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FINAL REPORT

A Review of the Induction of Cancer by Ionizing Radiation

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prepared for

PUBLIC HEALTH COALITION
Ontario Public Health Association
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EXECUTIVE SUMMARY

At the request of the Public Health Coalition, **GLOBALTOX INTERNATIONAL CONSULTANTS INC.** has reviewed the literature concerning induction of cancer by ionizing radiation. This literature review was undertaken with a view to providing evidence in the on-going hearings into the Ontario Hydro 25 Year Demand Supply Plan. The following are the principal conclusions arising from this report:

CONCLUSION 1: Effects of Ionizing Radiation

Ionizing radiation causes both acute and chronic effects. Acute effects, associated with relatively high single or short-term exposures, result from massive cell killing. Chronic effects, associated with long-term exposures, can occur even at very low dose rates, and include cancer.

CONCLUSION 2: Mechanism of Carcinogenesis

Ionizing radiation can act either as an initiator (i.e. cause genetic changes in a cell) or promotor (i.e. causes growth of a tumour from an initiated cell). Since ionizing radiation has both initiating and promoting activity, it is considered a potent complete carcinogen.

CONCLUSION 3: Use of Japanese A-Bomb Survivor Data

Most efforts to set acceptable limits on radiation exposures have been based on information derived from the on-going study of Japanese A-Bomb survivors. The Atomic Energy Control Board's current limit of 50 mSv/yr is based primarily on such data. For a variety of reasons, the Japanese A-Bomb survivor data is likely to substantially underestimate risks to persons exposed to long-term, low dose levels of ionizing radiation.

1 BIOLOGICAL EFFECTS OF LOW DOSE IONIZING RADIATION

1.1 Overview: The Controversy Surrounding Low Dose Effects

It has almost been a century since X-rays were discovered in 1895. In that time a wealth of information has been accumulated on the deleterious effects of ionizing radiation. Early radiologists used to focus the X-ray beam by taking several exposures of their own hands. Many of these clinicians developed skin cancer. Studies on the effects of ionizing radiation applied to the reproductive organs of plants and animals have demonstrated that adverse effects can be passed on to subsequent generations. We now know that these two endpoints are related: Cancer can arise when DNA is damaged and the altered cells grow out of control. Heritable changes passed from one generation to another result from mutation of DNA in the germinal tissue. And so, it has become clear that many of the chronic adverse effects of ionizing radiation are produced by its ability to permanently alter DNA.

The effects of ionizing radiation are often separated in two types, acute and chronic effects, based on the time between exposure and the onset of the effects. *Acute* effects are seen within minutes, hours or days of exposure to ionizing radiation. They are due to massive cell killing in parts of the body that are critical for survival. The effects of whole body exposure to high doses of ionizing radiation such as would occur during a nuclear reactor accident include radiation sickness, anaemia, sterility and death. For these endpoints, there appears to be a "threshold", a dose above which the effects have a probability of occurring, and below which they do not occur. This is a useful concept when applied to radiotherapy where the goal is cell death in a selected target tissue and the dosage required to kill cells in that tissue can be calculated. The threshold doses for some of the more sensitive acute effects are shown in Table 1.

TABLE 1: Estimated Threshold Doses for Ionizing Radiation-Induced Effects

Organ Site	Effect	Single Dose (Sv)	Annual Dose ($Sv \cdot y^{-1}$)
Testes	Sterility temporary permanent	 0.15 3.5 - 6	 0.4 2
Ovaries	Sterility	2.5 - 6	>0.2
Eye - Lens	opacities cataract	0.5 - 2 5.0	>0.1 >.15
Bone Marrow	anaemia	0.5	>0.4

Source: ICRP 1984

Cancer and hereditary disorders are *chronic* endpoints or effects that occur long after exposure has taken place. These chronic effects of ionizing radiation are the most controversial since some of these effects, notably cancer, do not appear to have a threshold. That is, exposure to any low dose of ionizing radiation may result in cancer, although it would occur with a low frequency. It is extremely difficult to make causal associations with any accuracy between exposure to radiation and induction of cancer, partly because of the long delay between the exposure and the diagnosis of cancer and partly because of the lack of a threshold dose. This explains why there is a lot of uncertainty about the adverse health effects of low doses ionizing radiation.

