EPA Charge Question 3, Potential suggestion to expand the information available to EPA on the potential influence of Basic Science on the shape of the dose-response

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I am wondering if we need to add some of this additional basic scientific information to address Charge Question 3. We can provide them with references and other information that would be helpful if they chose to use any of this information. The use of the biophysical model that results in the LNT is one of the areas of uncertainty that, in my opinion needs to be addressed. We can discuss it at the conference call on November 28th.

BEIR VII uses a biophysical model that suggests that each and every ionization increases the probability of a DNA breakage and that this results in a linear increase in the risk for mutations and also cancer. This model is dependent on independent action of the cells, lack of cell communication and a linear link between initial DNA damage and the development of disease. Recent research has been conducted to provide solid data on the response of molecules, cells, tissues and organisms to very low doses of radiation. This research has demonstrated that several of the assumptions used in the BEIR VII biophysical model are not valid.

Many new biological phenomena have been observed following low doses of radiation. For example, it has been demonstrated that following exposures to low doses of radiation there are unique changes in gene and protein expression which are related to new biological effects that were not recognized when the BEIR VII biophysical models were developed. These new biological effects include radiation induced apoptosis and adaptive responses as well as bystander effects, and genomic instability. It has been determined that genetic background plays a major role in the magnitude and impact of these biological responses to radiation.

Two different types of adaptive responses have been identified (Ref) The first is where low doses of radiation decrease the amount of damage observed relative to background levels. The second is where a small “priming dose” of radiation given before

a high acute “challenge dose” results in a decreased response relative to the high dose alone. In many studies of the adaptive response different sets of genes are activated following either high or low doses of radiation, thus suggesting unique biological responses as a function of dose and as a function of genetic background in cells that are capable of adaptive responses. Cells and tissues that demonstrate an adaptive or protective response following low dose exposures have repair and stress genes up regulated. Identification of these genes is providing a scientific basis for defining metabolic pathways activated by radiation and determining mechanisms of action. Low-dose activation of protective mechanisms like changes in cell cycle, support the existence of non-linear dose-response relationships for low-LET radiation.

Using recently developed microbeams and other technology to expose individual cells and study the response of the “hit” cells and the response of neighboring cells demonstrated the presence of “bystander effects”. These effects demonstrate that a cell traversed by an alpha particle or “hit” by a focused low LET beam communicate with neighboring cells and can produce changes in “non-hit” cells. These changes have been shown to be both “harmful” and “protective” and are most marked following exposure to high-LET radiation (ref). This impacts current use of “hit-theory” in defining radiation risk since the radiation target is much larger than the individual cell. The research demonstrates that cells communicate within each tissue so that the assumption of independence of action of individual cells used in the BEIR VII biophysical model do not hold. Since non-hit cells show biological responses, it is not appropriate to calculate radiation dose to individual cells or cell types in tissues. It also makes it more difficult to define the biological target for the interaction of radiation with cells and the induction of cancer. The data suggest that tissues and organs respond as a whole rather than as the sum of the number of cells “hit”, and that the dose should be calculated to the whole organ/tissue rather than to individual cells (ref). This has been demonstrated both in whole animals and in many cell systems.

Tissue interactions have been shown to modify the expression of cellular and molecular damage and to be critical in the expression of cancer. This damage as well as cancer incidence can be modified with treatment after radiation exposure. (ref) Research has been conducted to understand cell/cell and cell/tissue interactions and how they modify cancer frequency (ref). Data from this research verified that the initial DNA damage increases linearly with radiation dose but that even the initial DNA damage and repair is modified by radiation type, dose and dose-rate. But more importantly it

has shown that biological repair of this damage as well as other the cellular and organ responses are very non-linear over the low dose region. These new findings have important significance for understanding the adequacy of regulatory standards.

Radiation-induced genomic instability is seen at a high frequency in cells many cell divisions after the radiation exposure. The instability results in increased frequency of mutations, chromosome aberrations, and cell killing. Radiation-induced genomic instability seems to be one of the early stages in the carcinogenesis process and has been seen both *in vitro* and *in vivo*. Genomic instability suggests there are frequent radiation-induced changes following radiation, not rare mutational events. These observations challenge the importance of the role that initial mutations play in radiation-induced cancer. The BEIR VII biophysical model suggests that since DNA damage increases as a linear function of dose that there must be a linear increase in cancer risk.

The magnitude of the response for all of these new phenomena have been shown to be dependent on the genetic background of the cells, tissues and organisms in which they are being measured. With a better definition of the range of inter-individual variability and the development of tools that make it possible to identify individuals that are sensitive and resistant to both early and late effects of radiation. However, currently it is not possible to identify radiation resistant or radiation sensitive individuals or to use this information in a regulatory framework.

These recent scientific advances provide a scientific basis for the observed non-linear dose-response relationships seen in many biological systems. These new biological findings that make it necessary for the field of radiation biology to adopt new paradigms associated with the biological responses to low doses of radiation and to modify the models used to support the extrapolation of dose-response relationships into dose regions where it is not possible to measure changes in cancer in human populations.

It is important that these new paradigms be recognized by regulatory and scientific community to better evaluate the risks and hazards associated with low doses of ionizing radiation.