AEC STAFF COMMENTS ON LETTER FROM

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Long-term toxicity studies sponsored by the Atomic Energy Commission have been in progress for many years (some longer than 20 years) to determine the biological effects of various internally deposited radionuclides. Studies related to ^{90}Sr - ^{90}Y administered by different modes are being conducted at the University of Utah, Argonne National Laboratory, University of California at Davis, Pacific Northwest Laboratory and Lovelace Foundation.

The studies at the University of Utah and Argonne National Laboratory have involved the administration of graded dose levels of single intravenous injections of ^{90}Sr - ^{90}Y into mice and Beagle dogs. By design, the experiments at the University of Utah (1) also include other dogs given graded dose levels of ^{226}Ra intravenously in order to compare the observed effects from ^{90}Sr - ^{90}Y with those for ^{226}Ra. This enables one to extrapolate the effects observed in dogs to those expected in humans based on the effects seen in human subjects containing significant body burdens of ^{226}Ra. Each dose level is referenced as a multiple of the permissible concentration of ^{226}Ra in man, 0.1 μCi (70 kg man assumed). The ^{226}Ra dose levels range from 1.11 to 1620 times the reference level and the ^{90}Sr - ^{90}Y levels range from 10 to 1620 times the reference level.

The Beagle is an excellent choice for an experimental animal for an extrapolation to man. Essentially the same fraction of the total beta energy emitted by ^{90}Sr - ^{90}Y is absorbed by the skeleton of both the Beagle and man. The dog's bone and bone marrow anatomy and physiology is also similar to man. Also, the incidence of spontaneous bone tumors in the Beagle is quite low, minimizing the chance for misinterpreting radiation-induced tumors as being of spontaneous origin.

Daily ingestion of graded levels of ^{90}Sr - ^{90}Y by Beagle dogs from mid-gestation to 1.5 years of age has been the mode of exposure at the University of California at Davis. Average daily intake of ^{90}Sr - ^{90}Y ranged from .03 to 36 μCi per day (2,3). At the Pacific

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Northwest Laboratory, miniature swine have ingested graded levels of ^{90}Sr - ^{90}Y daily for three generations. The feeding levels range from 1 to 625 μCi ^{90}Sr - ^{90}Y per day (4,5).

The inhalation route of entry of ^{90}Sr - ^{90}Y into the body is being investigated in the Beagle dog at the Lovelace Foundation (6). In this experiment, the dogs received single, short-term inhalation exposures to an aerosol containing graded levels of ^{90}Sr - ^{90}Y when they were young adults and are being observed during their lifespan.

Since many of these experiments are still in progress, it is impossible to say that everything is known about the effects of ^{90}Sr - ^{90}Y. However, an analysis of our current state of knowledge regarding the biological effects of ^{90}Sr - ^{90}Y does emphasize several points:

1. These experiments have all involved the administration of equilibrium amounts of ^{90}Sr and its short-lived daughter ^{90}Y. Once the ^{90}Sr is deposited preferentially in the skeleton due to its biological behavior, the ^{90}Y produced is also tightly bound in the skeleton and deposits most of its energy there. The biological effects observed to date are those that would have been predicted from the selective irradiation of bone and bone marrow.

2. When the skeleton is exposed to very high dose rates of radiation from the deposition of large quantities of ^{90}Sr - ^{90}Y, both solid tumors of the bone and death from disorders of the blood forming tissues have been observed. The relative importance of these two general classes of effects of irradiation of bone and bone marrow appears to depend on the mode and age at administration. For instance, bone tumors were observed in highest incidence following single doses of ^{90}Sr - ^{90}Y which produced a high initial dose-rate followed by protracted low-level irradiation. In contrast, death from disorders of the blood forming tissues was observed in highest incidence in studies with continuous intake of ^{90}Sr - ^{90}Y at high level starting early in life.

