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RADIATION PROTECTION GUIDELINES FOR THE SKIN

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INTRODUCTION

An ICRP Task Group was appointed in 1987 with the instruction that the scope of the Task Group's work should include: 1) a review of the available dose-effect data for cancer induction and non-stochastic effects in the skin that could be used to determine risk estimates for these effects; 2) a review of the evidence concerning cells are at risk and to determine at what depth dose measurements should be made, and 3) a re-examination of dosimetry considerations and weighting factors for skin with reference to the effects of "hot particles" and ultraviolet radiation.

Historical Background

Physicians and technologists that worked with X rays and radium during the period from the end of the last century to at least the mid 1920's incurred considerable skin doses. The first solid cancer that was recognized to be caused by radiation was a cancer of the skin (Frieben, 1902). The fact that it occurred so soon after the discovery of X rays is an indication of the magnitude of the doses that the early workers incurred. Today the evidence suggests that the mean latency period of radiation-induced skin cancer following radiotherapy is over 24 years (UNSCEAR, 1977).

The first attempt to quantitate radiation protection was made in 1925 by Mutscheller with the suggestion of what was called a tolerance dose which was expressed as 1/100 of a threshold skin erythema dose per month (Taylor, 1984).

Fluoroscopy was a major source of radiation exposure of the skin from the earliest days and in 1928 a recommendation was made at the 2nd International Congress of Radiology that the gloves worn (by the radiologist) during fluoroscopy examination should have a protective value of not less than 0.5 mm lead (ICRP, 1928).

The way these recommendations were couched gives an indication of one of the major problems of setting protection standards in those days, namely, there was no international agreement on how to express radiation exposure or dose until 1928 when the Roentgen was introduced. It was another six years before the threshold erythema dose was translated into an exposure measured in roentgens by the U.S. Advisory Committee on X ray and Radium Protection (this committee begat the National Committee on Radiation Protection which begat the National Council on Radiation Protection and Measurements the present day NCRP). The U.S. Advisory Committee considered the tolerance dose to be 0.1R per day measured free in air. Later in the year the International X-ray and Radium Protection Commission which became the ICRP introduced a value of 0.2R per day (ICRP, 1934). These tolerance doses were changed to 0.3 rem per week in 1948 in the U.S. and by the ICRP in 1950.

Although the skin reactions were used initially as a benchmark for radiation protection, none of the early recommendations included specific dose limits for skin. In 1949 at a Tripartite Conference it was recognized that exposures at a low intermittent rate over a period of years could cause skin cancer (Taylor, 1984). It was stated that all the cancer cases had shown typical radiation-induced effects in the skin before cancer occurred and in most cases many years before. Interestingly, the cancers were reported to be usually squamous cell carcinomas. For radiations of low penetration it was concluded that skin was the critical tissue and cancer was the risk of concern.

The recommendations that were made at that conference were expressed as a permissible weekly dose (Table 1). It was considered that a person could receive such a dose for the rest of their life without risk of appreciable injury in their lifetime. The recommendation of a 1.5R/week to the basal layer of the epidermis of the hands and forearms assumed the basal layer to be at a depth of 70 mg/cm^2 or 70 μm. These recommendations were of particular interest because they

introduced the idea of measuring dose at the depth that the critical target cells are assumed to be. Their selection of a depth of 70 μm has stood the test of time, some forty years. Another interesting aspect was the choice of an RBE of 5 for protons and 15 for alpha particles.

In 1954, the National Committee on Radiation Protection recommended in Handbook 59 (U.S. Dept. of Commerce, 1954) a limit of 0.6 rem/week when the area of skin exposed was significant. This landmark report is concise and at the time cost the princely sum of thirty cents! ICRP followed suit and defined the significant area as being 1 cm^2 and applied to whole-body irradiation. The limit for the skin was twice that for other critical tissues.

In 1959, ICRP replaced the 1.5 rem/week with a limit of 20 rem a quarter or 75 rem per year for partial exposures, such as hands and forearms. The previous 0.6 rem/week limit, which applied to whole-body exposures, was changed to 8 rem in 13 weeks or 30 rem/year. In 1969, ICRP suggested that if fatal cancer was the criterion for setting a dose limit for skin then 100 rem a year would be appropriate. If nonstochastic effects, such as radiodermatitis, was the criterion then lower dose limits would be required. In 1977, ICRP decided that nonstochastic effects were the primary concern for skin and a limit of 0.5 Sv per year would prevent them. In 1978, it was suggested that the risk coefficient for fatal skin cancer was 10^{-4} Sv for exposures of essentially all the body surface corresponding to a weighting factor of 0.01 and implying a dose equivalent limit of 5 Sv/year for cancer. The reader interested in the evolution of radiation protection standards and the understanding of the relevant radiation effects might consult Taylor (1964, 1971, 1981), Medical Research Council (1972), and Sowby (1986).

