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External Radiation Dose to Owners of Canines Treated with (^{117m}Sn) Radiosynoviorthesis for Osteoarthritis

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Abstract—**A novel device in the veterinary market uses a colloid containing radioactive ^{117m}Sn to treat osteoarthritis in the synovial joints of canines. The technique of injecting a radioisotope to restore synovia is referred to as radiosynoviorthesis. The outpatient canine procedure uses a maximum administration of 222 MBq of ^{117m}Sn injected into one or more joints. Due to the 13.91 d half-life and 158.6 keV gamma output of ^{117m}Sn, abiding by the annual public dose limit of 1 mSv is of primary regulatory concern. The therapy protocol starts with a pre-screening questionnaire to establish owner and animal behavior patterns. The questionnaire is used to determine the duration of written time and distance limitations post therapy. In this study, external radiation doses to owners were measured by providing optically stimulated luminescent dosimeters (OSLD) for up to 30 d post-treatment of the pet. Twelve owners were measured over various time frames at two licensed locations independent of each other. In one location, the average (OSLD) measured 0.029 mSv over a 14-d wear period. In the second location, the average (OSLD) measured 0.057 mSv over a 30-d wear period; both values were well below the recommended annual public dose. The overall average extrapolated external radiation dose was estimated at 0.092 mSv, while the maximum dose estimate was 0.25 mSv. The (OSLD) results and extrapolated owner doses provide reasonable assurance that the public dose limits will be met. Health Phys. 123(2):128–132; 2022**

Key words: dogs; dose; health effects; radiation, medical

INTRODUCTION

Radiosynoviorthesis is a therapy used to treat arthritic joints with radiation from an injected radionuclide. While the use of radiosynviorthesis in people is common in Europe, the therapy has not been routinely licensed in the United States in humans or animals. A commonly used approach to verify proof-of-concept technologies involves lab animal research studies. Occasionally, post proof-of-concept studies will involve a veterinary drug or device becoming commercialized in addition to a similar human drug or device. A new device used to treat arthritic synovial joints for veterinary use emerged in 2019. This new therapy contains radioactive ^{117m}Sn in a liquid colloid. This isotope has several conversion and Auger electrons that provide the therapeutic effect as its primary mode of action; it has a primary gamma emission of 158.6 keV and a half-life of 13.91 d (Domingo 2017). The therapy can be performed as an outpatient procedure, meaning that the pet arrives for treatment and is released to the public after recovery approximately 1 h post administration. The total amount of radioactivity injected is based on body weight and is dependent on the total number of joints treated.

Using canines as an example, the smallest amount of activity to be injected is 22 MBq for a 4.5 kg dog into one joint and up to 222 MBq for a 50 kg dog receiving multiple joint injections. The radioactive material stays confined in the synovial cavity and is not metabolized (Lattimer et al. 2019). An exposure rate measurement post administration is used as justification for outpatient release (Arno et al. 2021). Adding together the elements of an emerging technology, gamma emission, half-life, and amount of radioactivity injected, a legitimate concern is controlling the radiation dose to the general public and maintaining license conditions that follow the ALARA principle (Wendt et al. 2020; Arno and Smith 2021). ALARA is an acronym that stands for "as low as reasonably achievable." Complying with the ALARA principle is a grey area in the radiation safety profession that allows an individual to assess what is reasonable and what is not. Generally speaking, the public dose limit is a reasonable ALARA threshold and is dependent on the type, amount, and form of radiation used.

The parent regulatory guidance document for the veterinary use of radioactivity is NUREG 1556 Vol. 7 Rev 1 (US NRC 2018). The primary professional guidance document

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Table 1. Owner pet distance categories.

Category Number	1	2	3	4
Examples of typical interactions (per person per day)	"The Typical Dog"	"The Foot Sitter"	"The Lap Sitter"	"The Co-Sleeper"
Holding the dog close to the chest	5 min	5 min	5 min	5 min
Snuggling, close up grooming, laying on the floor next to the dog	15 min	15 min	3 h	11 h
Feeding, playing, sitting at feet, walking, petting, grooming	4 h	12 h	4 h	9 h
All activities beyond 3 feet	unlimited	unlimited	unlimited	unlimited

for veterinary radiotherapy is the National Council of Radiation Protection and Measurements Report Number 148 (NCRP 2004). Both documents include explicit recommendations for feline hyperthyroid therapy using ^{131}I. Both documents provide general guidance for licensing and radiation protection principles for maintaining a radiation protection program while retaining animals at the licensee location. However, neither document provides explicit guidance for the release of animals containing radioactivity aside from feline hyperthyroid therapy with ^{131}I. Guidance documents such as US Nuclear Regulatory Commission (NRC) Reg Guide 8.39 (US NRC 2020a) exist for human therapy release, and these guidelines permit a maximum of 5 mSv public dose per administration.

