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Evaluation of potential dose to members of the public from treatment of dogs with Synovetin OA™ containing Sn-117m.

Introduction

Synovetin OA is a colloid containing Sn-117m that can used to treat osteoarthritic dog elbows. One of the concerns with this treatment is ensuring that dose limits for members of the public will be met. Exubrion Therapeutics, the makers of Synovetin OA, wishes to develop generic release criteria acceptable to the NRC such that individual NRC or Agreement State licensees could successfully submit radioactive materials license applications or amendments using those release criteria. This evaluation analyzed normal dog behaviors and establishes the release criteria which may be used to release dogs treated with Synovetin OA in accordance with the dose limits for members of the public.

Canine Osteoarthritis

Radiosynoviorthesis (RSO) to treat chronic pain and inflammation of osteoarthritis (OA) in dogs has been deployed in animal health due to the lack of treatments which veterinarians can turn to in cases where the primary and secondary line of treatments are found to be inadequate. As in human medicine, veterinary practitioners initially treat OA or arthritic pain with prescription non-steroidal anti-inflammatory drugs, all of which have been developed to address acute pain (Fox 2017). If those drugs fail, veterinary practitioners very often use prescription opioids with their inherent difficulties for both the dog and the caretaker. These therapies are generally easy to use (e.g. oral daily medicines or periodic injections) and dispensed or administered by the general practitioner. If those options fail, dog caretakers faced with treatment failure are left to try various unproven oral nutraceutical and invasive cell therapies, many times with limited success. Ultimately, these dogs are referred to specialists (typically orthopedic surgeons) for treatment of pain associated with OA when these initial type of treatments are found to be inadequate especially when the arthritic pain becomes chronic (Appendix A). These are the more severe cases which includes those dogs that are suffering from OA secondary to elbow dysplasia.

The population of dogs most often affected with OA tend to be large and giant breed dogs such as Labrador retrievers, golden retrievers, bulldogs, St. Bernards, German Shepherds, Bernese mountain dogs, chow chows, bearded collies, boxers, mastiffs, Rottweilers, American Staffordshire terriers and Newfoundland dogs (Racine 2019). In Exubrion Therapeutic's studies in which 92 elbows were treated in 69 dogs selected because they were affected by naturally occurring OA of the elbow, the average weight of the affected dogs was 67.5 lbs. In a recently published peer reviewed journal article, dogs greater than 77 lbs. had a higher OA score

indicating more severe OA than those less than 77 lbs. (Gilbert 2019). There is a correlation between size and activity levels of these large breed dogs.

Treatment of Canine Osteoarthritis with Sn117-m

RSO using the Sn-117m colloid targets pro-inflammatory macrophages which engulf the micro particle colloid and causes apoptosis (slow, non-inflammatory death) of the macrophage. Research has shown that different pain receptors are involved with chronic pain associated with OA (Perretti 2017). By targeting the macrophage, multiple inflammatory and pro-inflammatory enzymatic cascades are affected rather than one or two enzymatic pathways as is the case with NSAIDs (Kraus 2016). In short, RSO with Sn-117m colloid provides a broader based approach to reducing inflammation within the affected joint in which the less expensive easy to administer but more specific enzymatic targeting drugs have proven to be inadequate.

Dosage of the Synovetin OA is proportional to dog weight with up to 3 mCi being injected in each joint for the largest dogs. Over 99% of the injected Sn-117m colloid remains within the treated joint (Lattimer et al 2019). Therefore, the biological half-life is not relevant and excretion of the Sn-117m is not a concern. Approximately half the decay energy of the Sn-117m is released by internal conversion electrons with a relatively short range and the remainder is released by gamma rays and X-rays. The predominant gamma ray energy is 158.56 keV.

The presenting signs for OA are exhibited in a variety of ways, including reluctance to exercise, exercise intolerance, inactivity stiffness, lameness, inability to jump (up and down), muscle atrophy, joint swelling, capsular and extracapsular fibrosis, joint effusion, reduced range of motion, crepitus, pain on joint manipulation, and behavioral changes such as aggression (Fox 2017). Signs vary from very mild and intermittent to severe and persistent. External factors such as the amount of exercise performed and the weather may influence the severity of signs that the owner reports. The tendency for most patients is for clinical signs to gradually worsen, although this can occur at a variable rate with interposing periods of remission and flares of disease (Innes 2018).

Dogs to be treated by RSO will be those dogs which are refractive to primary and secondary treatments in the elbow. The 'poster child' for OA in dogs is the middle-aged to older (>4 years), large breed (>50 lb. [22.5 kg]) dog that is overweight to obese. Veterinary instructions for caring for dogs with severe OA include: "Be sure the dog is able to stand on a non-skid surface while eating and drinking. Have the client explore the home for potential 'problem spots.' Steps in and out of house, patio stones, and garage floors can create unintentional challenges for the painful dog. Ramps are recommended for getting into and out of vehicles." (Fox 2017).

This population of lame dogs are reluctant to jump on furniture to sit in a caretaker's lap or to jump up to sleep on an elevated bed.[1] Initially following RSO treatment it is expected the patient will have a continuing level of pain and lameness until the inflammation of the synovial lining is sufficiently reduced which can take weeks. This initial continuing pain post treatment will

1 Dr. Steven Fox clinical observations, June, 2019.

continue to limit the patient from jumping on beds and furniture. In 3 studies treating naturally occurring OA subsequent to elbow dysplasia with RSO of the label dose of the Sn-117m colloid, the patients showed a gradual improvement of lameness with the caregivers reporting that it took a few weeks to notice an improvement in mobility.

