1/24/02

Mr. John Mullauer
Health Physicist, Region III
United States Nuclear Regulatory Commission
801 Warrenville Road
Lisle, IL 60532-4531

Dear Sir,

The treatment of feline hyperthyroidism using I^{131} has become commonplace in veterinary medicine. Usually this is performed at an academic institution or a specialty practice equipped to deal with the radioactivity before and after it is administered to the cat (oral, subcutaneous or intravenous), the radioactive waste produced by the cat, and the exposure to people caring for the cats. Dr. Ralph Weichselbaum (with whom you have spoken about this issue), Dr. Carl Jessen, and I have attempted to publish a manuscript in which we tried to use pretreatment variables to predict the length of time the cat would have to be isolated. During the scientific review of this manuscript, we had the misfortune of dealing with what I will refer to as a "hostile reviewer" (hereafter referred to as the second reviewer). The problem, at least as we interpret it, is that the reviewer has **issues** how long we keep the cats and the low-level at which we dismiss (unrestricted) them (e.g. $\leq$ 2.0 mR/hr at the level of the thyroid gland). We also sense that this reviewer does not want the manuscript because it brings up a somewhat conservative approach to the handling of radioiodine-treated cats.

With that as background, Ralph, Carl and I decided to seek a determination (as mentioned in the NRC Regulations) about the dismissal restrictions on these cats. It seemed futile to argue about the manuscript when the real issue was radiation emission at dismissal. As you will see from the exerpts pasted-in from the reviewer's comments, he/she is using different parts of the NRC Regulations including what is the minimum isotope quantity which must be labeled to make his/her arguments. Our further concern is whether this is a matter of using what is written to one's own ends (e.g. the business of treating cats and getting then out of a facility quickly???). The reviewer did not want to recognize that not everyone thought the way he/she did about dismissing radioactive cats in either a restricted or unrestricted manner. Thus we are coming to you for a determination. Our concern and confusion was only fostered by a search of the world wide web. Searching on the term "hyperthyroid cat", I found several web pages describing dismissal times as early a 2 days post radioiodine administration. The standard dose is about 3-5 mCi and we would keep such a cat for 15 to 20 days (e.g. until the gamma emissions were at or below the level defined above). While some of these early dismissals are "restricted" (e.g. limited cat contact, flushable cat litter, hopefully no cat urine outside the litter, etc.), others were not so specific. We need to know what the NRC will approve. Copy of the manuscript is also enclosed.

The "second reviewer" has referred to our approach as "unethical" because it involves what he/she considers excessive and unnecessary separation of the cat from its owner. As you know, we have been told that our endpoint is at the level wherein the cats are "running on fumes" from the original I^{131}dose. We have also been told that we don't understand the difference between mR and mRem when it comes to the interpretation of the NRC regulations. Our approach was to keep it in terms of emissions from the cats which differed from the opinion of the "second reviewer" who told us of the approach defined below:

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d. It is unfortunate that the authors are not aware of the relationship between radiation emitted by the thyroid gland and radioiodine metabolism. Using the references given in the previous review, it is easy determine that the total amount of radioiodine left in the cat, when surface exposure rate is 2mR/hr, would be between 0.2 to 0.25 microCi depending on the cat size and compartmental model used. This is the reason why this reviewer stated earlier that the cats were running on "radioiodine fumes". At such low level of radioiodine in the body, no association is expected to be found between time to reach that level and any biologic parameters. The authors may be interested to know that the exemption limit for iodine is 1 microCi for uncontrolled release and 10 microCi for confined (indoors) release (CFR10 Part 20 Section 20.1905 and section 20.402 Appendix C).

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To provide further perspective, I have enclosed below the points made by the "second reviewer" which are related to the endpoint at which the cats can be dismissed. Particularly, we have not addressed calculated "permissible body burden" in the I^{131}-treated cats which seems to be a point made by the "second reviewer". If I am interpreting his/her argument correctly, their point is that regardless of the emission rate at surface (e.g. our endpoint of < 2.0 mR/hr), if the body burden is calculated to be sufficiently low (e.g. < 1.0 micro Curie), it does not matter. While there may be some overlaps in the regulations, we should know if calculated body burden outweighs emissions at surface. Similarly, we need to know if extrapolated human absorption by the owners from I^{131}-treated cats supersedes emissions at surface near the thyroid. If this is the case, our respective facilities are being too conservative. If this is not the case, the "second reviewer" is blocking the publication of our manuscript based in part on their interpretation of the NRC regulations.