The NRC evaluated the ^{117m}Sn colloid manufacturer's public dose assessment and provided licensing guidance in a technical evaluation report (TER) (USNRC 2020b). The TER provides a summary of the manufacturer's method to maintain dose to members of the public below federally established limits of 1 mSv y^{-1} using a screening process that evaluates habits of the owners with regard to the pet. These habits are based on a time and distance relationship to which the pet family must adhere regarding post-treatment of the animal (Arno 2020). Specific release instructions are given to individual pet owners based on these measurements. The manufacturer's protocol requires the licensee to follow up with the owner approximately 1 wk post release to assess the owner's compliance with the release instructions. At this time, the authorized user (AU) can make an informed decision to extend release instructions based on the compliance disclosure of the owner. The current prospective study collected results from owners of animals treated with ^{117m}Sn by using optically stimulated luminescent dosimeters. The data were measured by two different, independent licensees over different time periods to validate the methodology provided by the manufacturer and approved by the NRC ensuring compliance with the public dose limit of 1 mSv y^{-1} (USNRC 2007).

METHODS AND MATERIALS

Once a canine candidate for radiosynoviorthesis therapy was selected, the licensee used the manufacturer-provided prescreening questionnaire to establish a time and distance relationship between the proposed animal to be treated and the members of the household. The questionnaire asked several open ended and explicit questions, which allowed an AU to establish if the owner(s) fit into one of four owner-pet distance categories detailed in Table 1.

The owners were also provided with an example of the release follow-up instructions required should they and the AU make the choice to move forward with the therapy. The specific release instruction duration ranged between 2 and 6 wk and was dependent upon the category selected from Table 1 and an exposure rate measurement taken 1 m from the treated joint(s) post injection. Table 2 is used to prescribe the duration of the release instructions using the release exposure rate measurement and the owner distance category.

The release instructions provide guidance to limit contact to the treated dog's joint(s). The limitations are directed as follows: up to 5 min d^{-1} of direct contact, up to 15 min d^{-1} at 30 cm, and up to 4 h d^{-1} at 91 cm from the treated joints. Following the duration of the release instructions (2 to 6 wk), the owners may return to routine interaction with the treated pet.

Two independent licensees in two different agreement states collected measurements from dosimeters given to owners

Table 2. Release instruction duration.

	"The Typical Dog"	"The Foot Sitter"	"The Lap Sitter"	"The Co-Sleeper"
Release exposure rate measurement (μGy h^{-1}) at 1 m	duration of release instructions (weeks)			
0.4385	2	2	2	2
0.877	2	2	2	2
1.754	2	2	2	3
2.631	2	2	2	4
3.508	2	2	3	5
3.946	2	2	3	6

Table 3. Occ_i factor justification.

	Typical Dog	The Foot Sitter	The Lap Sitter	The Co-Sleeper
Category	1	2	3	4
Time at d1 (h)	0.083	0.083	0.083	0.083
Time at d2 (h)	0.25	0.25	4	11
Time at d3 (h)	4	12	4	9
d1 (cm)	"contact"	"contact"	"contact"	"contact"
d2 (cm)	30	30	30	30
d3 (cm)	90	90	90	90
Ratio / Occ(i)	1.00	1.73	4.09	10.30

whose dogs were treated with ^{117m}Sn radiosynoviorthesis. In each location, owners were provided with instructions to wear the dosimeter on their waist or torso any time they were near their treated animal. At one location, the owners were instructed to return their dosimeter after 14 d. The second location requested that the owners return the dosimeters after 30 d. At the second location, the owners were provided with multiple dosimeters including a dosimeter to wear when near their treated dog, one dosimeter to leave in a common room, one dosimeter to leave at their bedside, and a control dosimeter to be held in an envelope inside a cupboard away from the treated pet.