Compliance with Public Dose Limits

In order to comply with public dose limits, the use of Sn-117m is governed by three layers of controls:

1. Identify the common human-dog interactions that could potentially cause a person to exceed the public dose limit. As the following analysis shows, the normal people have with most dogs (particularly most severely arthritic dogs) would not cause those people to approach the public dose limit. Therefore, changes in behavior are not required for most dogs. Nevertheless, the following two controls are applied in all cases.
2. Specify those behaviors that could create a risk of excess exposure to a member of the public. Pre-screen all potential patients for those behaviors and determine whether or not the caregivers can modify those behaviors for the prescribed period of time. If they cannot, the patient will not be offered treatment with Sn-117m.
3. To create an additional margin of safety and to remind the caregivers of any restrictions, caregivers will be given a set of release instructions and asked to sign them immediately prior to treatment to confirm their intent and ability to comply.

Occupancy factors and human-dog interactions

This evaluation analyzes human-dog interactions, specifically the common behaviors and the times and distances involved. The following analysis is based on: the published literature, interactions with the 69 severely arthritic dogs and their pet owners involved in Exubrion's three studies, discussions with dozens of practicing veterinarians who see arthritic dogs on a daily basis and countless pet owners (including focus groups conducted to assess pet-pet owner interactions). In reviewing this material, there are two important distinctions to point out (particularly relevant to the precedent case in cats):

1. The size and weight range of dogs is far greater than cats. As previously noted, size is a major determinant in behavior patterns (what pet owners will do with a 15 lb. dachshund is substantially different from what they will do with a 75 lb. golden retriever).
2. While the literature and most people's perspectives of dog behavior is generally based on healthy dogs, this product is for severely arthritic dogs. That arthritis affects the dog's ability to move and willingness to interact in general.

In this section, we will identify the common groups of behaviors (including times and distances) and we will use those in a subsequent section to assess the public dose that would result.

The most comprehensive study of dog-human interactions found was a study by Westgarth (2008). This study found that 83% of large/giant dogs rarely or never lie on a person's lap compared to only 29% for toy/small dogs and 49% for medium-sized dogs and that younger dogs are more likely to exhibit these behaviors than older dogs. 68%, 49%, and 29% of large, medium, and small dogs respectively rarely or never lie on furniture. An important consideration is that these behaviors are for healthy dogs. A dog with osteoarthritis has difficulty with physical activity, like running and especially the jumping which would be required to get onto a person's lap or furniture. Since osteoarthritis is a condition which impacts predominantly older dogs, it can be safely assumed that these dogs are even less likely to lie on a person's lap or on furniture. This same study found that only 14% of dogs sleep on a human bed. This percentage applied to all dogs in the study and was not broken down by dog size. It is reasonable to assume that, as with the statistics regarding lying on a person's lap or on the furniture, smaller dogs are more likely to sleep on the owner's bed than larger dogs so only some percentage less than 14% of large dogs sleep on their owner's bed.[2] Once again, this percentage applies to healthy dogs. An osteoarthritic dog (also, older by definition, since the disease develops slowly over time) would have significant trouble jumping up onto an owner's bed and would be even less likely to co-sleep with its owner.

Typical human-dog interactions can be roughly broken down into three groups: standing, sitting, and co-sleeping. Of importance when considering interactions is both the activity and the distance involved.

Skin is the only organ for which addressing dose to the maximally exposed portion is a regulatory issue and even for the skin the dose to a minimum of 100 cm^2 is evaluated. For all other organs, the average dose to the entire organ is used. Additionally, organ dose is not relevant for evaluating dose to a member of the public. Therefore, only whole body dose is calculated.

In the reviewer notes for the December 21, 2001 response to the May 18, 2001 technical assistance request for release criteria for cats treated with radioactive iodine, the NRC states "The distances provided are put into perspective by relating them to distances from the highest activity measured from the cat to the center of the area of the person that NRC defines as the 'whole body.'" The center of the torso is the center of the area of the person that NRC defines as the "whole body."

Standing

"Standing" would apply to most waking activities in relatively close proximity to the dog other than a dog next to a seated owner. The most common standing interactions would be feeding, walking, and petting.

When feeding a dog, the amount of time in close proximity to the dog is quite limited. A typical interaction would be a dog expectantly waiting for its food in somewhat close proximity to its owner's legs while its food dish is filled. However, once the dish is filled and the dog begins

2 "Owner" is taken to be any person living in the same household with the dog.

eating, the distance between the dog and owner is much greater since the owner does not hover over the dog as it eats. The majority of time during this activity is at a distance of approximately 3 feet or more with only a minor portion, much less than a minute, at a distance of 1 foot and the entire process occupies only a couple minutes.

Walking a dog is another activity where the majority of the activity is conducted at a distance of 3 feet or more. With the potential exception of very well-trained dogs that heel well, a typical dog will be walked with the dog at or near the extent of the leash. With a common minimum leash length of 3-4 feet, the length of an owner's arm, and taking consideration of the height difference between the dog's neck and leg joint, 3 feet is a reasonable minimum distance from a treated joint to a person's torso with greater distances more common. Figure 1 shows a large dog (107 lb) being walked by a small adult (4 ft 11 in tall). Scaling from the yardstick included in the photo, the distance from the dog's elbow to the center of the person's torso is approximately 5 ft.

Figure 1. Large dog being walked by small adult.

Westgarth's results indicate only 19 % of large dogs are walked 3 or more times per day and that the average walk duration is 16 minutes to one hour long, with smaller dogs less likely to be walked 3 or more times per day and younger dogs more likely to be walked longer. This is another activity where an osteoarthritic dog is much less likely to participate, leading to less and shorter walks for such a dog. Therefore, on-leash dog walking is assumed to be performed twice a day for no more than 30 minutes each time, or one hour per day as a reasonably conservative estimate.