1.2 The Mechanisms by Which Radiation Induces Cancer

Ionizing radiation is damaging to biological tissues because it gives off energy as it passes through tissues. The energy has several effects as shown in Figure 1. Since water (H_2O) is the most common molecule found in cells, the most frequent consequence of ionizing radiation passing through a cell is the ionization of water, forming peroxides, oxygen and hydroxyl

Figure 1: Reactions Induced by Ionization of Water by Ionizing Radiation

Ionization

$H_2O \rightarrow H_2O^+ + e^-$

$H_2O + e^- \rightarrow H_2O^-$

Formation of Free Radicals

$H_2O^+ \rightarrow H^+ + OH^*$

$H_2O^- \rightarrow H^* + OH^-$

$RH + OH^* \rightarrow R^* + H_2O$

Reactions of Free Radicals

a) $OH^* + H^* \rightarrow H_2O$ reformation of water, no adverse outcome

b) $OH^* + OH^* \rightarrow H_2O_2$ formation of hydrogen peroxide

c) $R_1^* + R_2^* \rightarrow R_1 — R_2$ crosslinking

d) $R^* + O_2 \rightarrow R^*O_2$ formation of organic peroxides

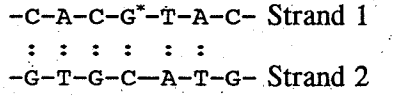
$R^*O_2 + H^* \rightarrow ROOH$

radicals, and related compounds. These are very short-lived chemical species which are very reactive. These molecules are often positively charged and will seek out electrons. Large molecules, which tend to have lots of electrons, will often react with the ionization products of water. The large molecules in cells tend to be proteins and nucleic acids, like RNA and DNA. The consequences of free radicals reacting with macromolecules like DNA are the formation of DNA strand breaks, cross-links between the 2 strands of DNA and of chromosomal aberrations (double stranded breaks). Free radicals also damage cellular membranes, causing cell death.

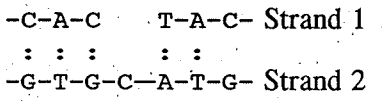
Single strand breaks occur spontaneously in DNA, partially due to exposure to background levels of ionizing radiation (from cosmic and ground radiation), and are commonly repaired. It has been estimated that 10-50 spontaneous strand breakages and repairs occur per

cell per minute (Myers et al. 1980). These breakages are easily repaired since the damaged base can be detected, removed and replaced. The missing base can then be correctly determined by the opposite base on the intact strand of DNA, since a given base only bonds with a given opposite base (Figure 2). If exposure occurs to a dose of ionizing radiation which exceeds the background levels, then more stand breakage occurs and the probability of misrepair occurring increases. Simply stated, the greater the occurrence of damage the more likely that the DNA will be incorrectly repaired. If the strand is misrepaired and a chemically damaged DNA base is replaced with a different base, this is referred to as a *point mutation*. This event often is insignificant. Since the base pairs are read in three's (triplets or codons) to code for a given

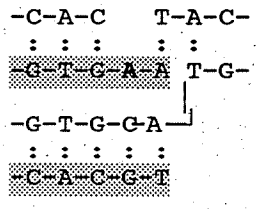
Figure 2: Point Mutations



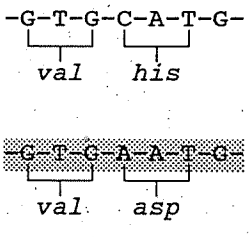
Step 1: Damaged base "G*" is located on Strand 1



Step 2: Damaged base is excised. Normally the "C" on strand 2 would serve as a template for faithful repair.



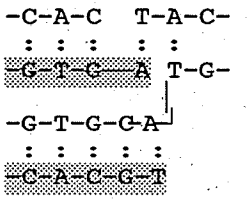
Step 3: DNA replication begins before repair is complete. The new strands of DNA are shaded. An "A" is put in instead of "C" on the newly synthesized strand 2.



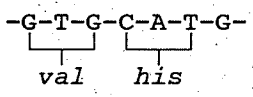
Original Strand 2 of DNA codes for the amino acid sequence valine-histidine. "G-T-G" is the code for valine and "C-A-T" is the code for histidine. The New Strand 2 of DNA (containing an "A" where a "C" should be) codes for the amino acid sequence valine-asparagine. Only a single amino acid is altered (histidine is replaced with asparagine). "A-A-T" is the code for asparagine.

