1. Executive Summary and Recommendations

The process of extrapolation, which involves projection from the known to the unknown, can be a daunting task. A quote from a leading biometrician defines what the task needs: "To be useful, extrapolation requires extensive knowledge and keen thinking" (Snedecor, 1946). In preparing this Report, the National Council on Radiation Protection and Measurements (NCRP) faced the task of evaluating extrapolation of the risks of radiation-induced cancer to humans from experimental data. There is extensive information from experimental studies at the animal, cellular, chromosomal and molecular levels that might be used in deriving approaches to the problem of extrapolating risk estimates across species. But there are also gaps in the database. Therefore, uneasiness persists in the acceptability of extrapolations from nonhuman data, with the exception of the use of data from mice in the derivation of dose and dose-rate effectiveness factors (DDREF). Furthermore, although considered a choice of necessity rather than an ideal solution, data obtained from experimental animals have been used to derive an estimate of the dose-rate effectiveness factor (DREF) and radiation weighting factors.

The overall aim of this Report is to consider the possibilities, the difficulties, and the attempts to extrapolate estimates of radiation-induced stochastic effects across species, especially laboratory animals to humans. This Report is neither a compendium of stochastic effects studies, nor a detailed account of mechanisms of the induction of stochastic effects in different species. This Report does, however, discuss some of the similarities and differences of responses to radiation at the molecular level.

This Report concentrates on life shortening and cancer, with some comments on the use of data from mice, augmented by data from humans, in the estimation of the risk of radiation-induced heritable diseases. Unless it can be shown that the aspects of the mechanisms of importance in extrapolation are similar in cancers that arise from cells that differ in type, there must be concern about pooling the data for different types of tumors in a specific organ. The fact that extrapolations of risk estimates across strains of mice

are feasible (Goldman *et al*., 1973; Grahn, 1970; Norris *et al*., 1976; Sacher, 1966; Sacher and Grahn, 1964; Storer *et al*., 1988) may have been because the cells of origin of the tumors were the same in the same specific organs in the different strains.

The goals of this Report were broad and included an evaluation of the full range of somatic risks, the quality and quantity of the data from which extrapolation could be projected, and existing and potential methods for the extrapolation process. A number of different methods of extrapolation of risk estimates of radiation-induced cancers had previously been proposed but there has been neither a systematic examination of the similarities and differences among species at the molecular, cellular, tissue and whole-organism levels, nor of the appropriateness of the data available to attempt extrapolations.

Data from experimental animals are used in the estimation of genetic risk and in the derivation of factors to account for the effect of dose rate and radiation quality because of the lack of human data. However, direct estimates of risk of radiation-induced cancer at specific sites in animals have not been used.

1.1 Why Is Extrapolation Still Required?

Extrapolation is still required because the available data on irradiated human populations have several important limitations. The risk estimates for radiation protection are based largely on the data from the atomic-bomb survivors, who were exposed to an acute, high dose of gamma rays, and radiotherapy patients who have been treated with high-dose-rate fractionated exposures. A large number of people have been exposed occupationally, some protracted over long periods but in complex time patterns that have made it difficult, if not impossible, to determine the effect of total doses of low-dose- rate radiation. Hence, there is the need for data from experimental studies to determine values of DREF. Most of the exposures of humans are to very small multiple exposures of high-dose-rate radiation. Diagnostic radiation is one example. In the case of occupationally exposed individuals, much of the exposure occurs at ages of reduced susceptibility, and the reduction in effectiveness is not solely due to the reduced dose rate.

There are also inadequate data of the effects of high linear-energy transfer (LET) radiations such as fission neutrons of relevant energies and heavy ions for the estimation of risk in humans. There are some experimental weighting factors, but more data are needed.

It is the aim of this Report to examine the problems and potential of extrapolation of experimental findings in laboratory animals to risk estimates in humans. It is necessary to determine the criteria on which the suitability of the data for extrapolation purposes can be decided. For example, consideration is given to whether risk estimates of cancer induction should be based on cancers originating in the same types of cells and not just the same organ.

1.2 Summary of Findings

This Report has five sections following a brief introduction. First, the history and existing methodologies of extrapolation are presented. Second, a discussion is presented of selected neoplastic disease endpoints of particular importance to humans. Third, radiation-induced damage at molecular and cellular levels is reviewed in detail as the underpinning of comparisons at the tissue and organ levels. Fourth, extrapolation models and examples are given and include a discussion of the complex fields of radionuclide toxicology and chemical toxicology is included. Fifth, is a summary of the Report's findings followed by a glossary of terms and references.