Petting and the desire to be petted is the last of the "standing" activities. Petting is an activity that consists of hands-on contact with the dog. Additionally, the posture of the human is more likely to result in close contact with the dog, i.e., kneeling, sitting, bending over, etc. For this activity, an assumed distance of 1 foot is appropriate. The actual distance is likely to be longer given that the majority of petting is on the dog's torso or head and the geometry considerations with regard to dog joint proximity to the person's torso. However, 3 feet is likely not conservative. Figure 2 shows a typical posture for a person petting a dog. Figure 3 shows a worst case scenario of a person sitting on the floor being affectionate with a dog. Even in this position, there is still a distance of more than a foot from the dog's elbow to the person's torso. More common would be a person standing or seated in a chair with a commensurately greater distance.

Figure 2. Dog petting.

Figure 3. Dog petting.

While petting can be a frequent activity with dogs, each petting session typically does not last very long. Discussions with a focus group of dog owners indicated that a typical petting session would last 15-20 seconds and focus primarily on the dog's head. On a day with a lot of petting, there might be 8 to 10 such petting sessions, with fewer on other days, such as when at work or if the dog is outside often. This indicates petting commonly occupies up to 200 seconds, or 3.33 minutes per day. To be conservative, this is rounded to 5 minutes. Additionally, most petting, being petting on the head, would result in a human torso-dog joint distance of more than a foot, but less than 3 feet. While 2 feet is a reasonable estimate for the typical distance, it is conservatively assumed that the distance might be as little as 1 foot.

Sitting

The primary sitting interactions with a dog that are not already addressed above would be situations where a dog rests at its owner's feet or by the side of the owner's chair and dogs that sit in their owner's lap. For people that do not work from home, the opportunity for this behavior is limited to a couple hours in the evening each day. Stay-at-home parents are generally active and moving about during the day, making this estimate reasonable for them as well. An estimate of 3 hours per day would encompass the majority of the time after dinner and before bedtime and would apply to either a dog resting by its owner's feet or sitting in its owner's lap. It is assumed that a given dog exhibits either one behavior or the other.

As discussed in part above, a distance of 1 foot from a dog's leg joint to the human torso center of mass is appropriate for lap sitting. When in a person's lap, the dog's legs are separated from

the person's torso by the dog's torso which also functions as a radiation shield since the dog's legs will be under it or stretched out away from the person's torso.

The maximally exposed part of the body for long duration close contact, as with lap-sitting, is not the center of the torso but rather the upper leg. NRC Regulatory Guide 8.40 Table 1 assigns each upper leg a weighting factor of 0.005 for external dose. Even for an anatomic region as small as the thigh, the dose rates are highly non-uniform when close to what is effectively a point source. The dose to the skin closest to the dog's elbow is not the dose to the anatomic region of the thigh. The average dose to the entire anatomic region of the upper leg is much lower. We submit that the center of each anatomic region provides a much more accurate estimate of the average dose to that anatomic region than using the maximally exposed portion. Given that the torso accounts for 88% of the total weighting factor, and a further 10% is on the head, use of the center of the torso is a reasonable means of estimating the average dose to an individual.

While the dog is resting at its owners feet or by the owner's chair, it will normally be lying down, either on its side or in a prone position. In either case, the dog's joints are effectively at floor height. In the case of a prone position, they are located underneath the dog, attenuating any radiation emitted towards the person. A standard chair seat has a height of 18 inches, limiting the lower extent of a person's torso to that height. The center of the torso would be some distance higher with an additional foot being conservative for the average person. Coupled with the lateral offset of the dog (i.e., not under the chair), a distance of 3 feet from a dog's leg joints to the midpoint of a seated person's torso is a reasonable estimate. Figures 4 and 5 show typical positions.

Figure 4. Dog at feet.

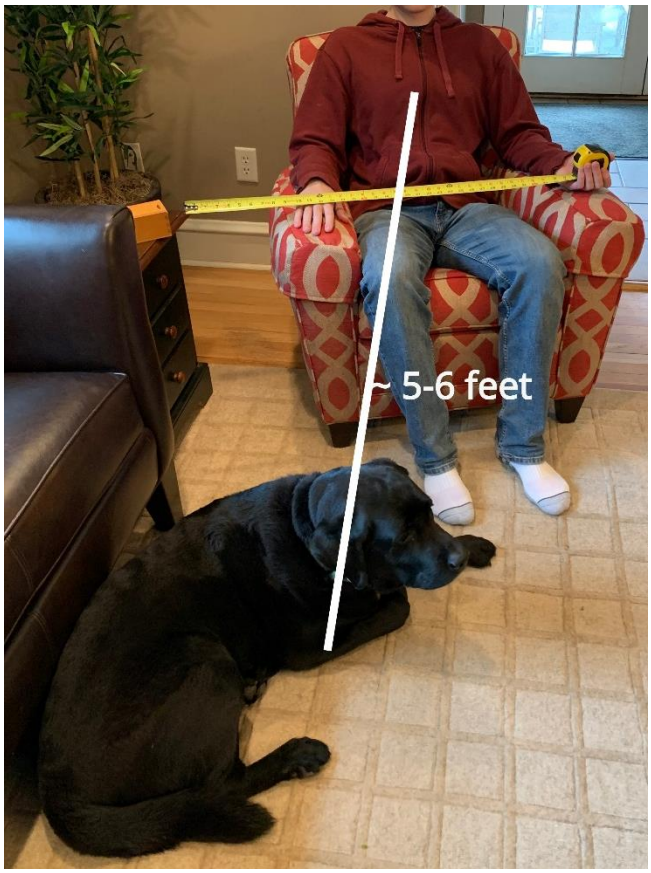

Figure 5. Dog near feet.