Three major issues have persisted through the years. First, the location of cells at risk and therefore the depth at which the dose should be measured. There has been more consistency through the years about the recommendation about the depth at which to measure the dose than

about any other aspect. The depth of the cells that determine the critical effects is considered to be 5-10 mg cm^{-2} or 50-100 μm with 70 μm as a mean value. Two problems arise with a single depth for dose measurement because the critical cells for stochastic and nonstochastic effects and the depth at which they lie must be different. Furthermore, the depth of the basal layer varies from 30 μm or less to more than 300 μm over the surface of the body (Whitton and Everall, 1973). In the areas with the thinnest skin penetration by alpha particles of sufficient energy may pose a risk that is poorly known.

The second issue that has persisted is the question of what area over which the dose should be measured. Exposures that are considered for radiation protection purposes range from whole body to the very small areas irradiated by hot particles of less than 1 mm in diameter. The dose is averaged over 1.0 cm^2 in the region of the highest dose equivalent in the case of accidental irradiation and 100 cm^2 in the case of surface contamination. The area over which the dose from hot particles should be measured is perhaps the most difficult question. Recently, NCRP (1989) have considered this problem and concluded that averaging the dose over a specified area to be inappropriate for hot particle exposures and have recommended that the dose be expressed in the number of beta rays emitted by the particle and expressed in Becquerels. It is important the there is agreement on both sides of the Atlantic about the threshold dose for the effect caused by a hot particle and which it is necessary to protect against. How transient has a lesion to be and how trivial must the residual lesion be before the radiation-induced lesion becomes sufficiently insignificant that it can be ignored in terms of radiation protection? The third issue is whether cancer or non-stochastic effects is the limiting effect.

Radiation-induced effects on the skin

The responses of the skin to radiation and their time of onset are known in considerable detail (Hopewell, this volume; see Jammet et al., 1986). Threshold doses for both acute and late effects are known with a precision that should ensure reliable radiation protection. There is one possible exception, namely, radiation-induced damage to the cells in the epidermis involved in the immune system. These effects have not received great attention and of greater importance is the lack of information about the radiation effects on the skin that effect immune function.

The cell that is now identified as the most peripheral sentinel of the immune system was described 121 years ago by Langerhans (Langerhans, 1968; Wolff, 1983 and Stingl et al., 1983). About 2-4% of the epidermal cells are Langerhans cells. These cells are dendritic with a very large surface area forming a network above the basal layer of the epidermis. The cells are produced in the bone marrow (Katz et al., 1979) and they migrate to various surface epithelia with the exception of the corneal epithelium. The number of Langerhans cells per unit surface area appears to be positively correlated with the thickness of the epidermis. The number of Langerhans cells in any one region varies little but it is not known how homeostasis is maintained. Langerhans cells lost as a result of damage to the epidermis are replaced from the precursor cells in the bone marrow as the epidermis regenerates and may take a couple of weeks (Lessard et al., 1968). The disease Histiocytosis X is characterized by proliferation of cells with the characteristics of Langerhans cells (Wolff, 1972).

The presence of Ia molecules on the surface of the Langerhans cells suggested that their function might be similar to the macrophage-like cells that process antigens and this proved to be correct (Stingl et al., 1978). It took a mere one hundred and ten years to discover the function of the cells after their description by Langerhans. There was not a lack of suggested functions

during those years.

