer or hyperthyroidism, but note that the rationale of the arguments applies also to other radionuclide therapy agents.

The purpose of this work is to critically evaluate the compliance-implementing procedures as proposed in the NUREG and to suggest alternative compliance methods. We examine the guidance methods to assess the external dose component, the internal dose component, and thus the TEDE, and by so doing, demonstrate that the guidance procedures are overly conservative and introduce an unnecessary regulatory burden not codified in NRC requirements. We propose alternative procedures to enable licensee compliance with 10 CFR 35.75, and we recommend that all licensees use these procedures instead of automatic reliance on the NRC guidance documents.

PATIENT RELEASE BASED ON NRC GUIDANCE

The external dose component (DDE)

NUREG-1556, Vol. 9, Rev.1, Appendix U (U.S. NRC 2005) provides model procedures for calculating the external dose to others from exposure to released patients. According to the NUREG, compliance with the NRC regulatory dose limit requirement can be demonstrated by licensees by either: (1) using provided default tables for activity or dose rate at 1 m for a variety of radionuclides; or (2) performing a patient-specific dose calculation.

Use of the "default" values. The "default" patient release values are based on integration of external dose to a maximally exposed individual to total decay after release of patients receiving radioactive material. Two very conservative assumptions are involved in modeling this dose in NUREG-1556, Vol. 9: 1) that the activity in the patient can be represented as an unshielded point source; and 2) that removal of activity from the patient is only due to physical decay of the radionuclide involved. This approach fails to consider the distributed nature of most radiopharmaceutical agents and does not account for the often significant biological elimination that diminishes activity levels in the patient (and thus dose rates outside the patient) over time. This method is highly over-conservative for ^{131}I sodium iodide. Therapy patients receiving ^{131}I do not retain 100% of the radioactivity for the physical half-life of the radionuclide (8 d); rather, a significant portion of the administered activity is not taken up by the thyroid gland and is rapidly excreted. For ^{131}I, the 5 mSv dose limit is predicted in the NUREG to be achieved with an administered activity of 1,221 MBq (33 mCi), or a dose rate of 0.07 mSv h^{-1} (7 mrem h^{-1}) at 1 m, for both thyroid cancer and hyperthyroid patients, representing a value of 4.10×10^{-3} mSv MBq^{-1} (15.2 mrem mCi^{-1}) (this dose per unit administered activity is an order of magnitude higher than if a patient-specific dose calculation is performed; compare to values given below based on eqn 1). In essence, use of NRC "default values" for $Na^{131}I$ represents a return to the historical "30-mCi rule" and is quite regressive, especially since there is no credible origin or scientific basis for this rule (Siegel 2000). Further, empirical data recently obtained by measurement of the dose received by family members of thyroid cancer patients receiving ^{131}I (Grigsby et al. 2000) support and confirm that the use of a 1,221 MBq activity limit for all patients is overly conservative.

Clearly, use of only simple knowledge of administered activity, without consideration of such things as radionuclide clearance from the body and the patient's lifestyle, require issuance of patient instructions to maintain doses to others that are as low as is reasonably achievable (ALARA) that would have to be in place for an extremely long time. Rational analysis suggests that the use of overly simplistic "point-source-radioactive-decay-only" models will significantly overestimate doses to others from $Na^{131}I$ (and many other radiopharmaceuticals), and this has been confirmed by actual measurements (Grigsby et al. 2000). Thus, there is no question that patient-specific dose calculations that would permit the release of patients from radioactive isolation with more than 1,221 MBq must be performed for ^{131}I therapy patients to provide a more complete and appropriate

estimation of dose (and patient release instructions) to individuals likely to be exposed to the patient.

Use of the patient-specific dose calculation. The "patient-specific" dose equation provided in the NUREG that can be used to estimate the likely external exposure to total decay, i.e., DDE at infinite time or $DDE(\infty)$ in mSv (mrem), to an individual from a released radionuclide therapy patient receiving oral $Na^{131}I$ for thyroid cancer and hyperthyroidism is:

$$DDE(\infty) = [34.6\Gamma Q_0]/(100\ \text{cm})^2\{E_1T_p(0.8)[1 - e^{-0.693(T_{NV})/T_p}] + e^{-0.693(T_{NV})/T_p}E_2F_1T_{1eff} + e^{-0.693(T_{NV})/T_p}E_2F_2T_{2eff}\}, \quad (1)$$

where:

- 34.6 = conversion factor of 24 h d^{-1} times total integration of decay (1.44);
- Γ = exposure rate constant for an unshielded point source, for ^{131}I = 0.595 mSv cm^2 MBq^{-1} h^{-1} (2,200 mR cm^2 mCi^{-1} h^{-1});
- Q_0 = administered activity in MBq (mCi);
- E_1 = occupancy factor for first 8-h non-void period = 0.75;
- T_p = physical half-life in days = 8.04 for ^{131}I;
- 0.8 = an assumed factor indicating that 80% of the administered activity is removed from the body only by the physical half-life of ^{131}I during the non-void period;
- T_{NV} = non-void period in days = 0.33 (8 h);
- E_2 = occupancy factor from 8 h to total decay = 0.25;
- F_1 = extrathyroidal uptake fraction = 0.20 in hyperthyroid patients = 0.95 in thyroid cancer patients;
- T_{1eff} = effective half-life of extrathyroidal component = 0.32 d in hyperthyroid patients = 0.32 d in thyroid cancer patients;
- F_2 = thyroidal uptake fraction = 0.80 in hyperthyroid patients = 0.05 in thyroid cancer patients; and
- T_{2eff} = effective half-life of thyroidal component = 5.2 d in hyperthyroid patients = 7.3 d in thyroid cancer patients.

Eqn (1) represents the dose to an individual likely to receive the highest dose from exposure to released ^{131}I patients as it is taken to be the dose to total decay. The equation contains 3 components: (1) a non-void period for the first 8 h after administration; (2) an extrathyroidal component from 8 h to total decay; and (3) a thyroidal component from 8 h to total decay. Eqn (1) can be solved for the external dose component per unit administered activity, Q_0.

In the case of thyroid cancer patients:

- $DDE(\infty)/Q_0$ (mSv MBq^{-1}) = 2.06×10^{-3} {0.135 + 0.0739 + 0.0887} = 6.12×10^{-4} mSv MBq^{-1}; and
- $DDE(\infty)/Q_0$ (mrem mCi^{-1}) = 7.61 {0.135 + 0.0739 + 0.0887} = 2.27 mrem mCi^{-1},

where the percentages of the total dose due to the non-void, extrathyroidal, and thyroidal components are 45%, 25%, and 30%, respectively.

In the case of hyperthyroid patients:

- $DDE(\infty)/Q_0$ (mSv MBq^{-1}) = 2.06×10^{-3} {0.135 + 0.0739 + 0.0887} = 2.39×10^{-3} mSv MBq^{-1}; and
- $DDE(\infty)/Q_0$ (mrem mCi^{-1}) = 7.61 {0.135 + 0.0156 + 1.01} = 8.84 mrem mCi^{-1},

where the percentages of the total dose due to the non-void, extrathyroidal, and thyroidal components are 12%, 1%, and 87%, respectively.

These 2 equations can be solved for the maximum allowable administered activities for authorizing patient release based on the 5 mSv regulatory dose limit. Eqn (1) can also be solved for the maximum allowable dose rates at 1 m, given by $\Gamma Q_0/(100\ \text{cm})^2$. These values are shown in Table 1.

These activity limits, as well as those in later sections, can be applied to all patient releases. According to the NUREG, the parameter values in eqn (1) are "acceptable" values (e.g., the occupancy factors and the representative uptake fractions and effective half-lives) to be used in class-specific dose calculations for patients with thyroid cancer and hyperthyroidism. Thus, individual dose calculations need not be performed on a case-by-case basis for these patients, unless a specific patient's situation warrants the use of parameter values different from those used in eqn (1). For example, the licensee may select more realistic uptake fraction and effective half-life values from the scientific literature or choose to measure the biokinetics in individual patients, measure the dose rate and/or use an occupancy factor <0.25, if appropriate. In these cases, as stated in the NUREG, a patient-specific calculation would be required

Table 1. Maximum activities and dose rates at 1 m for authorizing patient release for thyroid cancer and hyperthyroid patients (based on eqn 1).

	Activity in GBq (mCi)	Dose rate in mSv h^{-1} (mrem h^{-1})
Thyroid cancer	8.2 (221)	0.49 (49)
Hyperthyroidism	2.1 (57)	0.12 (12)

in place of the use of the class-specific values given in Table 1.

This class-specific approach is highly conservative and unnecessarily restrictive. Several assumptions were made by the NRC in assigning values to the parameters used in eqn (1). The two biggest contributors to the conservatism are: 1) use of the exposure rate constant, which is an unshielded point source value; and 2) use of an 8-h non-void period and associated 0.75 occupancy factor. Since a patient is not adequately represented as an unshielded point source (particularly with respect to their extrathyroidal activity distribution), an exposure rate constant accounting for radionuclide distribution and patient attenuation must be used since without such considerations unrealistic and unnecessarily conservative results will be obtained, perhaps as high as a factor of 2 (Sparks et al. 1998; Siegel et al. 2002a).