For those individuals that work from home or are otherwise relatively sedentary, such as the elderly, an additional 8 hours of time sitting with a dog at their feet or by the side of their chair may occur and is generically referring to as "officing." This situation would only apply to those instances where the dog is close to them, i.e., at their feet or beside their chair; in many such instances, the dog is simply content to be in the room and may be some larger distance away, especially if a dog bed is present further removed from the person.

Co-Sleeping

Co-sleeping, defined as a dog that sleeps on its owner's bed, is the single behavior with the greatest likelihood of contributing the most dose to a person. For this reason, this behavior cannot be allowed, especially during the weeks immediately after treatment. As discussed above, a larger, older, osteoarthritic dog is highly unlikely to co-sleep not only because this behavior is not common among larger dogs, but also because an osteoarthritic dog for which other more common therapies have failed would not be capable of jumping up onto the owner's bed unaided. Therefore, instructions that forbid this behavior are reinforcing existing behavior patterns rather than attempting to contradict natural tendencies. In the event that co-sleeping did occur, human and dog sleeping would conservatively be about 8 hours per day based on Patel's (2017) observations of human and dog times in bed and sleep efficiencies.

Distances less than 1 foot

Previous evaluations of human-feline interactions focused on distances of 3 inches, 6 inches, 1 foot, and 3 feet (1 meter) and implicitly indicated that distances greater than 3 feet were not of importance, a conclusion with which we agree (Hickey 2001). A distance of 3 inches was especially discussed with regard to lapcats. While a cat's thyroid may be near the torso, a dog's leg joint will be further away even when in a person's lap. This is especially true when considering the center of the torso rather than the closest portion of the torso as discussed in Essig (2003). For dogs, most of whom are substantially larger than the average cat, this distance is not applicable. Additionally, in most postures of lap-sitting, such as shown in Figure 6, the dog's body will serve as a shield for most of the human torso for radiation coming from the dog's legs or the dog would be in such a position that the average distance would be a foot or more, i.e. stretched out perpendicular to the human's legs or with the dog's legs pointed towards the human's knees.

Figure 6. Dog in lap.

There is an important anatomic distinction between radiation from a cat's thyroid and radiation from a dog's leg joint. Importantly, the distance from a person's torso to a dog's leg joint is not the same as the distance from any part of the person to the dog's torso. When we think of the distance between a person and a dog, we commonly imagine the shortest distance involved, which would be the distance between the dog's torso and the person's arm or hand. However, this is not appropriate for this evaluation. Even for a child or small adult, the distance from the human torso to the dog's torso can easily be a foot or more greater than the distance from the human's hand to the dog's torso, especially when considering the center of mass of the torso rather than the lower portion of the torso. Additive to this distance difference is the fact that the dog's leg joints are at the lower extent of the dog's torso, also increasing the distance to the human's torso. On top of these distance considerations is the fact that the closer a person is to a dog, the more the dog's torso functions as a radiation shield in that the radiation would be

directed more vertically through the dog's torso to reach the person's torso, further reducing the net dose rate to the torso. Given these considerations, distances of 6 inches are not reasonable, and therefore radiation dose rates at 6 inches are not a consideration for lap-sitting.

The other scenario when a dog may be in close proximity to a human torso is those situations where the dog requires assistance such as in getting into and out of a vehicle, standing up on slick surfaces, or negotiating steps. Arthritic dogs are especially reluctant to jump up. For a large dog (≥ 110 lbs.) receiving the maximum Synovetin OA amount in both elbows that needs assistance to be placed into a car, there are commonly used methods (an assist by pushing on the rump of a dog, two towels encircling the chest and in front of the hips or a cart with the dog on a blanket can be used to transfer the dog to the car, or a portable ramp). These solutions present minimal if any exposure for a caretaker due to the short duration of the assistance and allow some separation to remain between the dog's elbows and the person's torso. Unlike post-surgical dogs, jumping out of a car is not as difficult nor discouraged for an arthritic dog post Synovetin OA treatment. Some of these same arthritic dogs when arriving home jump out of a car due to their excitement of returning home.

The videos contained in Appendix B demonstrate the actions a person would need to take a transfer dogs of different sizes into a vehicle. As can be seen, the duration of each of these activities is very short, on the order of a few seconds of direct contact with the dog. The methods listed in the previous paragraph would tend to result in distances on the order of 1 foot while the closer distances shown in the videos are for a quite short duration. The length of time the smaller dog is held in the first video is for less than 10 seconds while the duration of contact assistance for the larger dog in the second video is also for less than 10 seconds. While the total duration of the "get dog into vehicle" activity may be substantially longer, the duration of actual contact is quite short. The radiation dose from 10 seconds at a distance of approximately 6 inches is equivalent to the dose from 40 seconds at a distance of one foot. For calculation purposes, this is rounded up to 1 minute at 6 inches to account for multiple times the dog may be need to lifted in a single day. The preceding analysis shows that less than 6 minutes at 1 foot is common. However, the calculations and instructions here allow for up to 15 minutes per day at one foot. Among other things, that allows for small periods of time at closer distances to help the dog into cars, up stairs, etc.

Summary

Typical dog-human interactions are summarized in the table below for totals of 15 minutes per day at 1 foot and 4 hours per day at 3 feet not including co-sleeping, lap sitting, or officing. Co-sleeping, lap sitting, and officing would result in 11 ¼ hours per day at 1 foot and 9 hours per day at 3 feet.