Apart from the important function of antigen recognition and processing that initiates the cutaneous immune response, the skin is involved in the immune system in other ways. Streilein (1983) suggested that skin associated lymphoid tissue (SALT) is an integrated immune surveillance system that includes the Langerhans cells, distinct populations of T-lymphocytes, such as dendritic epidermal T cells (Bergstresser et al., 1983; Tschachler et al., 1983, 1989) that infiltrate the skin preferentially, and keratinocytes that secrete factors that affect growth of various cell types. One of these factors is the epidermal thymocyte activating factor, ETAF (Luger et al., 1981; Sauder et al., 1982) which is similar to interleukin-1 (Luger et al., 1982). The peripheral lymph nodes are considered to play an integrating role in this multicellular segment of the immune system. Another dendritic cell, Thy-1* dec, that is produced in the bone marrow is found in the epidermis (Bergstresser et al., 1983; Tschachler et al., 1983). The function of these cells is still under investigation but they appear to have a role in the induction of immunological tolerance to antigens in the skin (Sullivan et al., 1986).

Exposure to relatively low doses of ultraviolet radiation (UVR) alters the ATPase activity and probably other enzymes and proteins on the surface membranes of the Langerhans cells. The capacity to process antigens is reduced by exposure to UVR. The altered antigen processing results in the production of antigen specific suppressor cells. The disruption of antigen presentation by radiation may play a significant role in UVR carcinogenesis in the skin (Kripke, 1981, 1983).

Almost all the knowledge about radiation effects on the skin that alter immunocompetence is for UVR. There is a need for comparable studies of the effects of ionizing radiation on the components of the skin involved in immunocompetence. It has been shown that the ATPase activity of Langerhans cells is reduced in a dose-dependent manner by ionizing radiation (Cole et

al., 1984, 1985). However, there have been no systematic studies on the changes in the antigen presenting activity and the related effects on immune competence. It can be seen in Fig. 1 that reduction in the Langerhans cells, identified by the ATPase staining method, is dose dependent and parallels the radiation-induced decrease in delayed-type hypersensitivity which has been used as an assay of cellular immunity.

From the small amount of data for ionizing radiation it appears that effects on the immune system in the skin are likely to occur at doses lower than the threshold doses for some of the other, non-stochastic effects. It would seem particularly important to determine the effects of protracted exposures to β rays on immune functions associated with the cells in the epidermis.

Radiation-induced skin cancer

The studies of humans have produced increasing information about the risk of skin cancer after exposure to ionizing radiation. The accumulated data are presented by Shore in this volume and these data provide the risk estimates made in the Task Group's report. Radiation risk estimates have, at least up to now, been based on mortality. Skin cancer has a very low mortality rate and more importantly it is not known precisely what the mortality rate is for the different types of non-melanoma skin cancers. Nor is it know how the mortality rates may vary in different populations. Experimental animal studies have not helped other than to confirm that the mortality rate for both squamous or basal cell carcinoma is low. Squamous cell carcinomas do metastasize to regional nodes and the lungs in mice but only late in life. It is my impression, but as yet not quantitated, that metastases are more frequent with exposures to more than one carcinogenic agent. In the Task Group's report a mortality rate of 0.2% was judged to be the best estimate. This figure is a weighted average of the reported mortality rate for basal and squamous cell carcinomas.

The mortality rate of 0.2% replaces the previously assumed rate of 1%. Our choice of 0.2% is largely a judgement decision but is supported by the available data (see Shore, this volume). The mortality rate is very different for basal and squamous cell carcinomas and the ratio of these two types of skin cancer vary in the unirradiated population with latitude and in the case of ionizing radiation probably with dose. The incidence of metastases for basal cell cancers in populations with good medical care can be as low as 0.00028%! (Paver et al., 1973).

Obviously, agreement on the mortality rate of skin cancer is important as it drives the risk estimates. This problem alone might encourage a change to risk estimates based on incidence but reliable data for the incidence of skin cancer is notoriously difficult to garner.

Experimental data confirm that exposure to UVR over a long period, after an initial exposure to X rays, increases the carcinogenic effect of the ionizing radiation (Fig. 2). The interaction between UVR and X rays appears to be synergistic but the enhancement effect of UVR is probably not specific. We have found that the expression of X-ray initiated cells can be increased by protracted exposures to 12-0-tetradecanoyl phorbol 13 acetate (TPA) and psoralen and UVA (PUVA). Protracted exposures to ionizing radiation can also increase the expression of X-ray initiated cells (Fig. 3). PUVA, UVR, TPA and X rays induce quite different types of DNA and other damage. It is not clear whether there is a single mechanism of the enhancement or promotion effect, and therefore, one that is common to these different agents or whether the mechanisms are different and agent specific. When these findings are considered with the experimental results it raises the question of the importance of interactions between various agents and X rays in human skin cancer.