3. Pathologic effects have only been observed in animals exposed to high total doses of irradiation produced at high dose rates. For instance, in the Davis ingestion study which has entered its tenth year, no pathologic effects have been seen at continuous radiation doses to the skeleton from ^{90}Sr and its daughter ^{90}Y below about 2000 millirads per day. For comparison, the Radiation Protection Guide for bone marrow from FRC Report No. 2 for the average exposure of a suitable sample of the population would be

170 millirem per year or about 0.5 millirem* per day (7). Similarly, in the study now in progress at the University of Utah, adult dogs given single intravenous injections of ^{90}Sr - ^{90}Y amounting to 1620 times the reference level mentioned on p. 1 died with bone tumors 2 to 3 years later (8). The average skeletal dose rates were approximately 10,000 millirads per day. Bone tumors are also being observed in the next lower level (940 x reference level) where the dose rate is about 6000 millirads per day and the dogs have been under observation for over 5 years at the present time. Observations on these and dogs injected with lower activities will be continued.

4. In the dog, there is a 1,000 to 10,000-fold reduction in the ^{90}Sr - ^{90}Y concentration in soft tissues such as the testes, seminal fluid and ovaries compared to that of bone (9). It is, therefore, highly unlikely physiologically to get substantial doses to these tissues without first inducing lethal effects from the irradiation of bone and bone marrow. This was also demonstrated in the miniature swine experiments where feeding ^{90}Sr over three generations produced no significant differences in litter size, percentage of stillborn or birth weight compared to unexposed control animals (5). The feeding levels in both these studies resulted in body burdens in some animals that were 1,000 to 2,000 times the occupational permissible body burden of ^{90}Sr - ^{90}Y of 2 μCi.

In February 1971, the Atomic Energy Commission sponsored a symposium at the University of California at Davis entitled "Biomedical Implications of Radiostrontium Exposure," which brought together at one time most of the world's experts on this subject. In addition to scientists from all the AEC-sponsored long-term ^{90}Sr - ^{90}Y toxicity studies, there were also scientists present from the United Kingdom, Sweden, Netherlands and West Germany. The proceedings of this symposium will serve as a useful compilation of the current state of knowledge on this subject (10) as have several other volumes in the past (11, 12, 13).

A large segment of the Davis symposium was devoted to discussions of the extrapolations of these results to man. Dr. Charles Mays from the University of Utah presented an analysis of the available data for dose-response relationships for several radionuclides including ^{90}Sr - ^{90}Y. He concluded that none of the experimental data support a linear model for the induction of bone tumors by ^{90}Sr - ^{90}Y over a broad dosage range in several animal species. At low doses from β-emitters, the number of bone sarcomas is substantially lower than would be predicted from a linear non-threshold model. He felt that the data strongly support a sigmoid model in which the slope of the incidence curve is:

* For these beta-emitting radionuclides, the millirem unit is numerically equal to the millirad unit.

a. very shallow at low doses,
b. increasing in steepness as the high incidence values are approached,
c. leveling off at peak incidence, and
d. perhaps bending downward at super-high doses.

Because of the apparent sigmoid dose-response relationship, one cannot use a single number to describe the incidence of bone tumors for an increment of dose. However, Dr. Mays did attempt to estimate the risk to man from low levels of ^{90}Sr - ^{90}Y. His approach was the following: From dose-response data published recently for humans containing body burdens of ^{226}Ra (14), he calculated an upper risk limit of 45 tumor cases per 10^9 person millirads.* Other biological data have indicated that ^{90}Sr - ^{90}Y is about 1/10 as effective as ^{226}Ra in producing bone tumors. Therefore, he presented $45 \times 10^9 \times 0.1 = 4.5$ bone tumor cases per 10^9 person millirads as being an upper limit for the 50-year risk from low doses of ^{90}Sr - ^{90}Y. The corresponding lower limit would be zero. Because of the sigmoid (non-linear) response for ^{90}Sr - ^{90}Y, he chose 1 bone tumor per 10^9 person millirads as his best estimate of the 50-year risk from low doses of ^{90}Sr - ^{90}Y. The skeleton of an average man is currently exposed to a yearly dose of 8 millirads from internally deposited ^{90}Sr - ^{90}Y (15). Therefore, using his estimated risk of 1 bone tumor per 10^9 person millirads and a population of 2×10^8 people, for this dose of 8 millirads, it would be estimated that a total of 1.6 bone tumors might be produced during the next 50 years.

$$\frac{1 \text{ tumor}}{10^9 \text{ person millirads}} \times 2 \times 10^8 \text{ persons} \times 8 \text{ millirads} = 1.6 \text{ tumors}$$

* 10^9 person millirads = 1 million man rads

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