The formulism in eqn (1) was used to unify the results from each licensee. This formulism accounts for the time that the dosimeters were worn, the duration of the release instructions, and the dog owner distance category. The exponential components in eqn (1) account for ^{117m}Sn decaying with a half-life of 13.91 d. The variable $D_{t_i}$is the dose from the owner dosimeters with the index i corresponding to either 1 or 2, as the time worn was different for the two licensees. The exponential in the denominator is used to normalize the function based on the time the dosimeter was worn with the index i corresponding to either 1 or 2. Inside the brackets, the first integral calculates the dose during the time of the restrictions. The integral boundary t_{R_i} is the duration of the precautions, where R_i corresponds to the owner distance category and the exposure release measurement found in Table 2. The second integral accounts for the time after the restrictions end and is multiplied by an occupancy factor called (Occ_i). This factor is a ratio of the category 1 times and distances against the other category times and distances. Accounting for the inverse square law, the dose from category 4 is 10.3 times greater than category 1. The Occ_i factors are provided for each category in Table 3. The manufacturer-provided release instructions are designed to modify owner behaviors to fit into the category 1 (typical dog) times and distances, which is the purpose of normalizing the Occ_i to the category 1 owner. Using a point source approximation and the inverse square law is an overly conservative approach for an annualar source attenuated by boney structures (Arno and Smith 2021). Another elegant approach to the Occ_i could be to use the normalized dose rates of Table 4 in Arno and Smith (2021), but doing so does not substantially change the Occ_i values. Using the raw dosimetry data, eqn (1), and the calculated Occ_i factors from Table 3, an extrapolated owner total effective dose equivalent can be estimated.

$$D_{total} = \frac{D_{t_i}}{\int_0^{t_i} e^{-\lambda t} dt} \left[\int_0^{t_{R_i}} e^{-\lambda t} dt + Occ_i \int_{t_{R_i}}^{\infty} e^{-\lambda t} dt \right]$$

RESULTS

The results are provided for each independent licensee in Tables 4 and 5. These tables list the owner number, dosimeter number, administered activity, the raw dosimeter values D_{t_i}, the extrapolated D(total) using the formulism in eqn (1), the owner distance category, and the prescribed duration of release instructions. The maximum empirical dosimeter value was 0.06 mSv for licensee 1 over 14 d and 0.10 mSv for licensee 2 over 30 d. The maximum extrapolated dose for the entire study was from licensee 1 with 0.25 mSv for an owner who met the co-sleeper category (4) and their dog was injected with the maximum allowed activity (222 MBq). For licensee 2,

Table 4. Dosimetry results for Licensee 1.

		Administered activity (MBq)	14 Day dosimeter dose (mSv)	D(total) (mSv)	Owner distance category	Duration of precautions (wk)
Owner 1	Dog 1	222	0.06	0.245	Co-Sleeper (4)	6
Owner 2	Dog 2	126	0.06	0.245	Co-Sleeper (4)	6
Owner 3	Dog 2	126	0.01	0.041	Co-Sleeper (4)	6
Owner 4	Dog 3	70	0.01	0.041	Co-Sleeper (4)	6
Owner 5	Dog 4	70	0.005	0.020	Co-Sleeper (4)	6

Table 5. Dosimetry results for Licensee 2.

		Administered activity (mBq)	30 Day dosimeter dose (mSv)	D(total) (mSv)	Owner distance dategory	Duration of precautions (wk)
Owner 1	Dog 1	177.6	0.1	0.128	Typical Dog (1)	2
Owner 2	Dog 2	163	0.02	0.026	Typical Dog (1)	2
Owner 3	Dog 3	141	0.02	0.026	Typical Dog (1)	2
Owner 4	Dog 4	126	0.07	0.089	Typical Dog (1)	2
Owner 5	Dog 5	126	0.05	0.064	Typical Dog (1)	2
Owner 6	Dog 6	163	0.01	0.013	Typical Dog (1)	2
Owner 7	Dog 7	141	0.13	0.166	Typical Dog (1)	2

the owners were provided with additional dosimeters to keep on their nightstand and in a low background area in their house. In all cases, the dosimeter that the owner kept with them resulted in the highest dose, which is reflected in Table 5. The manufacturer-provided protocol requires owner(s) who meet the co-sleeper category to follow precautions for up to 6 wk (e.g., no co-sleeping). After the prescribed duration of the precautions expire, the owner(s) can go back to their typical behavior (e.g., co-sleeping). Theoretically, the majority of the radiation dose is received after the duration of the precautions for the co-sleeper category (4). This fact can be visualized by graphing the two bracketed integrals in eqn (1) while using 6 wk for t_{R_i} and 10.3 for Occ_4. This visualization is presented in Fig. 1. The first exponential section is the dose to the owner during the precautionary time frame up to 6 wk (t_{R_i}). The second exponential section is the dose to the owner after the precautions expire out to 20 wk (10 half-lives).