The experimental data and the clinical and epidemiological findings that exposure to sunlight of the regions of skin exposed to X rays increase the probability of skin cancer are in agreement.

Experimentally it has been shown that exposure of mice to UVR at one site enhances UVR carcinogenesis at a distant site (de Gruijl and van der Leun, 1982). It is thought the UVR induces suppressor cells that influence the development of the UVR-induced tumors. Recent evidence suggests the depletion of Thy-1* dec cells in the epidermis during protracted regimens of UVR is associated with impairment of the host's resistance to UVR-induced carcinogenesis (Alcalay et al., 1989). It will be important to establish whether this type of action of UVR holds for the development of tumors from cells initiated by ionizing radiation.

Dose-response relationships

In both rat and mice the dose-response curves for the induction of skin cancer by low-LET radiation are curvilinear or sigmoid. A characteristic of the sigmoid dose response curve is the rapid rise when dose levels that induce tumors is reached. The model used to fit the dose-response data for the rat has been the so-called linear quadratic model and Burns et al. (1989) have found experimental data are consistent with the model.

In the mouse, Papworth and Hulse (1983) found it difficult to fit any established model to their data without assuming a threshold. In order to retain the dogma that cancer is a stochastic process they suggested a nonthreshold induction process plus some factor(s) that suppressed tumor appearance. A nonthreshold dose-response curve shifted to the right could account for the findings and such a shift might be accounted for by suppression of the expression of the initiated cells. The findings that promotion by TPA increased the expression of radiation-initiated cells (Jaffe and Bowden, 1986; Fry et al., 1986) is consistent with the suggestion of Papworth and Hulse that some factor(s) restrained the appearance of tumors. In a study using both uniform and non-uniform exposures, Charles et al. (1988) could not fit the data for the full range of doses to any model but

below 30 Gy the best fit was linear and an exponential function to account for cell inactivation.

Another important factor influencing the risk of radiation-induced skin cancer is the time over which the radiation exposures occur. In general, reduction in dose rate and fractionation reduces the carcinogenic effect of ionizing radiation but protracted exposure to β rays appears to be very effective (Ootsuyama and Tanooka, 1988). Exposure to 60 fractions of 25 kV x rays is much more carcinogenic than 16 fractions with the same total dose (Fry et al., unpublished data). Therefore, there is still work to be done in order to understand time-dose relationships.

It has been suggested that localized gross tissue damage may produce a dramatic increase in tumor incidence by several orders of magnitude compared to uniform exposures (the so-called 'hot particle effect'). Evidence against this hypothesis has been published by Charles et al. (1988) in studies of non-uniform exposures. In their study, mouse skin was subjected to a wide range of beta-ray doses, down to 2 Gy (surface dose) using plane uniform sources of ^{170}Tm (Emax 0.97 MeV) and arrays of 8 and 32 small (2 mm diameters) sources distributed over the same 8 cm^2 area. At all doses the highest tumor incidence occurred following uniform exposures. The hypothesis of the 'hot particle effect' appears to be put to rest. With electrons and soft X rays the use of a sieve pattern of exposure, which is used in radiotherapy to protect the skin, reduced the tumorigenic effect (Albert and Burns, 1967) but with protons it did not (Burns et al., 1972).

SUMMARY

With the exception of the function of cells in the skin associated with immunocompetence nonstochastic effects have been well characterized and threshold doses are known with a precision appropriate for setting radiation protection standards. A dose limitation of 0.5 Sv per year and a working lifetime dose limit of 20 Sv should protect the worker population adequately and therefore, the current protection standards are quite adequate.

The risk estimate for skin cancer is very dependent on the selection of the projection model and on the mortality rate assumed. Based on the relative risk model, a mortality rate of 0.2% and summing risks for both UVR exposed and shielded skin the risk is about twice ($1.94/10^{-4}$ Sv^{-1}) that which ICRP derived in 1977. With the absolute model the risk is considerably less, about $0.5/10^{-4}$ Sv^{-1}.