In essence, dogs with osteoarthritis and thus a candidate for radiosynoviorthesis treatment, are self-selecting for dogs that do not spend prolonged time in close contact (touching) with their owner(s) because these candidates are older and larger dogs with mobility limitations. Therefore, any written instructions issued limiting contact are reinforcing existing behavior patterns rather than attempting to contradict natural tendencies.

Typical Human-Dog Interactions

Interaction	Distance	Time
Carrying	6 in	< 1 min/day
Feeding	1 ft	< 1 min/day
Petting	1 ft	5 min/day
Walking	3 ft	1 hr/day
Sitting[a]	3 ft	3 hr/day
Lap-sitting[a]	1 ft	3 hr/day
Co-sleeping	1 ft	8 hr/day
Officing	3 ft	8 hr/day

[a] A given dog exhibits one of these behaviors or the other, but not both since they are assumed to occur during the same time period.

Of course, it is understood that in veterinary medicine the patient itself cannot understand any limitations noted in the release instructions. However, in this case, the most significant behaviors to limit (lap-sitting and co-sleeping) are precisely those behaviors that the severely arthritic dog cannot engage in unaided by the human caregiver. So long as the caregiver is willing and able to honor those limitations the dog will not engage in them. And if the caregiver is unwilling or unable to do so then the dog will not be treated.

Self-shielding

The proposed release instructions are based upon the maximum exposure rate measured at a distance of 1 meter from the treated joint(s) of the dog. One meter is chosen because the veterinary technicians are accustomed to taking measurements at this distance as part of the receiving and shipping of radioactive materials. For the owners, distances are given in standard units, i.e., feet with distances of 1 and 3 feet for different activities since most people in the United States are more comfortable using standard units.

The maximum exposure rate will typically be measured either in the cranial or lateral direction with respect to the dog and at a height corresponding to the dog's treated joint(s). However, this height is quite low, corresponding to a human's knee height or less. The actual exposure rate experienced by a person will be modified by the height different between the dog's joint and the center of the person's torso and the interposition of the mass of the dog's torso, upper leg, and other bony and soft tissues. In general terms, there are 9 basic geometries that may be encountered thought of in terms of cardinal directions:

- Anterior, posterior, left lateral, and right lateral at treated joint height
- Anterior, posterior, left lateral, and right lateral at standing torso center height
- Dorsal (above)

The attached study in Appendix C measured the shielding effectiveness of the dog's torso for various size dogs and determined that a minimum average shielding effectiveness effect of 28% at 1 meter and 32% at 1 foot. These shielding effectiveness rates are used in this public dose evaluation.

Unrestricted Dose to Owners

The maximum exposure rate at which a dog may be released is 0.45 mR/hr. This criteria is based on ensuring that the maximum dose rate at a distance of 30 cm does not exceed 5 mrem/hr and thus does not create a radiation area. Based on this maximum expected exposure rate, these conservatively estimated contact times result in a dose of 51 mrem to an owner if the dog does not co-sleep with the owner, sit in its owner's lap, or lie at the feet of someone who offices at home, well below the 100 mrem in a year public dose limit.[3] If all three of those behaviors occur, the dose could be as high as 792 mrem for the largest dogs.[4] The doses resulting from smaller dogs would scale approximately linearly with dog weight due to the scaling of the administered activity with weight. The worst-case scenario for evaluating whether a person could receive 2 mrem in any one hour is a person that spends 1 minute at 6 inches, 15 minutes at 1 foot and the remainder of the hour (44 minutes) 3 feet. Under this scenario, the maximum dose would be 1.63 mrem.

It should be noted that for the common contact scenario and dogs released with a dose rate of 0.4 mrem/hr @ 1m or less, the calculated dose is only 45 mrem, which would allow for multiple treatments during a single year without exceeding the public dose limit.

Restricting Dose to Owners

Dogs that do not lap sit, co-sleep, of office will be the most common behavior pattern among dogs with OA and treated by RSO for the reasons discussed above. It is expected that well over 90% of OA dogs will have this behavior pattern. In this situation, no written instructions are necessary to ensure compliance with the dose limit. Consequently, the use of written instruction provides a margin of dose reduction and is not the primary way of keeping the dose to members of the public below 100 mrem for the vast majority of cases. For the case where the dog offices, this one behavior needs to be limited.

As is currently the situation with release of cats treated with I-131, the most important behavior to avoid is co-sleeping with lap-sitting second. Preventing co-sleeping for up to 9 weeks or lap sitting for up to 5 weeks after treatment is sufficient to reduce the dose to less than 100 mrem in a year for the largest dogs. The necessary duration of such written instructions scales approximately linearly with exposure rate upon release and thus administered dose and dog size with no written instructions needed for the smallest dogs for the lap-sitting scenario which are also the dogs most likely to have this behavior. Therefore, the duration of the written instructions is inversely proportional to the behavior modification involved, i.e., the dogs most likely to lap sit (smallest dogs) are the ones for which this behavior must be avoided for the shortest period of time.

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3 In the attached spreadsheet, see cell B36 on the "Common" sheet. The total dose from smaller dogs prescribed less activity and thus with a lower maximum exposure rate can be seen in the remainder of row 36.

4 In the attached spreadsheet, see cell B22 on the "prolonged both" sheet. The total dose from smaller dogs prescribed less activity and thus with a lower maximum exposure rate can be seen in the remainder of row 22.

It is assumed that after expiration of the written instructions, the family will return to its prior behaviors with the dog since that is what they are used to doing. With regard to the dog, the relief provided by the injection is not instantaneous. The improvement is gradual over the course of several months and thus the dog's behavior can be expected to remain the same over the relevant time period.