During the first 8 h after administration, 80% of the ^{131}I administered is assumed to be removed from the body at a rate determined only by its physical half-life to account for the time of the ^{131}I to be absorbed from the stomach to the blood and the holdup of iodine in the urine while in the bladder. The remaining 20% of the administered activity must be associated with some unknown physiological mechanism as it is unaccounted for during this initial 8-h non-void period. It is important to note that there are no scientific data to support the notion of a "non-void" period of any significant length. Patients are hydrated before the administration of $Na^{131}I$ and are strongly urged to drink plenty of fluids for several days afterwards. Patients often void before even leaving the Nuclear Medicine service, and frequently thereafter. $Na^{131}I$ is absorbed within 10–15 min after an oral administration (Loevinger et al. 1988) and upon reaching the blood is immediately filtered out by the kidneys; with large fluid intakes, the patient may typically void hourly.

A recent international controlled study of iodine biokinetics in radioiodine therapy of thyroid cancer (Hänscheid et al. 2006) indicated that the whole body retention of radioiodine was generally described by a biexponential activity-time curve, with no significant activity excretion time delay, based on whole-body probe and gamma camera scanning measurements. The total body residence times obtained (mean value of 24.1 h in hypothyroid patients) were in good agreement with the value of 23.2 h, a value that would be calculated based on the NRC guidance representative values for a 2-component total body retention curve involving extrathyroidal and thyroidal components. In addition, this latter total body residence time of 23.2 h with an associated activity excretion of 48% at 8 h, corresponding to generally hypothyroid patients, is in excellent agreement with that reported in MIRD Dose Estimate Report No. 5 (Berman et al. 1975) for the case of a maximum thyroid uptake of 5% in euthyroid patients. It should be noted that mean whole-body residence times have been observed to be longer for hypothyroid (24.1 h) than euthyroid (17.3 h) patients (Hänscheid et al. 2006). Thus, established models and recent data indicate that approximately 50% of the administered activity is excreted from the body during the NRC's presumed non-void period in the case of a thyroid cancer patient.

The inclusion of the non-void component in eqn (1) has a profound effect on the estimated dose an individual is likely to receive, particularly from released thyroid cancer patients. As demonstrated above, 45% of the total dose is attributable to the non-void component for these patients (Siegel 1999); thus, its inclusion represents an additional factor of 2 conservatism as the 8.2 GBq activity limit in Table 1 is likely to result in a dose of only 2.75 mSv, equal to 3.35×10^{-4} mSv MBq^{-1} (1.24 mrem mCi^{-1}). In support of this claim, a regulatory analysis on the revised 10 CFR 35.75 completed in 1996 (Schneider and McGuire 1996) made no mention of an initial non-void period and estimated, for example, that based on use of only a two-component model consisting of thyroidal and extrathyroidal biokinetics, the maximum likely dose to total decay to individuals exposed to a thyroid cancer patient would be 2.48 mSv from a 7.4 GBq activity administration, equal to 3.35×10^{-4} mSv MBq^{-1} (1.24 mrem mCi^{-1}). For hyperthyroid patients, inclusion of the non-void component has minimal effect (as demonstrated above, the percent of the total calculated dose attributable to this initial non-void period is 12%) and is really not necessary as it is mathematically redundant; approximately 14% of the administered activity is excreted from the body at 8 h based on the NUREG representative uptake fractions and effective half-lives.

Direct measurements are the best way to obtain the dose any individual is likely to receive based on the reality of daily life. Dosimeter measurements obtained in 65 household members of 30 patients who received outpatient ^{131}I therapy for thyroid carcinoma indicated that the measured radiation dose was on average a factor of 10 lower than the radiation dose predicted based on eqn (1) (Grigsby et al. 2000). These empirical data are further evidence demonstrating the overly conservative nature of the dose calculation as implemented through use of eqn (1).

The internal dose component (CEDE)

NRC guidance in NUREG-1556, Vol. 9, Rev.1, Appendix U uses the following equation for the likely internal dose component (i.e., CEDE) for individuals who may come in contact with a released patient who received oral $Na^{131}I$:

- CEDE (Sv) = Q_0 (MBq) $\times$ 10^{-5} $\times$ 1.43 $\times$ 10^{-2} Sv MBq^{-1}; and
- CEDE (rem) = Q_0 (mCi) $\times$ 10^{-5} $\times$ 53 rem mCi^{-1}, (2)

where 10^{-5} is the NRC assumed fractional intake and 1.43 $\times$ 10^{-2} Sv MBq^{-1} (53 rem mCi^{-1}) is the dose conversion factor to convert an intake of ^{131}I in MBq (mCi) to a CEDE in Sv (rem). It is obvious from this equation that the predicted internal dose component per unit activity will always be a constant value of 1.43 $\times$ 10^{-4} mSv MBq^{-1} (0.53 mrem mCi^{-1}). Thus, unlike the guidance for the external dose component, which permits variability and thus patient-specificity, only a fixed or case-specific internal dose component is considered for both thyroid cancer and hyperthyroid patients.