1.2.1 *Historical Aspects*

A brief review of the extrapolation of genetic risks from animals to humans revealed concerns about somatic effects, which are not readily studied by traditional genetic processes. There are substantial differences in approaches to studying genetic or somatic effects: the baselines, issues and methodologies of the two areas of investigation are different, with one important exception; it has become clear that risk analysis requires a biological commonality to link the different species. For geneticists, the commonality is simply the deoxyribonucleic acid (DNA) molecule and its associated metabolic management. For those dealing with somatic effects, there is, in addition to DNA, the common process of "dying out" (the actuarial life table), the importance of which slowly became appreciated between about 1925 and 1950. This Report recounts the attempts to extrapolate risk estimates across species, critically examines the strengths and weaknesses of these attempts, and supports and extends the contention that estimates of the effects of radiation on life or neoplastic diseases can be extrapolated across species to humans.

1.2.2 *Neoplastic Disease*

In this Report, seven tissues or organs (hematopoietic system, lung, breast, thyroid, skin, gastrointestinal track, and bone) were studied for the feasibility of extrapolation of cancer risks. These were chosen for their general importance in human cancer risk analysis and because extensive data exist from animal studies. There are distinct differences in the problems and their solutions that are encountered in undertaking risk estimation and extrapolation of risks for external and internal radiation. The studies related to external and internal radiation are reported separately. In the case of solid cancers related to external radiation, a major barrier to success for extrapolation and the testing of methods of extrapolation is the lack of data of cancer based on the specific type of cancer or the type of cell or origin. Most of the data that have been used in risk estimates, such as those from the studies of the atomic-bomb survivors used in the selection of radiation limits, are for specific organs, for example lung tumors, not squamous-cell carcinoma (SCC) or small-cell cancer.

Studies of animals, particularly dogs, have long been one of the principal sources of data for estimating the risk of the effects of exposure to internally-deposited radionuclides in humans. Such studies, for example, have been used to estimate risks of latent effects of exposures to bone, lung, liver and bone marrow. An important impetus for these studies was that there was either a complete lack or a paucity of relevant data based on human experience. The need for estimates of risk to humans resulted in the examination of approaches of how to extrapolate these results across species and the adoption of the relative toxicity ratio method (reference can be made to the glossary for a definition for this and other terms, acronyms and abbreviations). There are problems of dosimetry and complicating factors such as relocation of the radionuclide, that are specific to internal emitters; thus, internal exposures to radionuclides are discussed in Section 6.6.

The similarities of aspects of the risk of induction of cancer among species encourage the search for methods of extrapolation. Success in this endeavor will not only improve the current values of DREF and relative biological effectiveness (RBE), but also may make it possible to use the considerable body of experimental data in risk estimation. Between humans and experimental animals there are some fundamental differences that are difficult to assess, such as lifestyle, longevity and environment. Perhaps the most important problem in being able to derive and test methods of extrapolation is the fact that most epidemiological data for cancer

for humans that are used in radiation risk estimation are based on cancer site and not on cell type. In the case of mice lungs, the fact that lung cancers in many strains are exclusively adenocarcinomas, and small-cell cancer is *not* found, limits the potential for extrapolation. There have been few attempts to extrapolate risks of radiation-induced solid cancers, and in the case of hematopoietic diseases, despite all the information for leukemias in humans, dogs and mice, there has been no success in doing so. This Report also considers the problem of differences in host factors among species. In breast, there are important differences in the hormonal influence on tumors among species. One of the encouraging features is the demonstration of the similarities in the genes across the species that are important in the initiation of cancers. While this is obviously important, is it sufficient to allow some method of extrapolation? Another problem is the fact that much of the suitable data for the induction of solid cancers has been obtained after exposure at one age whereas human data, such as that from the atomic-bomb survivors, are for exposures at all ages. This, of course, is more important for the tumors with a marked age dependency such as thyroid cancer. Lastly, much of the data from experimental animals is restricted to a small number of strains. This is particularly true in the case of the dog.

Some of the characteristics of the organs discussed in this Report are briefly noted in the following subsections.