Proposed written instructions

Most dog behaviors and human-dog interactions do not need to be modified to successfully limit the dose to a member of the public to less than 100 mrem. This meshes well with the need to have instructions that the owner can adapt and maintain. The objective is to minimize the behavior modification needed. For that reason, we have identified those possible dog behaviors that would most substantially impact the dose. Those would be:

a) sleeping with a person,
b) sitting on the lap of a person for an extended period of time ("lapsitting"), and,
c) as a distant third, lying at the feet or beside someone that works from home or is sedentary ("officing").

Therefore, the veterinarian will conduct pre-screening prior to ordering treatment to identify up-front the dogs that engage in any of those behaviors or other behaviors resulting in similar contact distances and durations. The necessary release instructions will be tailored specifically for dogs that do and do not normally engage in those behaviors. In that way, the minimal possible change in normal behavior for each dog is required. These instructions will be discussed with the owners and agreement reached that they can implement and abide by the instructions.

The proposed written instructions are patterned after those contained in NUREG-1556 Volume 7 Revision 1 Appendix D for I-131 treatment of cats but altered to address the specific characteristics of Sn-117m. Examples of activities that are conducted at distances of 1 foot or 3 feet are provided.

The fill-in-the-blanks on the release instructions would be completed based on the following table. For all situations, maximum allowed activity times of 1 minute, 15 minutes, and 4 hours are used for distances of <1 foot, 1 foot, and 3 feet respectively. Where present, parenthetical values are the calculated values; however, the instructions to the veterinarians would contain only the non-parenthetical values. The minimum instruction duration has been set to 2 weeks to provide a margin of dose reduction even where not strictly necessary. Note that the major behaviors being limited are co-sleeping and lap-sitting. The times provided in the table are the conservative values for time spent doing activities at those distances in the absence of instructions to limit contact with the dog and thus are not behavior modifications at all but simply reminders to the owners to limit contact. For dogs that exhibit multiple listed behaviors, the most conservative (longest) is selected. The times are selected to result in a dose of less than 90 mrem to add a layer of conservatism and provide a margin of safety.

Release Instructions Durations and Allowed Times per person

Exposure Rate (mR/h @ 1 m)[a]	**0.45**	**0.4**	**0.3**	**0.2**	**0.1**	**0.05**
Dogs that do not co-sleep, lap-sit, or office[b] Maximum 1 min @ <1 ft, 15 min @ 1 foot, 4 hours @ 3 feet						
Instruction Duration (weeks)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
Extended Close Contact (Dogs that lap-sit[d]) Maximum 1 min @ <1 ft, 3 hr @ 1 foot, 4 hours @ 3 feet						
Instruction Duration (weeks)	5	5	3	2	2 (0)	2 (0)
Extended Intermediate Contact (Dogs that office) Maximum 1 min @ <1 ft, 15 min @ 1 foot, 12 hours @ 3 feet						
Instruction Duration (weeks)	2 (1)	2 (0)	2 (0)	2 (0)	2 (0)	2 (0)
Prolonged Close & Intermediate Contact (Dogs that co-sleep[c]) (Maximum 1 min @ <1 ft, 11 hr @ 1 foot, 9 hours @ 3 feet)						
Instruction Duration (weeks)	9	8	7	5	3	2 (0)

[a] All measured exposure rates should be rounded up to the next higher value in the table.
[b] Most dogs will fall into this category. No instructions are necessary for this scenario; instructions are provided solely for additional margin of dose reduction.
[c] Co-sleeping is not allowed for the duration of the instructions.
[d] Lap-sitting is not allowed for the duration of the instructions.
[e] Officing is are not allowed for the duration of the instructions.

Restricting this population of dog from doing these activities will not be difficult due to the self-limiting pain already present. In addition, these dog breeds which typically weigh 50 lbs. or more are not considered lap dogs due to the discomfort of having such a large amount of weight and bulk on a human lap. With regard to sharing a bed or couch, again, there is a size limitation that occurs with the space in addition to the pain a dog with OA pain will experience. It should be remembered that the dogs being treated with RSO are in pain and reluctant to jump and to be very active and that this pain and reluctance will continue for the duration of the applicable period of instructions limiting contact.

A veterinarian treating a dog with pain and inflammation of OA has multiple treatment modalities available. Just like dealing with a client who cannot pill a cat, the practitioner determines the best treatment for the dog based on the client. Therefore, if a client cannot be separated from their painful dog to allow Sn-117m colloid to be used safely, another treatment will need to be instituted. However, if the same client returns with their dog which is refractive to the prescribed treatment then the CLIENT has to make the decision whether they can be separated from their painful dog long enough to be treated with Sn-117m colloid to successfully treat the painful OA condition. A signed statement to this effect is part of the documentation associated with the discharge guidance following Sn-117m treatment.

<u>"Contact" Whole Body Dose</u>

Wendt et al (2020) modeled the contact doses from a treated elbow. However, it is not reasonable to treat these dose rates as applicable to calculating a whole body dose. They would

be applicable to calculating extremity and skin dose for veterinary staff however extremity and skin dose is not relevant for members of the public. For a member of the public, the only consideration is the whole body dose.

As discussed above, for distances greater than 1 foot, the center of the human torso is treated as the dosimetric point of concern. For shorter distances, this approximation requires refinement. At these shorter distances, and especially for "contact" doses, NRC Regulatory Guide 8.40 is used to refine the calculations.

A treated dog's elbow can be treated as a point source if the distance from the elbow to the point of interest is large compared with the greatest dimension of the volume, the synovial sac in this case, containing the Synovetin OA. This allows scaling of the dose rate at one meter to other distances using the inverse square law. With distances as short as twice the longest dimension of the source, the error in using the inverse square law is approximately 2% for a sphere and effectively zero for a cylinder (Gollnick 2000 p. 136). As an annular space, the synovial sac can be treated as somewhere in-between these two geometries. Wendt modeled the elbow as a 3 cm diameter cylinder thus distances of 6 cm or greater can be modeled using the inverse square law with reasonable accuracy.