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e. The authors' interpretation of the CFR is incorrect (Page 4). CFR10 Part 20 Section 20.1301states that " The licencee shall conduct operations so that 1) dose equivalent to public does not exceed 100 mrem (1 mSv) in a year and 2) the dose in any restricted area does not exceed 2 mrem (0.02 mSv) in any one hour ". The authors are correct in stating that Federal Regulation treats animals bearing radioactive as radioactive waste. However, they do not seem to perceive the difference between mR/hr (unit of exposure rate) and mrem/hr (unit absorbed dose rate). The references provided to the authors should suffice to demonstrate that an exposure rate of 2 mR/hr at skin surface above the feline thyroid gland does not translate into dose equivalent rate of 2 mrem/hr in a human being. It would be easy to calculate that if an owner was to hold his/her cat 24 hours a day in his/her arms with an initial surface exposure rate of 2 mR/hr, the absorbed dose resulting from exposure from the cat would never exceed 0.05 mrem/hr (5 10^{-4} mSv) in any hour and the cumulative absorbed dose would not exceed 13 mrem in a year.

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Study design. The choice of an exposure rate of 2mR/hr at skin surface of the thyroid gland as an endpoint in this study precludes any analysis of simple biologic parameters affecting radioiodine metabolism. The low exposure rate measured reflects the fact that the thyroid glands were running on "radioiodine fumes" when the cats were released. The wide variation of times to reach that point is therefore not surprising and should be discussed in the Discussion section to explain that explanatory variables were not found in this study. The choice of the predictive parameters analyzed in this study should also be strongly justified. There is evidence in the literature that these parameters are not ~~simply related to~~ radioiodine and thyroid hormones metabolism. (Broome, AJVR, 1987; Hays, Endocrinology, 1988; DiBartola, JAVMA, 1996).
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Title and abstract are misleading. 2 mR/hr exposure rate for release of radioactive sources (cat bearing radioiodine in this study) is not dictated by the guidelines of the US Code of Federal Regulation. An exposure rate of 2mR/hr at skin surface of the thyroid gland may be a specific criterion for release of cats treated with radioiodine in the State of Minnesota (if so, it should be noted), but it is not required by the US Code of Federal Regulation and has no justification in terms of radiation protection. The purpose of the code of federal regulations is in part to control the disposal of licensed material by any licensee in such a manner that the total dose to an individual member of the public does not exceed the standards for protection against radiation. 10 CFR Part 20, "Standards for Protection Against Radiation," requires that after release of animals bearing radioactive material (i.e., unsealed radioactive source): 1) the total effective dose equivalent to individual members of the public does not exceed 1 millisievert in a year and the dose rate from the radioactive source (treated animal) does not exceed 0.02 mSv in an hour for continuous contact between animal and member of the public (§ 20.1301) and 2) amount of radioactive material released (urine and feces) does not exceed values in Appendix B to § 20.1001--20.2401. The methods for calculating absorbed dose from exposure to animal patients regarded as unsealed radioactive waste by the regulation is provided in 10 CFR Part 35. Using this formula a 2mR/hr exposure at skin surface is unnecessarily low and far below the limits required by the US CFR. In CFR 10, a radiation field of 2mR/hr is used as a criterion to categorize public vs controlled/restricted areas.

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The use of such a conservative criteria of release in the study results in an unnecessarily long isolation period which would be considered as unethical by most veterinarians.
As a result, the authors must indicate in the Introduction or Discussion section that their choice of criteria of release is based on fear of litigation in the state of Minnesota or any other reasons but has no radiobiologic, dosimetric or radiation safety basis.

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h. Unless the pancake probe was calibrated by the manufacturer for Iodine-131, measurements with the instrument are about 20% lower than the instrument reads (these measurements were made in our State Laboratory, data are also available from the manufacturer). This indeed introduces another confounding variable in the study. In addition the geometric configuration of the thyroid size - window size of the GM detector is unfavorable for accurate measurements. In essence this means that the exposure rate was variable at the time of release and for the most part unknown. The authors may want to contact a qualified radiation safety officer to determine what would be the most appropriate instrument for their study.