Table 1

Maximum Permissible Tissue Dose Limits

Rems/Week (1949)

	In the Basal Layer of the Epidermis	
Radiation	Whole Body Exposure	Exposure of Hands Only
Beta, X and Gamma Rays	0.5	1.5
Protons	0.1	0.3
Alpha Rays	0.033	0.1

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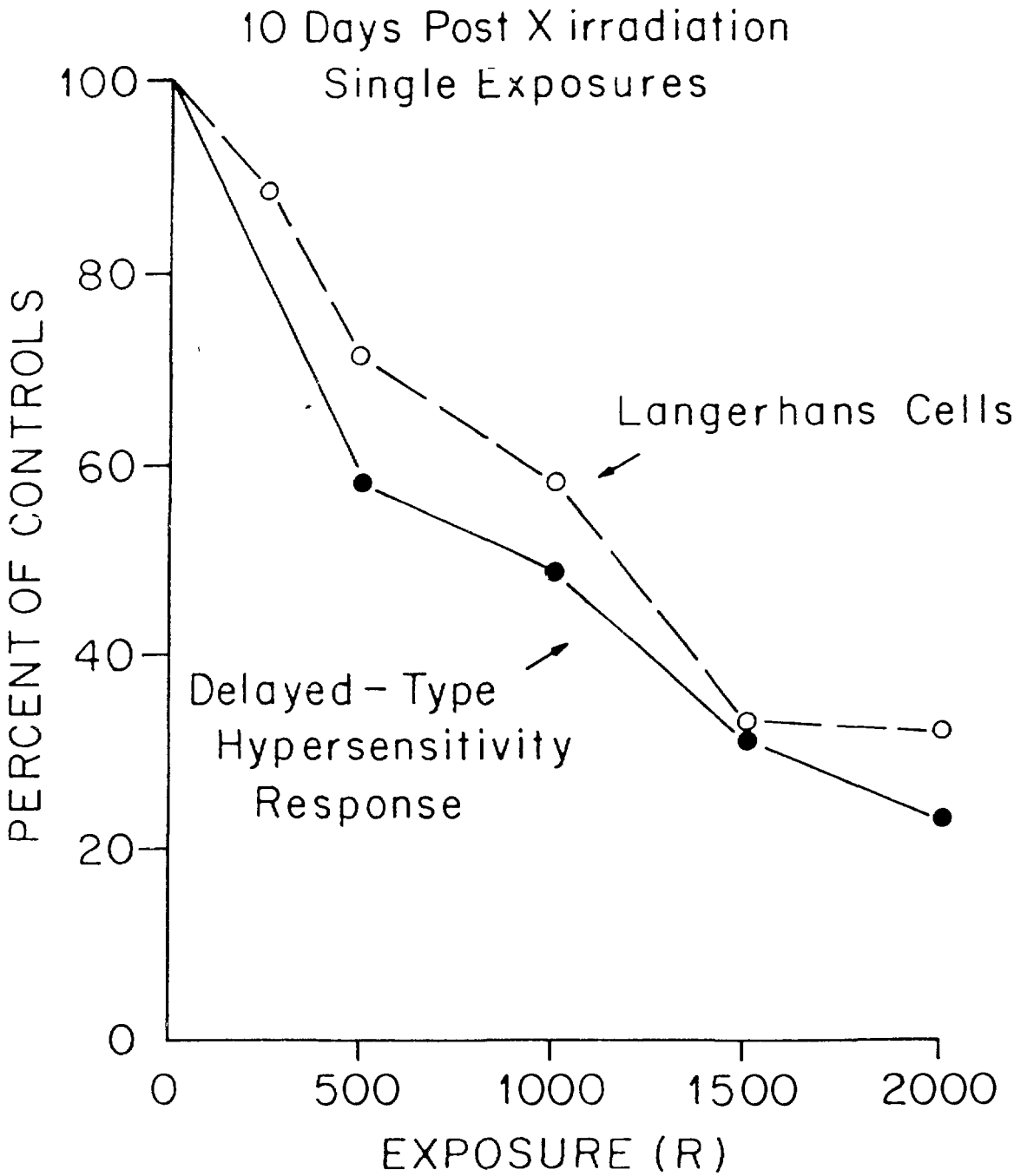
FIGURE LEGENDS

Fig. 1. The percent of the control number of Langerhans cells stained by the ATPase method (Baker and Habowsky, 1983) and delayed-type hypersensitivity as a function of X-ray exposure 10 days post irradiation.

Fig. 2. Cumulative incidence of epidermal tumors in SKH:hr-1 female mice as a function of exposure to 25 kV X rays: X ray alone: •---•, and X ray plus 250 J/m^2 UVR (280-400 nm) 3 times per week for 24 weeks.