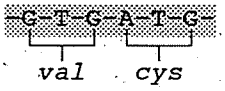
amino acid (protein building block), the protein resulting from a point mutation will only have 1 amino acid altered. This alteration may render the protein ineffective and in the worst case, kill the cell, or it more likely, it may have no consequence at all for the cell's or the organism's survival. If instead of inserting the wrong base into the sequence, a base is deleted entirely (Figure 3), or a new base is added to the sequence, then a *frameshift mutation* has take place. This type of damage is called "frameshift" since the addition or deletion of bases alone or in multiples other than three, will shift the entire frame of reference and the resulting protein will have a nonsense structure. The consequence of this type of mutation is often cell death, since the protein coded for is not just miscoded where the damage occurred, it is miscoded for the entire length of the DNA strand.

Figure 3: Frame Shift Mutation (deletion)



Steps 1 and 2 as shown for point mutations (Figure 2).
Step 3: Instead of an *incorrect* base being inserted, *no* base is inserted. Effectively, a base is deleted from the newly synthesized strand 2.





Step 4: Original Strand 2 of DNA codes for the amino acid sequence valine-histidine. New Strand 2 of DNA is missing a base due to the deletion. All amino acids coded for after the deletion will be incorrect. As an analogy, delete the first "H" from the following sentence of three-letter words. After the deletion the code becomes nonsense:

THE CAT SAW THE RAT
↓
TEC ATS AWT HER AT

When chromosomal aberrations occur, the sequence in which genes are found on DNA is rearranged. Many types of cancers are highly correlated with specific and characteristic rearrangements of chromosomes (Rowley 1973). Genes that control certain functions (eg. cell

division) are themselves controlled by other genes that regulate the timing of the occurrence of the function. Cancers can result from chromosomal rearrangement because the control of cellular functions can be lost and, for example, a cell may divide without regulation. Misrepair of damaged DNA can also result in cancer induction. In fact, it has been demonstrated that a single point mutation (substitution of one base pair for another) was responsible for a human bladder cancer (Reddy et al. 1982). Point mutations can result from DNA strand cross-linking and misrepair as well as from strand breakage. It has been estimated that point mutations are responsible for about 50% of inherited diseases (Sankaranarayanan 1991).

The preceding discussion indicates some of the mechanisms by which ionizing radiation can genetically alter cells. It should be noted that these events are rare. The most probable consequences of ionizing radiation damage to a cell is repair of the damage or cell death, if the damage is severe. Occasionally, however, the damage can result in a heritable genetic disorder or cancer.

The first phase of the process of carcinogenesis (cancer induction) is referred to as *initiation*. Initiation is irreversible and can occur with a single exposure to any dose of ionizing radiation. This is why radiation carcinogenesis does not appear to have a threshold. Initiated cells can lie dormant for years without becoming tumours. Tumour induction is thought to require at least a second phase referred to as *promotion*. Many chemical carcinogens are either initiators or promoters. Some are capable of inducing both phases and are referred to as *complete carcinogens*. Ionizing radiation is a complete carcinogen. In addition to altering DNA, as described above, ionizing radiation can kill cells. Death of large numbers of cells in a tissue can act as a promoting stimulus. In other words, when many cells die, the remaining cells begin to divide to replace the lost cells. Some of these cells may been previously initiated. Since ionizing radiation can both initiate and promote, it is considered a potent complete carcinogen.

2 EVIDENCE SUGGESTING THAT LOW DOSE IONIZING RADIATION MAY BE MORE DAMAGING THAN PREDICTED BY THE JAPANESE A-BOMB SURVIVOR DATA

2.1 Introduction

There have been several attempts to characterize the risks associated with exposure to low doses of ionizing radiation. Most agencies, including Ontario Hydro, rely heavily on the work of 3 committees who have examined this question:

- BEIR V (5th report of the Committee on the Biological Effects of Ionizing Radiation) of the US National Research Council (1990)

- UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation, 1988) and

- the International Commission on Radiological Protection (ICRP, 1991).

