

## Agreement State Comment Resolution

### Exubrion Technical Evaluation Report

Comment No.	Comment	Response
1	<p>The TER relies on dose rate and distance measurements that are difficult to obtain. Exubrion reported that because of movement during the equilibration time of the meter, it is hard to get a stable dose rate reading. It would be equally difficult holding a meter steady at the prescribed distance of 3.3 feet. The poor correlation of Wendt et al1 exposure rate/weight data seems to corroborate that assertion. Exubrion should provide protocols to be added in the TER for attaining high confidence measurements to be used in guiding release decisions.</p>	<p>The NRC staff believes the difficulty of performing survey measurements of dogs is no different than performing surveys of previously approved animal release, such as horses or cats. As NUREG-1556, Volume 7, Appendix D does not require licensees to submit detailed survey procedures for licensing, NRC staff does not believe there is a need for Exubrion to submit it in this generic application. However, licensees are required to ensure adequate release surveys per 10 CFR 20.1501 and surveys shall be retained for 3 years per 10 CFR 20.2103(a). This should be evaluated during inspections.</p>
2	<p>The Board's letter dated August 11, 2020 asked, in part, "what happens to the radiopharmaceutical if it is not injected into the correct spot, is it then excreted? Does it travel to a different physical location within the animal where the owner needs to be aware of a different radiation hazard? Is it appropriate to release the dog?" NRC responded "Exubrion stated that they saw no bio kinetic transfer to any other organs in a study evaluating impacts of missed injection sites." This satisfies the question regarding transfer to organs, but was an increase in excretion noted? If so, there is a risk of contamination and not just exposure that needs addressed.</p>	<p>Exubrion performed a study in rats to investigate this. The worst case is an intravenous injection, where the study showed the material primarily distributed to the liver with little to no excretion. For injections other than intravenous, the material remained at the injection site.</p> <p>In addition, during the initial dog studies, there was an injection that accidentally missed the synovial sac. In that case, subsequent imaging revealed that the injected material remained at the injection site with no biodistribution elsewhere.</p>

## Agreement State Comment Resolution

### Exubriion Technical Evaluation Report

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3	<p>The TER states that “Licensees should use the information gathered during the pre-screening evaluation and discussions with the owner, not Exubriion’s evaluation of common dogs, to determine the typical time and distances the dog has with all individuals in the household. Based on the information about the interactions in the dog’s household, the licensee will determine if release is appropriate for each dog following treatment and provide instructions to the household in order to have confidence that public dose limits will not be exceeded.” This amounts to an individual dose assessment for each household member. Will the assessments be reviewed by the NRC during inspection and what guidelines will they use for the review? A standard license commitment to retain every household members’ time studies and dose assessments should be included for each treatment.</p>	<p>Exubriion preformed the dose assessment for four bounding categories of dog-human interactions and demonstrated they do not exceed public dose limits with instructions. As long as the household members typical interaction patterns do not exceed the bounds of these categories, licensees will not need to perform individual dose assessments. This procedure does not allow licensees to perform their own dose assessments to allow release when household members interaction patterns do not fit into one of these categories.</p> <p>The information gathered during the prescreening questionnaire should be used to determine which category should apply for the household. The procedure requires the licensee to retain the prescreening questionnaire. Therefore, this should be available for inspection.</p>

## Agreement State Comment Resolution

### Exubrion Technical Evaluation Report

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4	<p>NCRP Report No. 116, Limitation of Exposure to Ionizing Radiation, recommends an equivalent dose limit for the fetus of an occupationally exposed individual of 50 mrem (0.5 mSv) per month during the pregnancy. Excluding this treatment for households with pregnant women would seem sensible if their interactions fall within those extended and prolonged close contact categories or if individual assessments result in a dose of exceeding 50 mrem per month.</p>	<p>The NRC does not have different public dose limits for pregnant women or fetuses. The public dose limit is 2 mrem in any one hour and 100 mrem a year. However, NUREG-1556, volume 7, Appendix D does address pregnant women and their need to limit exposure to a radioactive animal. Exubrion addresses this in their prescreening questionnaire which has licensees question if close contact interactions with pregnant women can be minimized and discuss strategies to minimize their dose prior to treating the dogs.</p>