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If the "second reviewer" is correct and his/her approach/interpretation will be considered acceptable by the NRC, then the approach you use in your facility and the similar one we use at the University of Minnesota is apparently too conservative. What we hope to establish is whether we're being too conservative or whether the "second reviewer" is being too liberal with his/her interpretation of the NRC regulations. If that is the case, then a number of the differences between us and the "second reviewer" over our manuscript are rendered moot. Furthermore, we all (you, me, the U-MN, and "second reviewer" have legal concerns when treating hyperthyroid cats. We want to operate within the regulations. If our interpretation is correct, the "second reviewer" should be informed via Dr. Thrall (to preserve reviewer anonymity) that what they are doing is not approved by the NRC. The "second reviewer's" comment that our criteria for release "is based on fear of litigation in the State of Minnesota or any other reasons, but has no radiobiologic, dosimetric or radiations safety basis" seems at the core of this issue. I hope the NRC will provide some insight.

Please let me know if you need anything else other than this information and the enclosed manuscript.

Yours truly,

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Relationship between pretreatment patient variables and a low-emission end-point radioiodine isolation time for hyperthyroid cats

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Running Head: Feline isolation time following oral radioiodine hyperthyroid treatment

Abstract:

A 3.06 - 10.8 milliCurie (1.13 - 3.7 x 108 Becquerels) oral dose of Iodine-131 (radioiodine) was administered to 150 hyperthyroid cats. A forward stepwise regression analysis was used to determine whether pretreatment total thyroxine concentration (T-4), serum creatinine concentration, body weight, age, I131 dose, and concurrent cardiac medication administration (specifically excluding thyroid suppression drugs) could be used as pretreatment predictors of isolation time. The benchmark for unrestricted dismissal was a gamma radiation exposure rate of less than 0.02 millisievert/hour (interpreted as <2.0 mR/hr at skin surface over thyroid region at dismissal). The mean isolation time was 16.67 days with a standard deviation of 4.42 days. No clinically relevant, statistically significant relationship between the analyzed variables isolation time was found. The size of the standard deviation suggests that there are other influences on the metabolism and excretion of radioactive iodine that confound quantification and analysis.

Introduction:

Radioiodine therapy as an alternative to medical and surgical therapy for feline hyperthyroidism has been discussed in detail[1-17]. Despite numerous reports of radioiodine treatment, there is no information available on whether the pretreatment total thyroxine concentration (T-4), serum creatinine concentration, body weight, age, and concurrent cardiac medication administration (specifically excluding thyroid suppression drugs) have any clinically exploitable relationship to the duration of necessary patient isolation. Based on past experience and measurements, isolation times are specified by individual treatment facilities in terms of average length of stay depending on administration route, dose of radioiodine administered, past experience of the treatment facility, and interpretation of applicable regulations governing radioactive emission levels at dismissal. Other factors that may influence treatment success and potentially the duration of isolation include renal function and prior treatment with thyroid suppression drugs [18-20]. Because in some facilities the isolation time is a factor in not only the cost of the radioiodine treatment, but also the length of separation from the owner, a more precise estimate of projected length of stay may influence the owner's treatment decision or at least minimize the uncertainty of the separation time. The lower the maximum gamma emissions for inrestricted dismissal are for a given facility, the more relevant this prediction may become.

The purpose of this investigation was to determine if estimates of radioiodine isolation time based on thyroid surface emissions can be refined based on pretreatment parameters in an empiracle dose, constant route (oral) administration protocol. Specifically, the hypothesis tested was whether a significant relationship exists between pretreatment total thyroxine concentration (T-4), serum creatinine concentration, body weight, age, iodine-131 (I^{131}) dose, or concurrent medication administration (excluding thyroid suppression drugs) and the length of isolation for oral radioiodine treatment in hyperthyroid cats.

Materials & Methods:

Cats included in this study were presented for hyperthyroid treatment with radioiodine at a privately-owned, inpatient facility. Pretreatment parameters analyzed were serum creatinine concentration (mg/dl), total serum thyroxine concentration (T-4) [not free T-4] (ug/dl), body weight (kg), age (months) and the presence or absence of concurrent pharmacologic management of cardiac problems presumed secondary to the hyperthyroidism by the referring veterinarian. Only total T-4 values from 2 national/regional commercial veterinary clinical laboratories (with oversight by Diplomates of the American College of Veterinary Pathology) in which strict quality control measures have been documented were used in this study. The numeric values for all laboratory parameters including those for total T-4 were normalized (indexed) as a function of the specified normal range for that parameter in that laboratory.