Fig. 3. Percent incidence of squamous cell carcinoma as a function of time after exposure to 25 kV X rays; o---o X ray, 16 fractions of 6.45 x 10^{-2} C/kg, 2 fractions per week, •---• 16 fractions of 6.45 x 10^{-2} C/kg, 2 fractions per week, followed by 5 μg TPA 2/week for twenty-four weeks and Δ---Δ 64 fractions of 1.63 x 10^{-2} C/kg, 2 fractions per week.


10 Days Post X irradiation
Single Exposures
100
80
60
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PERCENT OF CONTROLS
Langerhans Cells
Delayed - Type
Hypersensitivity
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500
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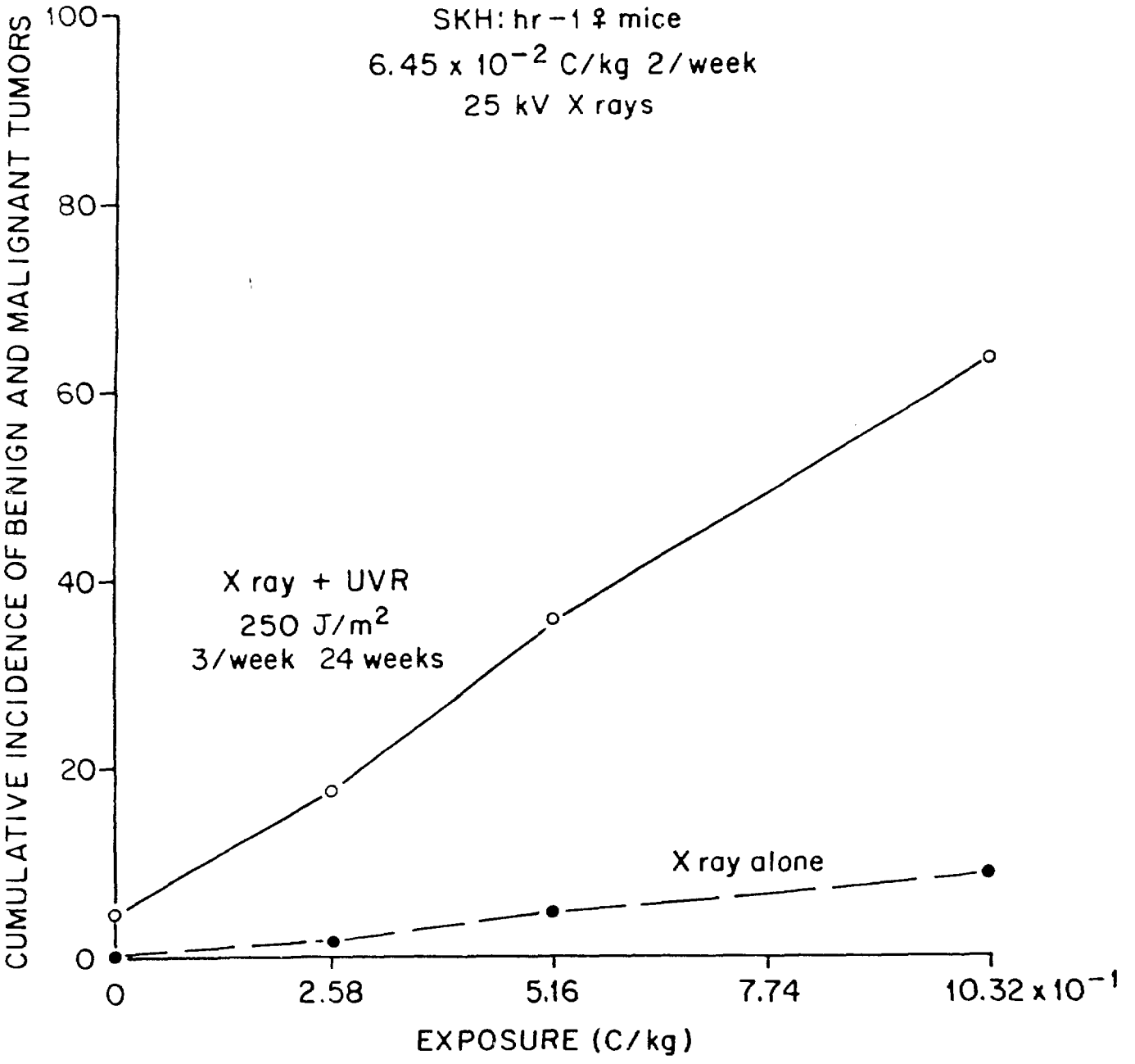
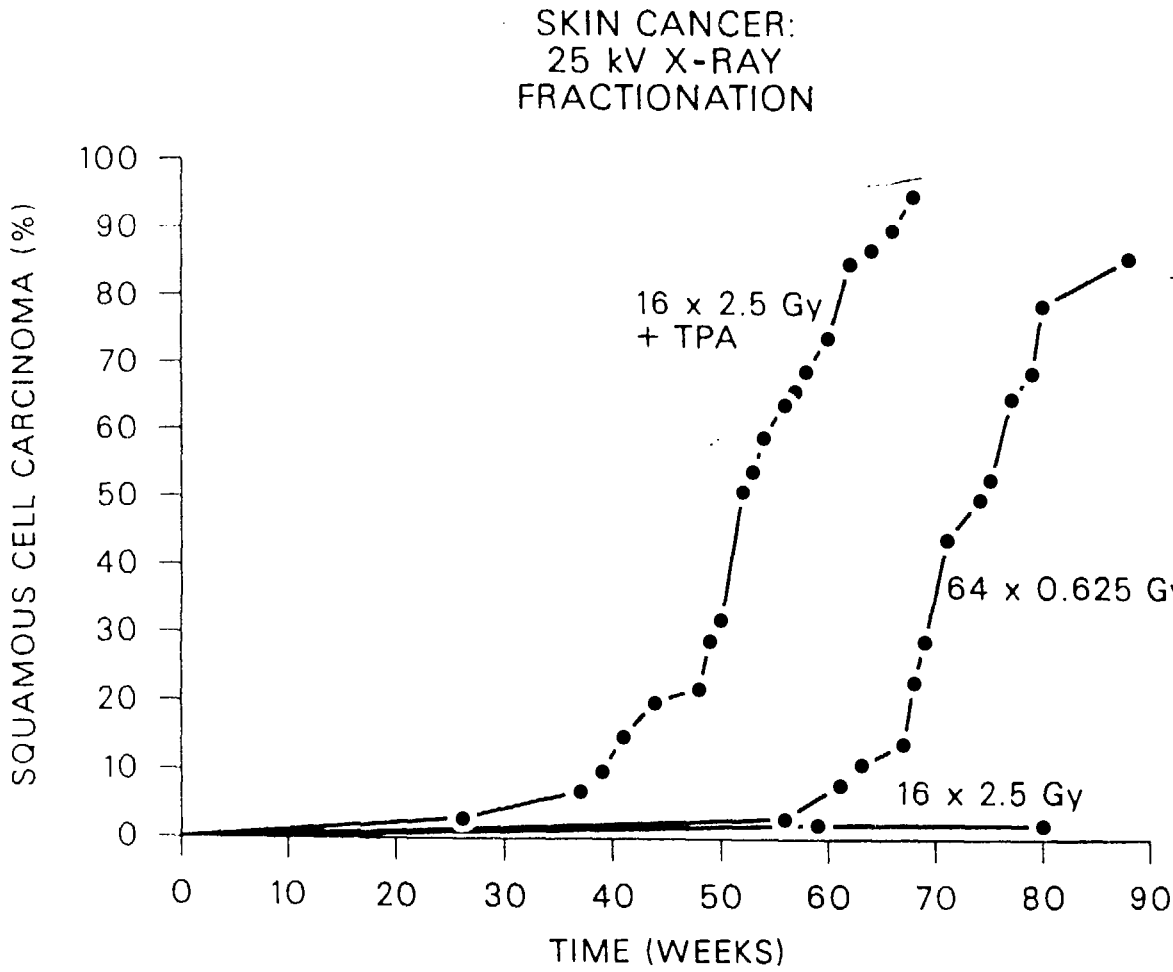
1500
2000
EXPOSURE (R)


SKH: hr-1 ♀ mice
6.45 x 10⁻² C/kg 2/week
25 kV X rays
CUMULATIVE INCIDENCE OF BENIGN AND MALIGNANT TUMORS
100
80
60
40
20
0
X ray + UVR
250 J/m²
3/week 24 weeks
X ray alone
0
2.58
5.16
7.74
10.32 x 10⁻¹
EXPOSURE (C/kg)



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