A common "rule of thumb" is to assume that no more than 1 millionth of the activity being handled will become an intake to an individual working with the material. This heuristic was developed for cases of worker intakes during normal workplace operations, worker intakes from accidental exposures, and public intakes from accidental airborne releases from a facility (Brodsky 1980), but it does not specifically apply for cases of intake by an individual exposed to a patient. Admittedly, there are limited data for thyroid uptakes in family members exposed to Na^{131}I patients. Two studies performed in the 1970's (Buchan and Brindle 1970; Jacobson et al. 1978) on the intakes of individuals exposed to patients administered ^{131}I indicated that intakes were generally on the order of 1 millionth of the activity administered to the patient and that internal doses were far below external doses. Based on these two studies, NUREG-1492 (Schneider and McGuire 1996), the regulatory analysis for 10 CFR 35.75, concluded that internal doses are likely to be much smaller than external doses and much smaller than the public dose limit, and therefore did not consider internal exposures in their analyses. In addition, the National Council on Radiation Protection and Measurements (NCRP) addressed the risk of intake of radionuclides from patients' secretions and excreta in NCRP Commentary No. 11, *Dose Limits for Individuals Who Receive Exposure from Radionuclide Therapy Patients* and concluded that "a contamination incident that could lead to a significant intake of radioactive material is very unlikely."

As given in eqn (2), NRC guidance recommends use of 10^{-5} for the assumed fractional intake. According to NRC, this value was chosen in order to account for the most highly exposed individual and to add a degree of conservatism to the calculation. However, no such "highly exposed" individual has ever been found, and no documentation substantiates that this "factor of 10" conservative approach is advisable, necessary, or accurate.

The total effective dose equivalent (TEDE)

Summing the values of $DDE(\infty)$ per unit administered activity, based on the patient-specific dose calculation given by eqn (1) and the CEDE per unit administered activity values based on eqn (2), the TEDE per unit administered activity is given as follows.

In the case of thyroid cancer patients:

- TEDE/Q_0 (mSv MBq^{-1}) = 6.12 $\times$ 10^{-4} mSv MBq^{-1} + 1.43 $\times$ 10^{-4} mSv MBq^{-1}; and
- TEDE/Q_0 (mrem mCi^{-1}) = 2.27 mrem mCi^{-1} + 0.53 mrem mCi^{-1}.

In the case of hyperthyroid patients:

- TEDE/Q_0 (mSv MBq^{-1}) = 2.39 $\times$ 10^{-3} mSv MBq^{-1} + 1.43 $\times$ 10^{-4} mSv MBq^{-1}; and
- TEDE/Q_0 (mrem mCi^{-1}) = 8.84 mrem mCi^{-1} + 0.53 mrem mCi^{-1}.

Using this approach, the internal dose component will always be 23% (1.43/6.12) and 6% (1.43/23.9) of the external dose component for thyroid cancer and hyperthyroid patients, respectively, irrespective of the administered activity.

NRC guidance states that when the internal dose component is less than 10% of the external component, it does not need to be considered (U.S. NRC 2005). Thus, internal contamination will never have to be considered for hyperthyroid patients whereas the summation of internal and external dose components will always be required for thyroid cancer patients if a patient-specific dose calculation is performed. In the case of the NUREG default-value approach, the TEDE is assumed to be equal to the external dose "because the dose from intake by other individuals is expected to be small." The values in Table 1 are therefore valid for the release of hyperthyroid patients, e.g., the maximum releasable activity is 2.1 GBq. However, the Table 1 values cannot be used for thyroid cancer patients, e.g., the maximum releasable activity of 8.2 GBq is not applicable. The dose calculation approach will always result in a maximum releasable activity for thyroid cancer patients of 6.6 GBq (179 mCi) (the constraint that the CEDE is always 23% of the $DDE(\infty)$, which forces a DDE of approximately 4.05 mSv and an associated CEDE of 0.95 mSv to be in compliance with the 5 mSv TEDE limit). Although not applicable, if the same logic is followed, but this time with the constraint that the CEDE always be 6% of the

$DDE(\infty)$, the maximum releasable activity for hyperthyroid patients would be 2.0 GBq (53 mCi).

The advice requiring inclusion/exclusion of the internal dose component in the NUREG for the TEDE calculation has no basis in regulatory requirements; in fact, it adds an "extra-regulatory" burden on licensees. It is also incorrect as it may violate NRC regulations. For example, Example 4 in the NUREG uses the "default" value external dose of 5 mSv for a 1,221 MBq ^{131}I administration and determines a CEDE of 0.17 mSv. Since the internal dose is only 3% of the external dose, it is stated that the CEDE determinations are never necessary in the TEDE calculation if the default-value approach is taken; however, the TEDE will exceed the regulatory limit of 5 mSv (5 mSv + 0.17 mSv = 5.17 mSv) and the licensee would be in violation of NRC regulations.