The normalization process consisted of setting all individual animal values for each test to 1.0 if the value fell within the specified normal range for that laboratory. If a value exceeded the upper limit of that laboratory's specified normal range, the individual animal value was divided by the maximum normal value and expressed as a value > 1.0. Similarly, if a value was less than the lower limit of that laboratory's specified normal range, the individual animal value was divided by the minimum normal value and expressed as a value < 1.0. Thus, the results for all animals were indexed for each laboratory thereby eliminating individual laboratory influence.

None of the cats were receiving concurrent thyroid suppression medications and all had a minimum withdrawal of 2 weeks from these medications, if applicable. Each cat was treated with between 1.13 - 3.7 x 108 Becquerels (3.06 - 10.8 milliCuries) of I^{131} orally in a gelatin capsule and was isolated until gamma radiation emissions were below 0.00000026 coulomb/kg/hr (2.0 milliRoentgen (mR)/hour) at the skin surface immediately adjacent to the thyroid glands. Radiation was detected using a calibrated Geiger-Mueller instrument[1]. Radiation emission levels from the cats were checked at least every other day during the initial part of the isolation and then daily as needed to define the time (within +/- 1 day) when each cat's gamma emission rates were less than Nuclear Regulatory Commission guidelines for an unrestricted area (gamma radiation dose of less than 0.02 mSv/hour from external sources)[21]. We conservatively interpreted this for the cats (considered the external source to their owners) as <2.0 mR/hr at skin surface over thyroid region at dismissal (acknowledging that mSv is a unit of absorbed dose while coulomb/kg and mR are units of exposure).

Indexed data on pretreatment parameters (serum creatinine concentration, total T-4), concurrent nonthyroid medication medication [e.g. beta adrenergic blocker, afterload reduction drug] administration, age, I131 dose and body weight) were compared to length of isolation (in days) using a forward stepwise regression analysis[22]. This analysis included all of the above parameters as independent variables; the isolation time was the dependent variable. For a variable to be included in the stepwise regression analysis, it had to have an F value probability < 5.0 %. To be statistically significant, the outcome of the derived relationship between an individual variable and isolation time as well as any derived isolation time prediction equation had to have a probability that the null hypothesis was true (i.e. there was no association among the studied parameters) of less than 5.0 % ($p < 0.05$).

Results:

One hundred fifty cats ranging from 7 to 18 years of age were studied. Of those, 38 were known to be on cardiac-related medication as defined above. One hundred eleven of the cats were known not to be on cardiac-related medication; one had incomplete data. The length of isolation ranged from 10 to 38 days; the mean length of stay was 16.67 days with a standard deviation of 4.42 days. The indexed pretreatment total T-4 values ranged from 1.0 to 14.9. The pretreatment body weight ranged from 2.2 to 7.7 kg. The indexed pretreatment serum creatinine concentrations ranged from 0.41 - 1.84. Only one independent variable (I131 dose) was sufficiently significant to be included in the regression analysis. The resulting equation was:

$$T \text{ (isolation time [days])} = C + [b \times I^{131} \text{ dose (in mCi)}]$$

$$T = 3.2a + [2.66b \times \text{mCi-}I^{131}]$$

Where "a" SE = 2.67, and "b" SE = 0.52

However, this equation, although statistically significant, had an adjusted $R^2 = 0.143$. In addition, the minimum 95 % confidence limit from this predicted length of stay equation was +/- 3.35 days from the predicted line. If the I^{131} dose was removed from the list of independent variables and the stepwise regression run again, of all other independent variables only the T-4 was sufficiently significant (F value probability < 4.6 %) to be entered in an equation. However, the adjusted R^2 for that equation was 0.02.

Discussion:

Based on this study, further refinement of isolation time as defined here cannot be achieved using the commonly available pretreatment parameters studied herein. Although a seemingly significant length of stay prediction equation was developed, its practical value was considered limited. The equation explained less than 15.0 % of the length of stay variance. In addition, the +/- 3.4 day span in the 95 % confidence intervals for the equation-derived dismissal date was little better than just using the mean isolation time (16.7 +/- 4.4 days). Other observations or parameters that were not quantified in this study may have some predictive value and should be further investigated. These include: semi quantitative assessment of pretreatment hydration, appetite, water intake, general body condition, thyroid gamma emission rate 12-24 hours after radioiodine administration, and cardiac function (from echocardiograms) because individually (or collectively) they may have statistically relevant relationships to isolation time. A subjective observation on the part of the senior author was that those cats which tended to eat and drink more readily seemed to have a shorter isolation time and that fluid supplementation may also at least subjectively help to shorten the isolation time. Neither of these could be quantified or statistically investigated here.