1.2.2.1 *Hematopoietic System*. Leukemia has been considered to be a major oncogenic effect in irradiated human populations. Rodents, dogs and humans have nearly identical hematopoietic systems, similarities in the cell types of myelogenous and lymphocytic leukemias and reticular-cell sarcomas, and some common underlying genetic components.

1.2.2.2 *Lung*. There are significant differences between animals and humans and their susceptibilities to lung cancer induction and the predominant type of cancer (Section 4.3). Thus, simple extrapolation of radiation-induced lung cancer from animals to humans is not reasonable. Selected risk analysis may be feasible for some tumors of the same cell types when there are appropriate experimental animal models, but this is not always the case. For example, small-cell carcinomas in humans lack a counterpart in experimental animal models. The extrapolation of risks from radionuclides has been reported and is discussed in Section 6.5. Further, the role of smoking (which may interact with radiation) cannot generally be evaluated in animal models.

1.2.2.3 *Breast*. The cellular components and the major anatomic and histologic features of mammary glands are similar among humans, dogs and rodents but there are important physiologic differences, for example, in the hormonal control of growth (Section 4.4). The marked strain-dependent differences for both naturally occurring and radiation-induced mammary cancer in the mouse and rat makes these rodents very useful models for the study of molecular, cellular and tissue aspects of the mechanisms involved. There has not been a systematic and critical study of how to extrapolate the extensive data on risk estimates of mammary cancer in different strains of rats and mice.

1.2.2.4 *Thyroid*. The physiology, morphology and tumor cell of origin are comparable among different mammalian species. Extrapolation of the estimate of risk of radiation-induced cancer appears feasible but no quantitative tests have been reported. For the thyroid (Section 4.5) as for the breast, the rat is considered to be the rodent of choice for extrapolation studies.

1.2.2.5 *Skin*. Provided that the data for humans are not confounded by interactions, extrapolation is feasible, but care must be taken to restrict the effort to tumors of the same cell type. It is important to appreciate that data from humans can be confounded by interactions with other chemical and physical agents. Factors such as ultraviolet (UV) exposures and how much of the skin is exposed are important in human skin cancer induction, and thus may be difficult to address in animal models. Furthermore, nonmelanoma skin cancer such as basal-cell carcinoma (BCC) can also be caused by skin exposures to UV light; this is a typical confounding factor with the assessment of radiation risks. Melanoma is considered only briefly because of the lack of evidence that ionizing radiation is a major etiological factor. These issues are discussed in Section 4.6.

1.2.2.6 *Gastrointestinal Track*. There are many similarities in the different gastrointestinal (GI) track tumors among mammalian species. Therefore, these tumors provide an excellent resource for the study of the mechanisms of carcinogenesis. However, there are not adequate data for analysis of dose-response relationships for the induction of tumors of the same type in either humans or rodents to test the possibility of extrapolation. The induction of cancer of the GI tract requires relatively high doses in rodents (Section 4.7).

1.2.2.7 *Bone*. Most of the data for the induction of bone tumors in laboratory animals comes from studies of internally-deposited radionuclides. Permissible body burdens for a number of radionuclides in humans have been derived from studies involving dogs. Whether osteogenic tumors arise from the same cells or the same lineage in dogs and humans is not clear, but the separate data for osteosarcomas and for fibroblastic and fibrohistiocytic types of bone tumors provide an opportunity for testing methods of extrapolation. High doses of external radiation are required to induce bone tumors in humans and experimental animals, and no attempts to extrapolate the risks have been reported (Section 4.8).

1.2.3 *Somatic Genetic Damage at Molecular and Cellular Levels*

The mechanism for the induction of chromosome aberrations and mutations by ionizing radiations are currently best understood for human cells. However, similar mechanisms of induction are known to prevail across a range of species. The processes that convert radiation-induced DNA damage into genetic alterations are errors during DNA repair or replication; some damage is irreparable. The errors, as judged by radiation-induced mutation rates, are broadly similar within a factor of two across mammalian species, with much of the differences in mutation rates accounted for by differences in DNA content. Thus, on the assumption that sensitivity to mutation induction is directly reflective of sensitivity to tumor induction, an extrapolation for radiation-induced tumors that allows for this factor of two is defensible.