In the transverse plane, the human torso can be approximated as an ellipse in which can be defined in terms of the length of the major and minor axes. Cross-sectional CT and MRI images from Novelline and Squire (1987) were measured to determine the minor:major axis ratio. The thorax axis ratio varied from 0.6 to 0.77 with an average of 0.71. The abdomen axis ratio varied from 0.74 to 0.85 with an average of 0.81. For the purposes of this evaluation, an average axis ratio of 0.75 was used as a reasonable average and conservative for the abdomen which is the more critical portion of the torso as discussed below.

In order to determine the absolute values of the ellipse major and minor axis, anatomic data from ICRP 89 (2001) and Tanner (1978) were used. The ICRP states that the trunk is equal to essentially half the human volume at all stages of development. This statement is extended to equate to approximately half the mass as well. NRC Regulatory Guide 8.40 divides the torso into two pieces, the thorax and abdomen. It is further assumed that each of these is approximately equal in length.

ICRP 89 Table 2.9, Figure 4.5, and the un-numbered body height table on page 63 are used to determine the overall trunk length and mass. Assuming a unit density, these values are used to determine the length of the major and minor axes. The salient values are provided in the table below. The values for males and females are the same up to 15 years of age. The values for males are used for adults to provide an upper bound; the values for adult females would lie between those for the 15 year old and the adult male.

The worst case scenario is both dog elbows touching the center of the abdomen directly above the abdomen center of mass on the ellipse minor axis as shown in Figure 7 in transverse cross section and Figure 8 in sagittal cross section. Using the maximum dose rate at release of 0.45 mR/hr at 1 meter, the minor axis radius distance based on the above table, and the 1.7 cm radius

of the elbow (including the skin), the following distances to the center of the abdomen and resulting dose rates using solely the inverse square law were determined. To simplify the calculation, it is assumed all the activity is in one elbow.

Age	Height, cm	Weight, kg	Torso length, %	Torso length, cm	Torso mass, kg	Major/minor axes, cm
1	76	10	40%	30	5	12.6/9.5
5	109	19	36%	39	9.5	15.3/11.5
10	138	32	33%	46	16	18.5/13.9
15	167	56	33%	55	28	22.2/16.7
Adult	176	73	33%	58	36.5	24.7/18.5

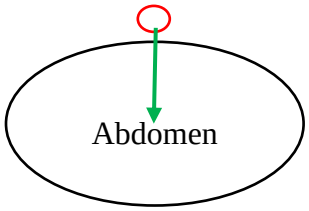

Figure 7. Transverse abdomen view.

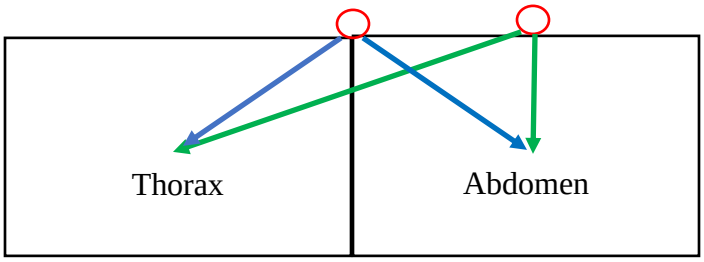

Figure 8. Stylized sagittal torso view. The red circles represent positions for the dog elbow.

Age	Distance, cm	Doserate, mR/hr	Min to 2 mR
1	6.4	61	2.0
5	7.5	44	2.7
10	8.6	33	3.6
15	10.0	24	4.9
Adult	11.0	20	5.9

This dose rate includes the contribution from both the abdomen and the thorax although the thorax is a minor contributor based on the increased distance. If the dog elbow were instead positioned at the torso center, at the junction of the thorax and abdomen, the resulting dose rate varies from 40 to 12 mR/hr for the 1 year old to adult and time to 2 mR from 3.0 to 10 minutes, less than with the elbow centered over the abdomen. Any other position of the elbow has a dose rate lower than when the elbow is centered over the abdomen.

Based on these values, written directions that limit "direct" contact will not result in a dose exceeding 2 mR in any one hour.

Board and Kenneling

Boarding and kenneling of a dog is an activity that has little close contact with a dog. It is important to keep in mind that commercial boarding and kenneling, including "doggy daycare," of a dog is not like an animal rescue operation, the SPCA, or a city/county animal shelter. It is a business staffed by employees and not staffed by volunteers. At an animal rescue operation, the SPCA, or a city/county animal shelter that might have volunteer staff, those entities are the dog's "owner" and none of them have the resources to fund this treatment and therefore interactions that occur at those facilities are not relevant.

At a commercial boarding facility, the dog spends the majority of its time isolated in a cage or dog run. During feeding, the kennel worker's proximity to the dog is not that close and the duration of the interaction is very limited. When let out to urinate/defecate or for playtime, it is leash led. The facility design is such that large dogs are kenneled at ground level and there is no reason for a kennel worker to have to lift the dog. Only small dogs might be in elevated cages. Other interaction with the dog is limited to when the dog is let out for exercise/playtime and one person is only loosely supervising 5 or more dogs. Close contact, such as prolonged petting and affection, is not done, in part because the operation is a business and the staff have many other tasks to perform, but also as a means of limiting the potential for infection spread between dogs. A given kennel worker is responsible for 30 or more dogs. Even if the worker had the inclination to spend time with an individual dog, to the dereliction of all the worker's other task, that would only allow no more than 16 minutes per dog per shift (day). Assuming as a worst case scenario that a kennel worker spent 30 minutes per day at one foot from a dog (petting distance), this would amount to a total dose of 33 mrem for the largest dogs released at the maximum release dose rate, 0.45 mrem/hr @ 1m. In reality, most interactions occur at greater distances and for less total time per day. The kennel should be supplied with a copy of the instructions to reinforced expectations and necessary behavior.