"Free" T-4 or T-3 (triiodothyronine), although not part of the general screening work-up for hyperthyroidism in cats, may merit investigation, when available. A previous report describes the potential for erroneous interpretation of a low total T-4 as hypothyroid in cats with nonthyroid illness[23]. That report compares total T-4 with free T-4 (which does not have the artifactually low value in systemically ill cats). In the circumstances encountered herein, however, we were not concerned with low total T-4 values. Therefore, the use of total T-4 seems practical, relevant, and it is readily available.

Pretreatment radioiodine or technetium pertechnetate uptake studies or thyroid imaging studies were not performed on these cats. Such studies have not received uniform acceptance for either refining the I^{131} dosimetry or improving the outcome of such treatments23-25. Therefore, a somewhat empirical I^{131} dose subjectively adjusted in relationship to the total T-4 concentration may be useful. Clinical observations performed on the cats involved in the current research seem to hold some promise for decreasing isolation time without increasing the rate of incomplete treatments (e.g. continued hyperthyroidism) using the range of 3.0 - 6.0 mCi. However, a relatively large amount of data must be accumulated and detailed statistical correlation must be performed before this clinical suspicion can be confirmed.

The variables proposed for further investigation above as well as those investigated herein should be evaluated for other routes of radioiodine administration for any relationship to necessary isolation time. A relevant relationship to isolation time for the currently studied variables is not anticipated for other routes of administration, however. Investigations similar to the one described herein should be performed in facilities wherein higher gamma emission rates for dismissal and where different radioiodine doses (empirical or calculated) as well as routes of administration have been used. There may be an opportunity to refine isolation time prediction under those circumstances that was not identifiable in this study. If nothing else, the relationship between radioiodine dose and isolation time could be further refined.

Our conservative interpretation of Nuclear Regulatory Commission Regulations regarding dismissal of radioiodine-treated cats has not been uniformly accepted among our peers. Alternative interpretations involving calculated absorbed human radiation dose based on exposure to radiodine-treated cats have also been used as a basis for dismissal. Although beyond the scope of this report, the use of such analyses were presented as counter argument in the peer scientific review of this manuscript. In addition, differences exist in the interpretation of the Nuclear Regulatory Commission Regulations for strict radiation emission limits (e.g. 2.0 mR/hr as used in this manuscript)[21] and the exempted microCurie limits calculated to be contained in the radioiodine-treated cats for either uncontrolled release or confined (indoor) release[26]. It is not the intent of this manuscript to establish the terms for radioiodine-treated cat dismissal. However, it seems unfortunate that variations in interpretations of the Nuclear Regulatory Commission Regulations has apparently resulted in a high degree of variation among the involved treatment facilities across North America and the required isolation times. It is not the intent of this manuscript to debate, analyze or justify the nuances of interpretation of Nuclear Regulatory Commission Codes potentially applicable to the dismissal of radioiodine-treated cats. Instead, our hope was to provide some insight for those using external exposure rates as the basis for cat dismissal.

A final concern that can affect the timing of dismissal for radiodine-treated cats is the contamination of the cat litter (as well as the home environment if the cat urinates outside the litter box). Facilities treating these cats are handling the items in contact with the cat early, as well as anything contaminated with bodily fluids or excrement, as radioactive waste. In addition, restrictions may be placed on how items such as cat litter and bedding must be handled and/or disposed of when the cat is initially at home. There are usually more restrictions placed on cats dismissed 2-7 days after I^{131} than on those with longer isolations times as used by the authors. Some landfill dumpsites are installing highly sensitive radiation detection devices to screen for low-level radioactive waste[27]. Our concern here is at what level will I^{131} contaminated cat litter (the type not flushed into the septic sewer) be detected and will that influence dismissal restrictions. Obviously, this will be a highly variable situation, but the consequences cannot be ignored.

Our goal is to continue the search for a simple mathematical approach to refine length of stay predictions using a straight forward gamma emission endpoint. However, in tandem with this, we hope to determine if there is a useful correlation between surface emission assessments and the potential for urine contamination so that home and environmental contamination risks can be addressed as well. It is apparent to us that a determination on the part of the Nuclear Regulatory Commission should be made for isolation times and dismissal limits for radioiodine-treated cats that would narrow the scope of interpretations of the Nuclear Regulatory Commission Regulations as they apply to these pets.

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