Multiple steps seem to lead to spontaneous and radiation-induced tumors in rodents and humans, mutations and chromosome alterations (structural or numerical) being involved at each step. But particular gene alterations involved for a specific tumor type tend to be different across species. Whether this difference is significant in terms of extrapolation is not clear. The data on radiation-induced tumors are, however, limited. Certainly a similarity would strengthen the confidence in the extrapolation. In addition, there are species-specific host factors that can alter the probabilities of tumor development from initiated cells. These factors need to be investigated further to establish how they influence radiation-induced tumor dose-response models and extrapolation across species. Additional data on the mechanism of tumor formation will improve the level of confidence in extrapolating from data on rodent tumors to human tumors.

1.2.4 *Extrapolation Models and Methods*

This Report considers separately the species extrapolation methods that have been used for external and internal exposures. For comparison purposes, a short review is first given of species extrapolation issues in chemical carcinogenesis. For external exposures both life-shortening and cancer risk estimations are reviewed including Bayesian methods for DREF estimation.

1.2.4.1 *Toxicity of Chemotherapeutic Drugs*. The correlation among mammalian species of the toxicity of chemotherapeutics provides encouragement to the radiation toxicologist for extrapolation methods. A judicious combination of pragmatism and pharmacologic chemistry has created feasible and practical approaches to the preclinical and clinical trials of anticancer drugs. The lesson here is to take advantage of the animal data collected for this purpose and look for the underlying physiological commonalities.

1.2.4.2 *Life Shortening*. Two actuarial methods of extrapolation were examined for the life-shortening endpoint. The first method (specially designed for single exposure to low-LET radiation) relies on two findings described in the Report. First, Gompertz models (*i.e.*, linear equations on a semi-logarithmic scale) used to describe age-specific death rates exhibit parallel displacements from the control that are proportional to dose (*i.e.*, can be described as a function of dose). Second, at least for the species compared in this Report ($B6CF_1$ mouse, beagle dog, and humans as represented by atomic-bomb survivors), the dose-dependent displacements of the age-specific death rates can be described by the same equation. This finding produces the desirable effect that species with good dose-response data can be used to predict dose-dependent life shortening in species for which information on radiation exposure is either poor or lacking. The second example presented in the Report describes a method that uses proportional hazard models (PHMs) to perform interspecies predictions of radiation-induced mortality. In this case, the endpoint examined is "intrinsic" mortality, which refers to causes of death that arise from within the individual. As such, intrinsic mortality and life shortening (an integrated measure of damage) are closely related. Simple PHMs were used to describe the dose response in a species chosen to be the "predictor" species. The resulting model was then used to predict cumulative survivorship [$S(t)$] curves at levels of dose observed in a "target" species, in which $S(t)$ is the value of the cumulative survivorship function at time "t," where t is the age when the

deaths from whatever cause are being examined. The ages associated with the predicted $S(t)$ values were scaled by a constant (the ratio of the predictor species'/target species' median ages of intrinsic death). When confidence intervals were calculated for the empirically derived $S(t)$ curves for each dose group observed in the target species, the scaled predictions from the PHM fell within these confidence intervals. In combination, these two examples demonstrate that not only can summary measures of life shortening (*e.g.*, days lost per centigray) be predicted from one species to another, but the entire schedule of age-specific death rates for life shortening can also be successfully predicted.

1.2.4.3 *Interspecies Prediction of Life Shortening and Cancer from External Irradiation*. The methodology for interspecies prediction of cancer from external irradiation relies upon the fact that the life span of all mammalian species can be described by the same mathematical formula that describes the species life table (*i.e.*, the exponential process of dying out). Intercepts and slopes are species-specific, but the equation is the same, and all species can be "created equal" by appropriate codification of the parameters.

Two examples are presented. In one test case, data from mice exposed to protracted daily gamma irradiation are used to predict the survival of beagles subjected to comparable exposure. In the second case, data from mice exposed to single doses of gamma radiation are used to predict observed survival of the atomic-bomb exposed individuals in Hiroshima and Nagasaki. Though the life tables for the latter are not yet complete, a remarkably consistent relation is apparent for the mouse to human extrapolation. The survival of unirradiated populations of mice, dogs and humans can all be described by a single cumulative function of median age at death.