The maximum activity release values given in this section are based on the assumption that the "patient-specific" dose calculation approach (use of eqns 1 and 2) used for determination of the TEDE is accurate. As described above, the NUREG approach is, at the very least, unjustifiably conservative, potentially by a factor as high as 4 in the case of thyroid cancer patients. The conservatism is due mainly to the assumption of an essentially non-existent non-void period, the use of an exposure rate constant representing an unshielded point source for the extrathyroidal activity biodistribution, and the use of an intake value of 10^{-5}. The more appropriate maximum fractional intake value of 10^{-6} should be used since this level is seldom, if ever, exceeded by the reported data. This "seldom exceeded" criterion was used in the NUREG in Footnote 1 of Table U.6 for selection of the thyroid uptake fraction in the hyperthyroidism case. The impact of these assumptions in the case of hyperthyroid patient release is much less significant since we have shown that the majority of the calculated total dose to others (i.e., 87%) is due to the thyroidal component.

When data are not available, use of conservative calculations may be reasonable, as they can identify or rule out a potential problem and may be used to add a margin of safety to procedures that do not have well-defined outcomes. However, when data are available, as they are in the case of patients treated with $Na^{131}I$ for thyroid cancer and hyperthyroidism, the overuse of conservatism does not serve the goal of radiation protection practice, which is to provide optimization of radiation doses (economic, social, and other factors considered) within a system of dose limitation. Massive conservatism violates the principle of optimization and places an undue burden on those enforcing dose limits and on those subject to the limitations; in this case, radionuclide therapy patients and their families. Importantly, the regulations, pursuant to 10 CFR 35.75(a), do not require any calculational conservatism, let alone that promulgated in the NUREG; licensees must only demonstrate that the TEDE to any other individual from exposure to a released patient is not likely to exceed 5 mSv. Maintaining this calculated dose to others ALARA is the purpose of the required instructions, pursuant to 10 CFR 35.75(b). In point of fact, a patient receiving 1,221 MBq of ^{131}I for hyperthyroidism can potentially expose individuals to a larger radiation dose than a patient receiving 7.4 GBq of ^{131}I for thyroid cancer if appropriate instructions are not provided, due to the much longer retention of a significant fraction of ^{131}I in the body in the former case.

Therefore, we recommend that licensees perform more realistic calculations (e.g., use of an appropriate shielding factor for the exposure rate constant, no non-void period, use of a fractional intake value of 10^{-6}) and not simply automatically adhere to the approaches provided in the NUREG in order to permit realistic release limits and patient instructions that still are clearly in compliance with NRC regulations.

PATIENT RELEASE BASED ON SNM/ACNP GUIDANCE

One alternative approach to that given in NRC guidance that can be used for patient release has been proposed in a Society of Nuclear Medicine and American College of Nuclear Physicians (SNM/ACNP) guidebook (Siegel 2004). Using eqn (1), but substituting an exposure rate constant equal to 0.459 mSv cm^2 MBq^{-1} h^{-1} (1,700 mR cm^2 mCi^{-1} h^{-1}) (Carey et al. 1995), a non-void period of 1 h, and an occupancy factor of 0.25 during this period, the maximum allowable activities and dose rates for authorizing patient release are given in Table 2.

In our opinion, licensees can quite justifiably use the values in Table 2 as their basis for patient release. The maximum activity and dose rate values are higher in Table 2 than in Table 1 due to the use of less conservative and more realistic parameter values. It should be noted that this method assumes that the TEDE is equal to the external dose. This is because the internal dose was

Table 2. Maximum activities and dose rates at 1 m for authorizing patient release for thyroid cancer and hyperthyroid patients (based on SNM/ACNP guidebook).

	Activity in GBq (mCi)	Dose rate in mSv h^{-1} (mrem h^{-1})
Thyroid cancer	18.2 (493)	0.84 (84)
Hyperthyroidism	3.0 (80)	0.14 (14)

considered to be negligible due to the use of an intake factor of 10^{-6}. This is certainly a preferred approach to that given in the NUREG as it results in more realistic activity and dose rate release limits.

PATIENT RELEASE BASED ON METHODOLOGY DESCRIBED IN THIS WORK

We recommend that the patient-specific dose calculation be performed as follows:

$$\text{TEDE} = DDE(\infty) + \text{CEDE},$$

where:

$$DDE(\infty) = [34.6\,\Gamma Q_0]/(100\text{ cm})^2 \times 0.25\{F_1T_{1\text{eff}} \times 0.6 + F_2T_{2\text{eff}}\} \quad (1a)$$

and

$$\text{CEDE} = Q_0\,(\text{MBq}) \times 10^{-6} \times 1.43 \times 10^{-2}\ \text{Sv MBq}^{-1}. \quad (2a)$$

Eqn (1a) includes only 2 components representing the thyroidal and nonthyroidal biokinetic components (the non-void period has been eliminated), the factor 0.6 represents a more accurate correction to the exposure rate constant given in eqn (1) (Siegel et al. 2002a) for the extrathyroidal component (the exposure rate constant is appropriately applicable only to activity confined to the thyroid gland), and F and T_{eff} are the same as those used in eqn (1) for thyroid cancer and hyperthyroid patients. Note that eqn (2a) recommends use of an intake factor equal to 10^{-6}.