The estimates of these three groups are based primarily on cancer mortality among survivors of the atomic bomb in Japan. These estimations of the effects of low dose ionizing radiation have a high degree of uncertainty associated with them, due partly to the problems of estimating individual dosages at the time the bomb went off, and partly to problems associated with mathematical modelling. As is pointed out in Ontario Hydro Exhibit #507 (Materials Relating to Environmental and Health Effects of Nuclear Generation, p. AP 2-3), last year ICRP drastically revised their estimates of the cancer risk associated with exposure to ionizing radiation to suggest that the risks are several fold higher than were previously thought.

2.2 Mortality Studies of Workers at Nuclear Facilities

Recent evidence has called into question the predictive value of studies on the Japanese bomb survivors in calculating the effects of low doses of ionizing radiation. Studies on workers at nuclear facilities in the US and England (Wing et al. 1991, Kendall et al. 1992), where dose was carefully monitored through the use of devices such as pocket ionization chambers, film badges and thermoluminescent dosimeters, suggest that the estimates derived based on Japanese bomb survivors may underestimate the risk by as much as a factor of 10. *(This is described in more detail in the report submitted by Alice Stewart).*

2.3 Childhood Leukaemia

Gardner has reviewed the evidence surrounding the Sellafield controversy (Gardner 1991). Cohort studies have shown an excess of leukaemia in children born in the town of Seascale near the Sellafield nuclear plant, but not in children who moved to the area after birth. This suggests that risk of leukaemia may be related to prenatal factors. A case-control study showed that the increased incidence of leukaemia was related to the cases' father's external radiation dose, recorded from film badge data at Sellafield. A case-control study in Shanghai (Shu et al. 1988) showed similar findings with a relative risk of 3.9 compared to 6.4 in the Gardner study.

AECB has conducted an analogous study on leukaemia around Canadian nuclear facilities (Elaguppillai, 1992). This studies found odds ratios greater than 1 at three facilities and less than 1 at two facilities.

Recently, Fremlin (1991) pointed out that the levels of radiation fathers were exposed to in Gardner's study were so low they were comparable to levels of background radiation

experienced in parts of Brazil and India where the incidence of childhood leukaemia does not appear to be elevated.

Other authors point out that the rate at which the dose is received is a factor not considered in the types of comparisons made by Fremlin. In other words, a large single exposure to a radiation, such as might occur at a nuclear facility is much more harmful than the same dose spread out over the entire year received from natural background sources. Animal data has shown that spreading the dose over a long period of time can reduce the risk of cancer by as much as a factor of 10 (see Shlyakhter and Wilson, 1991). ICRP has recognized this effect of dose rate by reducing the permissible limits for public exposure to 1 mSv, which is below the natural background levels of radiation in some places.

2.4 What is Wrong With the Japanese A-Bomb Survivor Data?

As previously noted, in setting limits on radiation exposure, most regulatory agencies and expert committees rely heavily on the data collected by the Radiation Effects Research Foundation (RERF), which studies the survivors of Hiroshima and Nagasaki. The RERF data seems to be at odds with a number of studies on the risks of ionizing radiation, such as those noted in Sections 3.2 and 3.3 above and, others, for example, on the effects of prenatal medical X-rays (Harvey et al. 1985, Knox et al. 1987). Stewart and Kneale (1984, 1990) have suggested that the RERF data probably suffers from selection bias. The survivors of the A-bomb have undergone a process of natural selection; that is they survived the blast and acute radiation exposure because they were healthier than those with the same radiation exposure who died shortly after the blast. This would further suggest that the RERF data underestimates the adverse effects of ionizing radiation, since these A-bomb survivors are a cohort who have been selected for their good health.

As a consequence of the A-bomb survivor data being the basis for radiation protection limits, it has been suggested that the legal limits underestimate risk by as much as a factor of 10 (Nussbaum, 1989). AECB's current limit is 50 mSv/yr, based primarily on the RERF data. Perhaps this limit should be reconsidered in light of the uncertainty surrounding the effects of low doses of ionizing radiation on human populations other than the survivors of Hiroshima and Nagasaki.

2.5 Summary

In summary, the estimation of the risk of cancer associated with exposure to low doses of radiation still remains highly controversial, full of uncertainties and methods are subject to periodic revision based on new evidence. Therefore, it is not possible to project with accuracy the long-term health effects of exposure to low doses of ionizing radiation.

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