

A Summary of Radiation Dose Guidelines and Limits Applicable to Human Subjects in Research Studies

These guidelines and limits are applicable to radiation doses, which are “indicated for research” and are not for the medical benefit of the subject (medically indicated radiation).

UMB RADIATION SAFETY POLICY GUIDELINES

All uses of radiation or radioactive materials in or on human research subjects must be specifically approved by the UMB Radiation Safety Committee. Proposed research studies will be reviewed with respect to the following radiation dose limit guidelines:

<u>AGE OF SUBJECT</u>	<u>RADIATION DOSE LIMIT</u>
Under 18 years	300 millirem (mrem) to any tissue in a 13 week period and 500 mrem annually
18 years or more	3,000 mrem to any tissue in a 13 week period and 5,000 mrem annually

NOTE: Pregnant subjects may not participate in research studies that involve radiation exposure. It is the responsibility of the investigator to ensure that female subjects are not pregnant prior to participation.

Radiation dose guidelines apply to the dose from all radionuclide procedures and all diagnostic radiology (x-ray) procedures related to the research study, together with doses from other research studies in which the subject may be participating or has participated in during the year.

The above dose limits should be observed when diagnostic and experimental purposes permit. When it is necessary to exceed these limits because instrumentation for required sensitivity is not available, the applicant is required to provide justification for higher doses with due consideration of the potential risks and research benefits.

Larger radiation doses may be considered by the Radiation Safety Committee where research subjects have limited life expectancy (two years or less) and the applicant adequately justifies the procedure and the importance of the anticipated scientific contribution. The limited life expectancy provision is pertinent only to consideration of the potential increased risk of stochastic, latent effects (carcinogenesis) that could result from radiation received as a research subject.

In any research use of radiation or radioactive materials with human subjects, the study should be designed to minimize radiation dose to the subject as much as is possible, consistent with obtaining the desired research information.

FDA REGULATORY LIMITS

Reference: Title 21 CFR Part 361

FDA (Food and Drug Administration) radiation dose limits are applicable only to the use of “radioactive research drugs,” as defined by the FDA regulations, in research studies with human subjects. Research protocols and Applications for Authorization that meet the criteria for use of “radioactive research drugs” must be approved by the UMB Radioactive Drug Research Committee, in addition to approval by the UMB Radiation Safety Committee.

<u>AGE OF SUBJECT</u>	<u>RADIATION DOSE LIMIT</u>
Under 18 years	300 (mrem) to the whole body, active blood-forming organs, lens of the eye and gonads from a single administration, and 500 mrem annually
18 years or more	3,000 mrem to the whole body, active blood-forming organs, lens of the eye and gonads from a single administration, and 5,000 mrem annually. 5,000 mrem to other organs from a single administration, and 15,000 mrem annually.

Radiation dose limits apply to the dose from all radionuclide procedures and from all diagnostic radiology (x-ray) procedures related to the research study.

Proposed research studies, which require radiation doses exceeding the FDA limits, cannot be considered as the use of “radioactive research drugs” and, therefore, reference to the FDA radiation dose limits is inappropriate.

Pregnant subjects may not participate in research studies using “radioactive research drugs.” It is the responsibility of the investigator to ensure that female subjects are not pregnant at the time of dose administration.

OTHER RADIATION DOSE LIMITS

Reference: Title 10 CFR Part 20

NOTE: The following radiation dose limits are not applicable to human subjects in research studies. They are presented here for general information and guidance.

OCCUPATIONALLY EXPOSED PERSON (RADIATION WORKER)

<u>AGE OF SUBJECT</u>	<u>RADIATION DOSE LIMIT</u>
Under 18 years	125 mrem to any tissue in a 13 week period and 500 mrem annually
18 years or more	3,000 mrem to any tissue in a 13 week period and 5,000 mrem annually

NON-OCCUPATIONALLY EXPOSED PERSON (“PUBLIC”)

<u>AGE OF SUBJECT</u>	<u>RADIATION DOSE LIMIT</u>
Any age	100 mrem per calendar year

RADIATION DOSE TO THE EMBRYO/FETUS FROM OCCUPATIONAL EXPOSURE TO THE MOTHER

Reference: National Council on Radiation Protection and Measurements (NCRP) Report No. 53 and US NRC Regulatory Guide 8.13

As recommended by the National Council on Radiation Protection and Measurements (NCRP), and adopted as UMB radiation safety policy, the radiation dose to the embryo/fetus resulting from occupational radiation exposure to the mother should not exceed 500 mrem during the period of gestation (nine months).