Upon rearrangement and summation of eqns (1a) and (2a), the TEDE per unit administered activity is as follows.

In the case of thyroid cancer patients:

- $\text{TEDE}/Q_0\ (\text{mSv MBq}^{-1}) = 2.82 \times 10^{-4}\ \text{mSv MBq}^{-1} + 1.43 \times 10^{-5}\ \text{mSv MBq}^{-1}$; and
- $\text{TEDE}/Q_0\ (\text{mrem mCi}^{-1}) = 1.04\ \text{mrem mCi}^{-1} + 0.053\ \text{mrem mCi}^{-1}$.

In the case of hyperthyroid patients:

- $\text{TEDE}/Q_0\ (\text{mSv MBq}^{-1}) = 2.16 \times 10^{-3}\ \text{mSv MBq}^{-1} + 1.43 \times 10^{-5}\ \text{mSv MBq}^{-1}$; and
- $\text{TEDE}/Q_0\ (\text{mrem mCi}^{-1}) = 7.99\ \text{mrem mCi}^{-1} + 0.053\ \text{mrem mCi}^{-1}$.

In both cases the internal dose component does not have to be taken into account, as it will always be less than 10% of the external dose component. The maximum activities for authorizing patient release are 17.7 GBq (481 mCi) and 2.3 GBq (63 mCi) for thyroid cancer and hyperthyroid patients, respectively, based on the DDE. A better approach would be to neglect the "10% of the external dose" NUREG guidance as discussed above and include the internal dose component in the calculation. The maximum activities for authorizing patient release are then 16.9 GBq (457 mCi) and 2.3 GBq (62 mCi) for thyroid cancer and hyperthyroid patients, respectively, based on the TEDE.

These activity limits are still conservative as they are based on the use of the DDE for the TEDE, which does not account for attenuation and scatter within the exposed individual (pursuant to 10 CFR 20.1003, the DDE is the dose equivalent at a tissue depth of 1 cm), and therefore only approximates the likely surface entrance dose to the exposed individual (Sparks et al. 1998). In situations where doses are calculated rather than measured, we recommend that licensees use the EDE in place of the DDE in the TEDE determination, and according to an NRC Regulatory Issue Summary (U.S. NRC 2003) no prior NRC approval is required. The EDE has been reported to be a factor of 0.6, on average, less than the DDE for ^{131}I (Sparks et al. 1998). Using this permissible extra-regulatory definition of the TEDE (i.e., TEDE = EDE + CEDE), the maximum activities for authorizing patient release are 27.2 GBq (739 mCi) and 3.8 GBq (103 mCi) for thyroid cancer and hyperthyroid patients, respectively. The administered dosages for these patients will virtually always be less than these activity limits, indicating that all patients are immediately releasable based on patient-specific calculations according to NRC regulations.

NRC regulations pursuant to 10 CFR 35.75(b) also require that released individuals be provided with instructions on actions recommended to maintain doses to others ALARA. Pursuant to 10 CFR Part 20.1003, ALARA means making every reasonable effort to maintain exposures to radiation as far below the dose limits as is practical. NRC has stated that "dose" in this context means the TEDE. Internal and external doses are not minimized separately, and ALARA efforts should be directed at minimizing their sum, the TEDE. Since the internal dose is such a small fraction of the external dose, the TEDE can be most effectively minimized by efforts to minimize the external dose component through adequate patient instructions. A three step approach is necessary (Siegel et al. 2002a):

1. An evaluation of individual's living and working conditions must be performed to ascertain whether or not the patient can be safely released;
2. An appropriate patient-specific dose calculation should be performed to ensure that no individual will likely be exposed to a dose in excess of 5 mSv; and
3. Written, not just oral, instructions that are simple and clear must be provided so that the patient can limit the radiation dose to others to as low as reasonably

achievable. The Authorized User (AU) physician must be satisfied that patient compliance with these instructions is highly likely.

Each of these three steps is equally important. Just because patients are releasable based on the patient-specific dose calculation does not mean that these patients should necessarily be released. For example, it is important to know if infants, young children, or pregnant women reside in the released patient's home (or are likely to come in contact with the patient) in order to conclude that the patient should be released and/or in order to provide meaningful instructions to minimize exposure to these individuals, which in the professional opinion of the AU physician will be comprehended by the patient and likely complied with. Any licensee releasing patients without giving due consideration to the three steps above should be considered to be not in compliance with 10 CFR 35.75 [licensees must also maintain a record of the basis for authorizing patient release pursuant to 10 CFR 35.75(c)]. Clearly, regulations will not prevent all unintended exposures. The underlying premise of NRC regulations is that AU physicians will understand radiation safety principles and practices and will make appropriate decisions. Licensees have certain responsibilities and need to implement policies and procedures to ensure adequate and effective radiation safety practices.

