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Dear Dr. Jameson,
We have attached our public comments on the addition of medical x-rays to the 11th report on known or suspected carcinogens as outlined on the NTP website. The attachment is a letter submitted to SCIENCE magazine on the issues of radiation risks, similar to a letter to be published in the Journal of Roentgenology. These comments point-out issues of risk not currently being addressed by the majority of the health physicists on the subject. In summary, we favor including diagnostic medical x-rays in the new list of carcinogens for the 11th report on the subject.

Sincerely,
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The Editor:

We read the comments on Chapin's statements made at the "Nuclear power plants and their fuel as terrorist targets", Policy Forum, 20th Sept. p. 1997, and the response by Chapin, et al in Science 299,201,10 January 2003, and found that several important radiobiological principles with respect to estimating the health risk of low doses of radiation were not discussed. We are addressing these issues below.

X-irradiation enhances chemical carcinogen-induced transformation in normal mammalian cells by about 9-fold, UV-induced transformation by about 12-fold, and oncogenic virus-induced transformation by 2-fold. X-ray doses which alone do not induce transformation, increase the frequency of transformation in normal fibroblasts when combined with phorbol ester, a tumor promoter. These studies have been referred to previously (1). Ionizing radiation, in combination with tobacco smoking, increases the risk of lung cancer (2). Thus, radiation interacts with several other agents to influence the incidence of somatic mutations and the risk of cancer. A low dose of radiation (2 cGy) does not produce detectable levels of mutations as measured by chromosomal damage; however, in the presence of caffeine, which inhibits the repair of DNA damage, such mutations become detectable (3). The efficacy of repair systems may vary from one individual to another due to variations in age, environment, diet and lifestyle related factors. Therefore, these variations can influence the repair of radiation-induced mutagenic events.

Human health risk should include not only cancer risk, but other risks such as birth defects, somatic mutations that may contribute to diseases other than cancer, and heritable mutations. The incidence of non-neoplastic diseases and intermediate health risk biochemical markers were studied in children living in radiation-contaminated areas near the Chernobyl nuclear accident site. The incidence of thyroid gland enlargement and vision disorders, mostly dry eye syndrome, was closely related to the levels of contamination (4). Increased levels of oxidized conjugated dienes, products of lipid peroxidation, were found among these children. In another report, increased levels of spontaneous chemiluminescence, an indicator of enhanced oxygen radical activity, in leukocytes of children living in contaminated areas were observed (6). The issue of heritable mutations is often ignored while estimating the health risk of low doses of

radiation. Humans are also exposed to cancer protective agents from the diet, but the levels of protective agents may markedly vary from one individual to another depending upon their diet. This could influence the risk of cancer and other somatic and heritable mutations.

Thus, humans are simultaneously exposed to varieties of mutagens and carcinogens, and tumor promoters as well as to cancer protective agents, in addition to radiation. Therefore, "radiation-induced cancer" in humans at low doses depends upon several confounding factors. They include environment, diet and lifestyle-related factors as well as age and the varied radiosensitivity of different organs. These confounding factors are not possible to correct for in any epidemiologic study. This may explain why radio-epidemiologic results have produced inconsistent results (2-3). Therefore, constructing a dose-response curve based on epidemiologic data, and on any mathematical model that cannot take into account biological variability, may not provide any meaningful data on the estimation of cancer risk in humans. In our opinion, both the linear no-threshold model and the non-linear-threshold model may not be not suitable for predicting cancer risk quantitatively.

The concept of radiation hormesis, which proposes that small doses of radiation may be beneficial, may be misleading. Adaptive responses are commonly observed with acute tissue insults such as seen with hyperthermia and acute trauma. Unlike other injurious agents such as heat and acute trauma, ionizing radiation is a potent mutagen and carcinogen; therefore, adaptive responses following exposure to low doses of radiation cannot be used as evidence for the statement that such doses are beneficial. On the contrary, they simply reflect that cells have been exposed to injurious agents and that attempts are being made to repair some of the damage.

Denying the health risks of low-dose radiation in humans is analogous to the tobacco industry's early claims that tobacco smoking is not carcinogenic and that nicotine is not addictive. We continue to support the well-established radiobiological concept that no radiation dose can be considered completely safe, and that all reasonable efforts must be employed to reduce the dose as well as the damage, no matter how small that damage might be.