As an operational technique, fertile female workers should limit their occupational radiation dose to no more than 250 mrem per month, so if a pregnancy is confirmed, the total radiation dose received by the embryo/fetus during the first two months would not exceed 500 mrem fetal dose limit. Pregnant workers should then avoid, or reduce radiation exposure in the work place.

I. Radiation Dose As Low As Reasonably Achievable (ALARA)

Superimposed on the radiation dose limits summarized in this handout is the requirement that radiation dose to workers, research subjects, patients, and the general public shall also be as low as reasonably achievable. This is referred to as the “ALARA” principle and requirement.

Conscientious effort should be made to reduce or minimize any radiation dose consistent with obtaining necessary diagnostic or research information. Consideration should be given to the use of as small a quantity of administered radioactivity as is practical for a research procedure, as well as the elimination of any diagnostic radiology (x-ray) procedures or nuclear medicine procedures that are not essential to the conduct of the research study.

Further information regarding radiation dose limits may be obtained by contacting the UMB Radiation Safety Office at (410) 706-6281.

II. Authorization For the Administration of Radioactive Materials to Human Subjects at UMB

A. General—Administrations of radioactive materials to human subjects at UMB fall under the jurisdiction of the Human Use Subcommittee (HUSC). Persons wishing to become authorized to possess and use such material in humans must first present an acceptable application to the HUSC describing their particular use. The degree of scrutiny to which the applicant/and or application is subject depends on the novelty of the proposed use. Thus, research applications are examined more closely than those that involve only routine, well-established uses. The categories of uses which may be authorized by the HUSC includes the following:

1. Well established medical uses
2. Investigational uses under an FDA approved protocol (manufacturer's IND or the like)
3. Investigational uses under a protocol proposed by the investigator (these will ultimately require FDA concurrence if they involve agents used for diagnostic or therapeutic purposes)
4. Investigational uses of radiolabeled forms of compounds for the purpose of elucidating the biochemistry and/or metabolic fate of the unlabelled substances in humans (limited to 30 subjects)

Applications in these several categories differ in kind with respect to the required qualifications of the applicant and the quantity and source of documentation and/or evidence required to support the proposed use.

B. Well Established Medical Uses—A medical use that is recognized as “well established” is not normally re-examined by the HUSC although the subcommittee reserves the right to do so (169-Yb –DTPA for example, though a well established agent for cisternography, is not permitted at UMB because of the risk of long term contamination due to the 32 day half life of 169 Yb). Ordinarily the HUSC grants blanket authorization for all well-established uses within the recognized competence of the physician-applicant. Competence is established by, board certification in a medical specialty that requires training in the safe use of radioisotopes for example, Nuclear Medicine. Or by equivalent evidence of an adequate level of training and experience. The subcommittee must also be satisfied that the proposed conditions of use are within the bounds established by the UMB Radiation Safety Committee (RSC), the institutional license and the regulations of the State of Maryland. Approvals are for a period of four years.

C. Investigational Uses Under FDA Approved Protocol—Physicians already holding approved authorizations to possess and use well-established radioactive agents in humans may apply for additional authorization to conduct investigational studies under an FDA approved protocol (IND). Similar applications from other physicians may also be approved provided that they meet the criteria set forth in item B above. In either case, the HUSC will require:

1. A copy of the approved protocol
2. Assurance that the protocol will be followed and
3. Annual reports of all administrations made under that particular protocol

Such administrations may or may not require informed consent from the subjects, depending on the status of the IND, but all such uses require prior approval of the UMB IRB and annual reports to the HUSC (via the Radiation Safety Office) of all administrations made under the protocol. In addition, the fact that the FDA approves an investigational use implies, but does not guarantee approval by the HUSC of this institution. The proposed use may be rejected on the grounds that it exceeds the latitude permitted in the institutional license or that the local facilities are inadequate or for such other cause. Approvals are for a period of one year and may be renewed.