The NUREG is of limited value in providing appropriate and adequate patient instructions. As a good example, the suggested durations of the instructions provided for the occupancy factor selection in Section B.1.2 do not differentiate between thyroid cancer and hyperthyroid patients. As demonstrated by our analyses of eqn (1), 30% of the total dose is attributable to the time period from 8 h post-administration to total decay in the case of thyroid cancer patients, while 87% of the total dose is delivered over this same time period for hyperthyroid patients. It seems appropriate, therefore, that the times necessary for the relevant instructions to remain in effect should differ for these two groups of patients. Finally, it is important to note that radioactive articles in the household trash of patients are sometimes appearing at solid waste landfills that have installed radiation monitors to prevent the entry of any detectable radioactivity. Even though the radioactivity levels potentially contained in any household waste of patients released in accordance with 10 CFR 35.75 pose an insignificant hazard to the public health and safety or to the environment, professionals can take steps to avoid issues with landfill owners and operators and even individual states (Siegel and Sparks 2002). It is probably wise to instruct patients to avoid or minimize use of items that cannot be disposed of via plumbing (toilet, sink, dishwasher, washing machine), such as plastic utensils and paper plates (Siegel 2004).

SUMMARY OF MAXIMUM RELEASABLE ACTIVITIES

Table 3 summarizes the maximum releasable activities for both hyperthyroid and thyroid cancer patients presented in this work.

All values in Table 3 were determined based on an occupancy factor of 0.25 for the extrathyroidal and thyroidal components. If a licensee determines that a lower occupancy factor (e.g., 0.125) is justified for a particular patient, then even higher activities would be calculated.

THE LICENSEE'S ROLE IN PATIENT RELEASE

More realistic calculations allow for even higher releasable activity levels, particularly for thyroid cancer patients. The guidance approach involving patient-specific dose calculations results in a releasable activity limit similar to our calculational approach for hyperthyroid patients (2.1 GBq vs. 2.3 GBq), but the activity limit

Table 3. Summary of maximum releasable activities.

Method (TEDE definition)	Activity in GBq (mCi)	
	Hyperthyroidism	Thyroid cancer
1. NUREG		
a. Default value (TEDE = DDE)	1.2 (33)	1.2 (33)
b. Calculation (TEDE = DDE)	2.1 (57)	8.2 (221) (NA)[a]
c. Calculation (TEDE = DDE + CEDE)	2.0 (53) (NA)	6.6 (179)
2. SNM/ACNP		
Calculation (TEDE = DDE)	3.0 (80)	18.2 (493)
3. This work		
a. Calculation (TEDE = DDE)	2.3 (63)	17.7 (481)
b. Calculation (TEDE = DDE + CEDE)	2.3 (62)	16.9 (457)
c. Calculation (TEDE = EDE + CEDE)	3.8 (103)	27.2 (739)

[a] NA = not applicable.

for thyroid cancer patients is significantly lower (6.6 GBq vs. 16.9 GBq) using the regulatory definition of the TEDE. The similarity in the hyperthyroid case is due to the fact that the majority of the estimated dose to others is due to the thyroidal component and the overly conservative assumptions made in guidance have minimal effect. If a licensee chooses to replace the DDE with the EDE, then the release limits are even higher (27.2 GBq and 3.8 GBq for thyroid cancer and hyperthyroid patients, respectively) and now significantly different even for hyperthyroid patients. Thus, it is reasonable to ask the question, "Why have licensees broadly adopted the NUREG guidance for patient release?"

Given that regulatory requirements for patient release have historically been unrealistically conservative and that the current NUREG guidance procedures are still overly conservative, particularly with regard to thyroid cancer patients, it is difficult to justify providing such information to nuclear medicine physicians to determine patient release limits. Perhaps many licensees have adopted these procedures because most of their clinical treatments involving $Na^{131}I$ can be managed under the guidance release limits of either: 1) 1,221 MBq based on the default-value approach; or 2) 2.1 GBq and 6.6 GBq using the patient-specific calculational dose approach for hyperthyroid and thyroid cancer patient treatments, respectively. Rarely, they might argue, is there a need for hyperthyroid treatments involving >1,221 MBq or thyroid cancer treatments with >6.6 GBq and, therefore, the higher activity release limits in our recommended approaches may not be required. The important point is that, quite distinct from medical judgments by physicians in deciding what activity prescription is best suited for their patients, the activity release limits we have determined here from a radiation safety perspective pose little or no adverse impact on the public health and safety. Many institutions are providing thyroid cancer treatments based on a dosimetric approach, rather than an empiric fixed activity, generally involving an activity prescription >7.4 GBq, and these institutions need not be subjected to an unnecessary "tie-down" license condition preventing them from releasing their patients with activities greater than 6.6 GBq.