Extrapolation models involve comparisons among different species or different populations within a species. In either case, differences among populations in mortality that are not related to the cause of interest (*e.g.*, accidents, infectious disease, environmental trauma) can conceal or distort a shared species response to radiation, especially for an endpoint like life shortening, which is based on all deaths. This mortality contamination problem was solved in the above extrapolations by coupling a biologically relevant partitioning of mortality, "intrinsic" mortality in the mouse to dog extrapolation, "solid-tissue tumors" in the mouse to human extrapolation, with widely available models for survival analysis that incorporate censoring.

Host factor differences also limit extrapolation. Although mice, dogs and humans often die from identical or nearly identical causes, these deaths need to occur at identical time points within the relative life span of the species to have utility in extrapolation processes. Since background mortality risks vary by age, these species-specific (host-factor) time shifts would probably cause an extrapolation based on a relative risk model to fail.

Finally, it is necessary to account for the fact that humans are exposed to radiations at a wide range of ages, while the animal data consist overwhelmingly of exposures of young adults. Radiation-induced mortality risks are known to vary by age at exposure. This appears to raise a barrier to testing methods of extrapolation because Radiation Effects Research Foundation data on atomic-bomb survivors are largely determined by effects from doses around 1 Sv at high-dose rates. When interspecies data involve large single doses or high-dose rates, the emergence of age-related effects and species dependent pathology syndromes cause the extrapolations to fail. In summary, interspecies extrapolations of radiation-induced risk for external exposure to radiation are feasible, reasonable and reliable when performed within fairly broad levels of pathology and level of exposure. It remains to be seen if extrapolations within defined levels of pathology detail are reasonable.

1.2.4.4 *Extrapolation of Dose-Rate Effectiveness Factors*. Since human data for prolonged exposures to almost all types of ionizing radiation are insufficient for direct estimation of risks, extrapolation of dose-rate effectiveness factors (DREF) using animal data has to be considered. This Report presents one example for extrapolation with data on female BALB/c mice exposed to ^{137}Cs external gamma radiation at low- and high-dose rates. A probability density function for a DREF in mice is estimated for mammary tumors with Bayesian methods and combined with a probability density for the breast cancer risk coefficient in female atomic-bomb survivors. This results in an estimated probability density function and a risk coefficient for breast cancer in humans after prolonged exposure. This probability density also describes the remaining uncertainty about the breast cancer risk in humans after prolonged exposure.

1.2.4.5 *Interspecies Prediction of Injury from Internally-Deposited Radionuclides*. Interspecies extrapolation for radionuclide toxicity has been conducted for many years, in particular for bone cancer.

The metabolic behavior, internal distribution, and deposition of the transuranics, radium and strontium, are predictable for mice, rats, dogs and humans, and the target organ, the skeleton, also responds predictably. This has permitted the use of available data from human exposures to radium, for example, to make predictions for dogs. The approach can be extended to other nuclides for which human data do not exist but animal data do exist and for which exposure or uptake patterns are different among species.

The toxicity ratio, which is based upon the ratio of dose-response slopes for the response to two different radionuclides tested in the same species, has encouraged extrapolation of risk assessment when the internal distribution and deposition of the nuclide is similar for humans and the test species.

The availability of occupational and clinical data involving exposures to radium, radon and/or thorium has provided baseline data necessary to test the reasonableness and practicability of the approach of estimating human cancer risks based on animal cancer studies using internal emitters.

Additional methods of analysis have also been explored. A Bayesian statistical model has been used to evaluate the extrapolation of bone cancer risks to humans from ^{239}Pu. A collection of studies with rats, dogs and humans on the effects of plutonium and radium was used in this effort.

Proportional hazards modeling has been employed to analyze intraspecies studies on the induction of bone and lung tumors by several different radionuclides. The comparison of bone tumor risks from ^{226}Ra in mice, dogs and humans has also been examined by the derivation of a power function relating a time-based parameter to skeletal dose rate.

Extrapolation methodology is obviously quite different for internally-deposited radionuclides than for external radiation exposures. For both situations, the availability of some reliable human data is critical to the development of reasonable extrapolation procedures. The human database provides (1) an essential feedback to plan laboratory studies and (2) a target against which new methods can be evaluated.

1.3 Conclusions

The extrapolation of some radiation-induced risks from laboratory animals to humans is feasible. Extrapolations have been performed for many years for external radiation exposures and internally-deposited radionuclides, though different methods must be used for the different patterns of radiation exposure.