- D. Investigational Uses Under a Protocol Proposed by the Investigator—Proposals in this category do not carry with them the imprimatur of prior FDA approval. They are therefore subject to scrutiny that searches beyond the qualifications of the investigator, the adequacy of the facilities and the permissible limits of the institutional license. The HUSC will examine the merits of the proposal itself with regard to the likelihood of success, given the research plan, the magnitude of the radiation dose risk and the plausibility of the data upon which the dose estimates are based. In general, the HUSC will not approve a proposal for an investigational use that involves a dose to the whole body, gonads, or any critical organ(s) in excess of 5 rads, nor one that admits of the possibility of such a dose to minors or gravid females. The subcommittee reserves the right to impose more strict dose limitations or to reject the application outright when, in its opinion, the submitted dosimetric data is less than convincing or when the aims of the study could be achieved at lesser risk or by some other means that do not involve exposure to radiation or from some similar cause. Approvals, when granted, will particularly specify the number of subjects that may be studied (that number is subject to negotiation, within limits) and the maximum administered dose (μCi or $\mu\text{Ci}/\text{kg}$). All such uses require informed consent from the subject, prior approval from the UMB IRB and annual reports to the HUSC of all administrations made under the approved protocol. Approval durations vary and may be renewed.
- E. Investigations of Biochemistry and Metabolism Using Radiolabeled Substances—Under a recent liberalization of federal regulations, the FDA has agreed to permit certain FDA-approved committees to act in that agency's behalf to grant users within the institution authorization to undertake studies of biochemistry and metabolism using trace quantities of radiolabeled substances. The regulations attach a number of conditions to such approvals, like:
1. Minors and gravid females must be excluded
 2. No more than 30 subjects may be studied
 3. The radiation absorbed dose to the whole body, gonads, and any "critical organ" must not, in general, exceed 3 rem and
 4. The quantity (mass) of administered, labeled substance must not exceed 10% of the pharmacologically effect dose on the toxic dose if the substance is exogenous or 10% of the amount normally present in the system being studied when the labeled compound is endogenous.

Because the last limitation above rules out pharmacologically active, toxic or system perturbing doses, the applicant need not be a physician licensed to prescribe drugs, although that would be the normal expectation.

Applications meeting all of the above limitations will be subject to the same sort of scrutiny described in item D. As an aid to both applicant and the HUSC, a coversheet (enclosed and entitled "Radioactive Drug Research Authorization Summary Sheet") is provided on which the applicant is to summarize the pertinent information in a concise form. The HUSC reserves the right to reject or amend the submitted protocols described herein in item D. Uses in this category also require informed consent from the subject, prior approval from the UMB IRB, and annual reports to the HUSC of all administrations made under the approved protocol. Approvals are for a period of one year and may be renewed provided that the total number of subjects in the ongoing study will not exceed thirty (30)

- F. Conclusion—It is hoped that the guidelines presented herein will clarify the procedures for obtaining human use authorizations in the several permissible categories. While the subcommittee will not write a user's application for him, the members recognize that not all worthy would be users are experts in radiation dosimetry or in the intricacies of the regulations. Given a conscientious first effort by the applicant together with a basically reasonable proposal, members of the subcommittee stand ready to assist applicants with the details of the application.

Radiation Drug Research Authorization Summary Sheet

Title of Study: _____

Name of Applicant: _____

1. Full chemical name and/or formula with identity and position of labeling radionuclide: _____

2. Vendor: _____

3. Route of Administration: _____

4. Radiotoxicity

- a. Activity to be administered _____ uCi
- b. Whole body radiation dose _____ rad
- c. Gonadal radiation dose _____ rad
- d. Critical organ(s) dose (specify) _____ rad
_____ rad
_____ rad

5. Chemical Toxicity

- a. If endogenous substance, amount normally present in the system under study _____ gm
- b. If exogenous substance, pharmacologically active or toxic dose _____ gm
- c. Mass of labeled substance to be administered (not to exceed 10% of a or b) _____ gm
- d. Means of assurance of sterility _____
- e. Means of assurance of apyrogenicity _____
- f. Adjunctive drugs, if any (describe amount, rout of administration, etc.)

6. Subject Selection (minors and gravid females must be excluded)

- a. Number of subjects (not to exceed 30) _____
- b. Number of administrations per subject _____
- c. Means of ruling out pregnancy _____
- e. Other selection criteria (describe):

Signature of Applicant: _____

Date: _____