Commercial Grooming/Tactile Therapy

Commercial grooming and tactile therapy are activities that occurs at a distance of 1 foot. Given that the maximum release doserate is 0.45 mrem/hr at 1 meter, a 2-week delay in commercial grooming and factoring in the dog torso shielding factor results in a doserate of 1.67 mrem/hr at 1 foot, sufficient to meet the 2 mrem in any one hour criteria for even the largest dogs.

Reliance on written instructions

NUREG-1556, Volume 7, Revision 1 states that written instructions should provide a margin for dose reduction but should not be relied upon as the primary way of keeping the dose to members of the public below 100 mrem. Although seemingly clear and straightforward, the exact intent of this statement is nonetheless not completely clear. As demonstrated by NMED report 010664, some reliance upon release instructions, included those contained in NUREG-1556, Volume 7, Revision 1, is necessary to limit dose to members of the public to less than 100 mrem from I-131 therapy for cats. The statement in the NUREG is taken to mean that credit can be taken for the

written instructions, but that the credit should be limited, i.e., the majority of the dose limitation should occur based upon other factors and that the written instructions are a secondary factor. This would be consistent with the approach taken in NCRP 148 (NCRP 2004) where there is no such restriction on the credit which may be taken for the written instructions. The NCRP approach is more emphatic in requiring particular components of the written instructions (cautioning against holding the animal, etc.).

Sn-117m therapy for dogs is similar in this regard as I-131 therapy for cats. The primary factors limiting dose to a member of the public are the natural behavior patterns for dogs in general and dogs with severe OA in particular. There are three potential behaviors which need to be controlled with dogs, co-sleeping, lap sitting, and officing, two of which happen to be the same behaviors which must most be limited with regard to cats and thus appear in the cat I-131 therapy instructions as the prohibitions against sleeping with the cat and minimizing the time in close contact.

Calculations

All calculations were performed using the following equation:

$$D = \frac{D_0}{\lambda} * \left[\left(1 - e^{-\lambda T_I}\right) * (Sh_3 * T_3 + Sh_1 * (T_1 + T_6)) + e^{-\lambda T_I} * (Sh_3 * T_{3inf} + Sh_1 * (T_{1inf} + T_{6inf}))\right]$$

Where:
D = Total dose to a member of the public
λ = Sn-117m decay constant, 0.05097 d^{-1}
D_0 = Exposure rate at a distance of 1 meter at release, mR/h
$C_{1m\text{-}3ft}$ = Exposure rate adjustment from 1 meter to 3 feet
Sh_3 = Exposure rate adjustment from 1 meter to 3 feet * 0.72 shielding adjustment
Sh_1 = Exposure rate adjustment from 1 meter to 1 foot * 0.68 shielding adjustment (also used for 6 in distance)
T_I = Duration of release instructions, days
T_3 = hours per day at 3 feet during duration of release instructions
T_{3inf} = hours per day at 3 feet after end of release instruction (default)
T_1 = hours per day at 1 foot during duration of release instructions
T_{1inf} = hours per day at 1 foot after end of release instruction (default)
T_6 = hours per day at 6 inches during duration of release instructions
T_{6inf} = hours per day at 6 inches after end of release instruction (default)

The attached[5] spreadsheet in Appendix D contains the supporting calculations. The largest (110+ lb) dogs are expected to have a maximum exposure rate of approximately 0.4 mR/hr at 1 meter. The expected exposure rate from smaller dogs will scale approximately linearly with size.

5 The spreadsheet is attached only to the electronic distribution of this report.

Conclusions

Treatment of OA in dogs with RSO is performed after the pain associated with OA has significantly impacted the dog's quality of life and other less expensive treatments have failed to provide satisfactory results. The majority of dogs treated with RSO are larger dogs with limited mobility. Even among healthy dogs, these dogs do not typically sleep in the bed with their owners or climb into their lap, and dogs with severe OA would be even less likely to do so. Conservative estimates of the amount of time, and associated distances, owners spend in routine activities with their dogs were performed based on behavior of normal dogs. In each instance, it can be expected that a dog with OA would spend the same or less time in each of those activities.

Calculations of the prospective dose to an owner based on these times and distances were performed which determined that for your typical dog (and vast majority of treated dogs) that does not sleep in its owner's bed or sit in its owner's lap, the dose from an RSO treatment with Synovetin OA would result in a dose of no more than 44 mrem from the largest dogs and proportionately less for smaller dogs. For dogs that do sleep in its owner's bed, sit in its owner's lap, or lie by its owners chair most of the day, written instructions prohibiting these behaviors are necessary to ensure that the dose to the owner remains less than 100 mrem. These prohibitions for Sn-117m treatment of dogs are consistent with the prohibitions necessary to ensure treatment of cats with I-131 does not result in a dose to a member of the public of greater than 100 mrem. The behavior modification of the dogs is limited, most routine daily behavior are unmodified, and the time period for which modification is needed is limited, making compliance relatively straightforward and manageable.

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Appendix A
Radiosynoviorthesis Flow Chart

Appendix B
Dog Interactions Video Clips
(electronic distribution only)

Appendix C
Canine Torso Shielding Evaluation

Appendix D
Calculations Spreadsheet