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Title: Low-level Radiation Risk

The article in the American Journal of Roentgenology entitled, "Cancer Risk from Low-Level Radiation", (1) contains misleading and incomplete information with respect to the cancer risk from low doses of radiation in humans. Therefore the conclusion, "This means, for example, that cancer risk---------may well be zero", may not be valid. Because of the importance of this topic for public health, we present another view on the estimation of cancer risk in humans following diagnostic doses of 10 cGy or less (usually 2 cGy or less).

The author has challenged the linear no-threshold hypothesis and has utilized the following sets of data in support of his conclusion: (a) selective radio-epidemiologic studies; (b) a position paper of the 6,000-member Health Physics Society; and (c) experimental data related to radiation hormesis. He has ignored numerous experimental and epidemiologic studies present in two radiobiological resource books (2-3) that conflict with his conclusion. Radio-epidemiologic studies have so many confounding factors that it is not possible to quantify cancer risk in humans from radiation exposure alone. Additional mutagens and carcinogens, as well as cancer protective factors are present in environmental, diet and lifestyle-related influences that may be either additive, synergistic or subtractive to the health risks from radiation exposure. It has been reported that x-rays, in combination with a chemical carcinogen, increases the level of radiation-induced transformation in normal fibroblasts by about 9-fold. X-irradiation also enhances the level of UV-induced transformation by about 12-fold. X-ray doses, when combined with phorbol ester, a tumor promoter, increase the frequency of transformation in normal fibroblasts. Ionizing radiation in combination with tobacco smoking increases the risk of lung cancer. A low dose of radiation (2 cGy) does not produce detectable levels of mutations as measured by chromosomal damage; however, in the presence of caffeine, which inhibits repair of DNA damage, such mutations become detectable. All of the above studies have been referenced previously (2). The efficacy of repair systems may vary from one individual to another due to variation in age, environment, diet and lifestyle related factors. Thus, humans are simultaneously exposed to varieties of mutagens and carcinogens and tumor promoters, as well as to radioprotective agents. Therefore, radiation-induced cancer in humans at low doses depends upon several

variables; and these variables are not possible to reconcile in any epidemiologic study. This may explain why radio-epidemiologic studies have produced inconsistent results. Therefore, constructing a dose-response curve based on epidemiologic data, and on any mathematical model that cannot take into account biological variability, may not provide any meaningful data on the estimation of cancer risk in humans. In our opinion, both the linear no-threshold effect and threshold effect curves are not suitable models in predicting cancer risk *in a quantitative sense*.

Dr. Cohen quotes a position paper of the Health Physics Society which states, "Below 10 rads—risks of health effects are either too small to be observed or are non-existent" (4). This position paper is inaccurate and does not reflect the environmental, dietary and lifestyle factors that might influence human carcinogenesis, and ignores experimental data on doses 10 rads or less that can induce somatic and heritable mutations, cancer and birth defects (2-3). Human health risk should include not only cancer risk, but other risks such as birth defects, somatic mutations that may contribute to diseases other than cancer, and heritable mutations (4). Denying the health risk of 10 rad or less in humans is analogous to the tobacco industry's early claims that tobacco smoking is not carcinogenic and that nicotine is not addictive. Tobacco smoke, a potent carcinogen, increases the risk of cancer in only 33% of smokers, suggesting that cancer causing events may be repaired in the remaining smokers. Therefore, doses of 10 rads or less may increase the risk of cancer in only a certain percentage of exposed persons. Thus, these low doses cannot be considered insignificant.

Dr. Cohen has referred to experimental data that support the concept of radiation hormesis, which proposes that small doses of radiation may be beneficial to humans. Adaptive responses are commonly observed with acute tissue insults such as seen with hyperthermia and acute trauma. Unlike other injurious agents such as heat and acute trauma, ionizing radiation is a potent mutagen and carcinogen; therefore, adaptive responses following exposure to low doses of radiation cannot be used as evidence for the statement that such doses are beneficial to humans. On the contrary, they simply reflect that cells have been exposed to injurious agents and that attempts are being made to repair some of the damage.

We continue to support the well-established radiobiological concept that no radiation dose can be considered safe, and that all efforts must be done to reduce the dose as well as the damage, (as promulgated by the international radioprotection standard of "As Low As Reasonably Achievable") no matter how small that damage might be.

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