The success of interspecies extrapolation rests upon the most basic common factors, which entail somatic-genetic aspects of damage and repair of the DNA molecule. This baseline then supports the consistent pattern of mortality seen among mammalian species. The mortality pattern then provides a quantitative, analytical basis to compare and unify the responses of different species to radiation injury.

The analyses in this Report on how data for life shortening can be used to extrapolate risks across species are very encouraging. It has been shown how the ratio of the median survival in control populations, based on a Gompertz distribution, can be used to adjust for the differences in life span among mammalian species. When these adjustments are used, the age patterns of radiation-induced mortality are markedly similar, thus allowing the extrapolation of risk to be made. There are, however, two differences that have to be considered. First, the fact that the animal data have been derived from animals that were exposed at the same age, whereas, the data for humans are from a general population in which persons of all ages were exposed. Second, the animal data are from populations with a restricted gene pool and with susceptibility to certain tumors, whereas, human populations are considered to be heterogeneous. There are suggestions as to how to overcome these differences. Even with these remaining issues it is suggested that it would be better to use life-shortening data for selecting values for DREF and RBEs because they are more representative of the total radiation effect than the data currently used that are restricted to a small number of relevant tumors.

It has been demonstrated that, at least for external exposures, a life-table-based model will provide an accurate interspecies prediction of death rates when summed across all causes of mortality or from all solid-tissue tumors. However, extrapolation of specific tumor mortality still requires some development. The findings for all-cause mortality support the recommendation that animal data on the effects of high-LET radiation (*e.g.*, neutrons) can be reasonably used to predict total mortality in human populations where few analytically useful data for humans exist.

The approach of extrapolation based on life shortening, the relative toxicity ratio and one of the proposed approaches to extrapolation of risk of solid cancers induced by external radiation depend on relative risk.

The extrapolation of responses to internally-deposited radionuclides has made extensive and practical use of a broad base of human experience. The experience of evaluating response and

metabolic parameters in animals has led to sensible extensions to other radionuclides in test species with extrapolation back to humans. This type of extrapolation modeling seems effective in those cases where uptake, distribution, deposition, and pathologic response need to be accommodated by the prediction model.

1.4 Recommendations

1. There has been productive work on the comparison of radiation-induced life shortening among animal species and its extrapolation to humans. The current values of DDREF and radiation weighting factors are based on experimental data but the animal tumor data are considered inadequate; it is recommended that the use of the life-shortening data be considered. The studies of life shortening suggest that the data for this effect might be used with advantage to derive values for DREF and RBEs because they provide an integrated index of both cancer and noncancer effects. Such data should be obtained from appropriate regimens of protracted but terminated exposures. It is also important to focus on specific cancer types. In these analyses, the appropriate cell types and cellular events should be linked with the animal pathologic response. By incorporating molecular information, biodosimetry and radiation effects at the molecular level, uncertainties should be reduced and the quality of animal extrapolations enhanced.
2. It is important for risk extrapolation that the results from animal studies are archived, maintained and made available to researchers. This would involve good documentation in electronic form for the individual studies and identification of possible problems with the studies. This resource then could be used by more investigators concerned with the issue of animal extrapolation.
3. Develop both human epidemiological and experimental animal data that are based on specific types of cancer and not just cancer site.
4. Continue to develop and compile information about the comparative aspects of the mechanisms of radiation-induced cancer.
5. Develop approaches to extrapolation that take into account the problem of age-dependent susceptibility and differences in the heterogeneity of human and experimental animal populations.

6. Test the hypothesis that susceptibility for induction of cancer by radiation is related to the background rate.
7. Extrapolation of risk estimates from experimental systems are still required for radiations such as mid-energy neutrons and heavy ions and this entails obtaining relevant animal data. Furthermore, if values of DDREF and radiation weighting factors continue to be based on experimental data, additional data for life shortening and cancer should be sought.
8. To conduct space flights safely, it is important to obtain information about the potential adverse health effects from heavy-ion exposures. There are limited animal studies in this area, and it is recommended that attempt to determine the predictive value of neutron exposures for estimating the risk of heavy ions be continued. It would be important to validate these predictions by conducting whole animal studies using actual heavy-ion exposures.
9. The use of high-dose diagnostic radiology and nuclear medicine with both acute and chronic exposures places large numbers of patients at potential risk. It is recommended that animal and human data be used to estimate future risks of these procedures.