## Agreement State Comment Resolution

### Exubrion Technical Evaluation Report

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5	<p>Under Notes to License Reviewer, the first bullet on page 18 of the TER, describes that license reviewers obtain “a commitment that the licensee will not use this procedure to release a dog whose typical behavior patterns, without instructions, do not fit into the time and distance limitations listed for one of the categories described in the procedure as these categories are the only ones evaluated.” This bullet is confusing, does it intend to mean that the treatment should not be performed, or that another procedure for release should be followed?</p>	<p>Exubrion<del>s</del> demonstrated that public dose limits will not be exceeded for the maximum amount of times described in the four behavior categories described in the application. Therefore, this procedure can only be used to release dogs when all household members fit into one of these categories. If a licensee wishes to release a dog where a household member does not fit into one of these categories, more evaluation would need to be done to demonstrate public dose limits would not be exceeded. This would require a license amendment. The final TER provides more information on the categories.</p>

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### Exubrion Technical Evaluation Report

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6	<p>Under Notes to License Reviewer, the second bullet on page 18 of the TER, states that "...the licensee will not release a dog if a child is in the house under the age of 5 who does not fit into the common contact or extended duration or immediate contact scenarios, because the other scenario is not evaluated by Exubrion's technical basis and the typical interaction patterns could exceed the public dose limits." What is "the other scenario" that was not evaluated by Exubrion? Is the objective of this point meant to restrict releasing a dog into a household with children under the age of 5 where a pre-established contact scenario does not fit with what is discovered during pre-screening or is it to reject the candidate for treatment all together?</p>	<p>This language was updated in the final version of this document. The objective of this language is to not use this procedure to release dogs where household members behavior does not fit into one of the pre-established categories evaluated by Exubrion. If a licensee would like to allow release to a household where behaviors do not fit into the categories, additional evaluation and procedures would be necessary. This would require a license amendment.</p>

## Agreement State Comment Resolution

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7	<p>The TER describes "...that licensees must investigate any public exposure where limits might have been exceeded, even if it is due to individuals not following instructions, and to report those to the NRC per 10 CFR 20.2203." The Board supports this requirement; however, concern exists over the discussion of 500 mrem being an acceptable limit to protect health and safety.</p> <p>The TER concludes that "Even if no instructions are followed, the staff determined that the highest likely exposure to a household member, who is a member of the public, would likely be below 500 mrem. As this dose will be received by someone who would likely be benefitting from the exposure and is at a level allowable by the NRC in other circumstances where individuals benefit from the exposure, such as patient release, the staff finds the risk from this dose acceptable given the licensee provides adequate instructions and means to prevent the exposure." Licensees may lower their safety focus knowing that acceptable limits from other parts of the 10 CFR should still be upheld in worst case scenarios and ignore the need to follow up or calculate doses to adhere to 10 CFR 20.1301. An increased dose allowed to members of the public, as a consequence of patient release, is due to the life-saving or quality of life improving treatments to a human person, not an animal. The Board objects to the conclusion that an increase in dose from a treated animal is a beneficial exposure and recommends removing any discussion of other parts of regulation or the 500 mrem limit.</p>	<p>The NRC removed language from the TER regarding benefits to the owner and reference to other regulations other than the public dose limit. In addition, the NRC updated the TER to clarify that it is the individual licensee's responsibility to ensure compliance with public dose limits. As described in the TER, the NRC staff believes Exubrion's proposed procedure provides adequate measures to ensure public dose limits will not be exceeded when owners provide complete and accurate information.</p> <p>However, staff performed calculations to bound the worst case dose if an owner provides incomplete or inadequate information during prescreening or if a household member chooses to not follow instructions after the owner confirms they will. The staff finds the likelihood of such a scenario to be low given the conservatism in the calculations and assumptions used in the scenario and that the licensee provides adequate instructions and means to prevent the exposure. Therefore, the staff finds Exubrion's proposal adequate to protect the public's health and safety.</p>

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8	Step A3.7 of the Procedure is confusing where it states "Note that only [one] category will apply for the entire household." If all the household members do not fit into the same category, then is the most restrictive category used? How does that reconcile with the TER where it says Exubrion's evaluation of common dogs should not be relied upon?	Licensees should not use Exubrion's evaluation of typical dog behavior. Instead, licensees will need to conduct a prescreening evaluation with the dog owner to understand the individual dog's typical behavior, including all typical dog-human interactions, in order to determine the behavior of the dog. The licensee will then use the prescreening information to choose the appropriate category for the household. The TER has been updated for clarity on this point.