DISCUSSION

Empirical, real world validation of theoretical methodology is important in the scientific community especially when that theory is applied to public radiation dose. This study provides empirical data with some limitations such as a small sample size, assumptions over owner compliance with their dosimeters, and assumptions about their behavior after the duration of the release instructions. However, the results are consistent, and the public dose risk from veterinary radiosynoviorthesis is substantially less than those already accepted for human medicine in the United States.

The dosimetry results provided in Tables 4 and 5 are reasonably low. However, the data set of owners is also small. More data should be gathered to ensure that license commitments and public dose regulatory requirements are met. The methods provided in this study can be used for future validation efforts with simple adjustments to the formulism in eqn (1). It is also worthy to note that owners who meet the "foot sitter" or "lap sitter" categories are not represented in data provided in Tables 4 or 5. The Occ_i values for these two categories fall between the "typical dog" and the "co-sleeper," but it would be more thorough to validate each category in the time and distance theory provided by the manufacturer.

Owner behavior, their ability to properly wear a dosimeter, and their ability to adhere to release instructions limiting time and distance to their beloved pets is also a legitimate concern. It is possible that the owners did not follow the instructions for wearing their dosimeters at all times near their treated pet. In two cases for licensee 2, owners disclosed that their dosimeter went through the laundry, indicating a loss of control for a time. It is also entirely possible that the owners did not follow the release instructions provided by the licensees. The TER (USNRC 2020b) details a worst-case scenario wherein a category 4 owner of a dog who is injected with the maximum activity of ^{117m}Sn (222 MBq) ignores the release instructions entirely (e.g., sleeps in direct contact with joints of the treated dog immediately after administration).

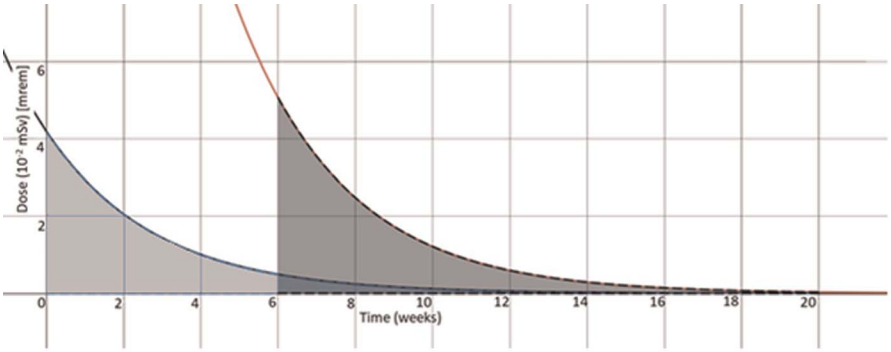

Fig. 1. Visualization of dose over time for category 4 owner.

The resultant effective dose equivalent is calculated at 5.02 mSv, which exceeds the annual public dose limit of 1 mSv. Attaining this worst case scenario is physically difficult. The owner would need to be less than 100 cm from their pet's treated joints for 20 h per day for 20 wk straight. Even so, it is worthy to note that the worst-case scenario presented by the NRC of 5.02 mSv slightly exceeds what is already allowed for human use—5 mSv per administration. Human therapy and diagnostic administrations of radioactivity are also provided on a much more frequent basis with much more radioactivity in most cases. The NRC also recognizes in a 2017 Information Notice, regarding human release of patients post radioiodine therapy, that people are able to follow specific instructions to meet public dose criteria (USNRC 2017). This study provides confidence that owners are capable of following specific release instructions. It also provides some empirical unforeseen layers of conservatism in the theory. The lower-than-expected doses are possibly due to owners overestimating their routine proximity to their pets or the duration of time attributed to common daily interactions.

Therapies in animals routinely pave the pathway forward for human uses through proof of concept. At this time, there are no comparable therapy options that may provide the same pain relief to humans or pets suffering from osteoarthritis. While radiosynoviorthesis is currently commonplace in Europe, it is very likely that the United States will continue to see this technology emerge.

CONCLUSION

Owners with pets treated with ^{117m}Sn radiosynoviorthesis were provided with dosimeters to use in their household post-treatment. The average results extrapolated over time were approximately 10% of the allowed annual public dose limit. The maximum results extrapolated over time were approximately 25% of the annual public dose limit. The results from the owner dosimeters and extrapolated doses provide support that the release methodology recommended by the manufacturer meets the federally established annual public dose limit of 1 mSv. In summary, these results are consistent with the ALARA principle and indicate that the release methodology provided by the manufacturer resulted in additional layers of safety for the owners taking care of their treated pets and living in the same household.

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