If more realistic activity limits, as presented and discussed in this work, were given to physicians by their Radiation Safety Officers (RSOs), higher activity administrations might be more routine. For example, treating autonomous hyperfunctioning nodules with empiric fixed dosages of ^{131}I that have been determined solely on the basis of the quantity of activity that would not require hospitalization (currently believed by many to be 1,221 MBq) is a common practice. However, for large nodular thyroid glands, administered dosages, if calculated based on volume and fractional uptake of iodine, could exceed this activity limit (Iagaru and McDougall 2007). It is important to note that RSOs are not required to blindly accept and adopt optional NRC guidance, but they are required to release radioactive patients in a manner that complies with 10 CFR 35.75 and, therefore, must be proficient in determining the likely dose to others from exposure to such released patients. We have shown that less conservative activity levels can achieve these goals. RSOs generally are not able to devote the time or resources necessary to perform complex modeling calculations to verify the adequacy of NUREG recommendations. Thus, it is common practice for licensees to simply adopt NRC guidance documents without critical assessment of their strengths and weaknesses. Uniform adoption of a single standard across the profession also facilitates the work of NRC inspectors. We have demonstrated, however, that a more scientifically sound but still easily implementable approach, i.e., one not requiring patient-specific biokinetic studies and dose calculations, can achieve the same goals as use of the NUREG, and lessen the burden on licensees, patients, and others.

CONCLUSION

Licensees must comply with NRC regulations but are under no obligation to adopt NRC guidance. Presently, there appears to be a considerable degree of confusion as to what is required by the regulations and what is optional, i.e., guidance. Rigid adherence to the guidance recommendations has placed an undue burden on nuclear medicine therapy patients and their families, as well as licensees responsible for ensuring compliance with NRC requirements. We have shown that guidance-suggested releasable activity limits are similar to those we have calculated for hyperthyroid patients, 2.1 GBq (57 mCi) vs. 2.3 GBq (62 mCi), but are much lower for thyroid cancer patients, 6.6 GBq (179 mCi) vs. 16.9 GBq (457 mCi) using the regulatory definition of the TEDE. Higher limits are both possible and reasonable, if the permissible extra-regulatory definition of the TEDE is used in which the EDE, rather than the DDE, is determined. We maintain that professionals evaluating compliance with 10 CFR 35.75 should use the approaches presented here to comply with NRC requirements. These approaches are easily implementable by licensees, as they do not require patient-specific biokinetic studies and dose calculations.

A repeat of the quiescence with which NRC's "30-mCi rule" was accepted by those in the radiation safety community is not justified. As chronicled by Siegel (2000), this activity limit, lacking scientific justification or evidence demonstrating it would actually

present a hazard to the public health and safety, was responsible for inappropriately low treatment activities, unnecessary patient hospitalizations and increased health care costs for over 50 y.

Use of the 1,221 MBq activity (or 0.07 mSv h^{-1} at 1 m dose rate) patient release limit based on the NRC guidance "default" approach should never be employed by any licensee permitted to release patients pursuant to 10 CFR 35.75. These values indicate lower limits for which NRC does not believe it necessary to perform patient specific calculations to demonstrate that others potentially exposed to a released patient will not likely receive a radiation dose that exceeds 5 mSv. However, the assumptions made by the NRC in arriving at these guidance values are inaccurate and unjustifiably conservative. Even if a licensee were to follow the patient-specific dose calculational approach provided for in NRC's NUREG guidance document, thyroid cancer and hyperthyroid patients receiving greater than 6.6 GBq and 2.1 GBq, respectively, would always have to be hospitalized. There is also no scientific basis or justification for these so-called "forced activity level" confinements. The NUREG patient release methodology also introduces a regulatory burden not as yet codified in NRC requirements. Indeed, patients, particularly thyroid cancer patients, can be released in accordance with NRC regulations with much higher activities, as demonstrated in this work, without adversely impacting on the public health and safety.

Patients and their families share the largest burden when overly restrictive release criteria are enforced. Alternative guidance for patient release by stakeholder professional organizations is available for use (Siegel 2004). Licensees may adopt and implement the approach presented here, or they could develop their own appropriate approach given that a wealth of scientific literature now exists (Siegel et al. 2002b; Mathieu et al. 1999; Barrington et al. 1999; Zanzonico et al. 2000; Venencia et al. 2002; Siegel et al. 2002a). Possible consequences of overly rigid adherence to the NUREG procedures include the under-treatment of patients, issuance of overly restrictive release instructions, and unnecessary confinement of patients to hospital beds. The significant and unjustified additional cost to patients and their loved ones, the requirement for hospitals to prepare and decontaminate unneeded rooms so that staff can receive unnecessary radiation exposures, and the adoption of substandard patient release policies associated with licensee adherence to NRC patient-release guidance should be critically re-evaluated given the guidance presented in this work. These procedures are in compliance with NRC requirements and their use can lessen the burden on licensees.

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