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**Project Title:**

STOCHASTIC MODELS FOR RADIATION CARCINOGENESIS: TEMPORAL FACTORS AND DOSE RATE EFFECTS

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## Abstract

Current radiation protection standards are based largely on the experience of the cohort of A-bomb survivors. An important question, however, is whether the risks estimated in a Japanese war-time population exposed to instantaneous radiation can be transported to contemporary western populations typically exposed to protracted radiation in the workplace or elsewhere. Additional complications arise when age- and time-related factors in radiation exposure must be considered. A recent analysis, using conventional epidemiologic methods, of a large Canadian cohort of workers occupationally exposed to low-LET radiation yielded estimates of excess relative risk that were an order of magnitude higher than those estimated from the A-bomb survivors' data. Can such inconsistencies be resolved? In this research we developed and used methods based on the biological principles of multistage carcinogenesis to analyze substantial data sets and to explore the consequences of measurement error on inferences regarding radiation carcinogenesis. These methods, which complement the traditional epidemiologic approaches to data analyses, can incorporate age- and time-dependent factors, including age at start, age at stop, and protraction of exposure in a transparent way. Analyses of lung cancer incidence in the Canadian cohort referred to above using these methods shows that discrepancy between the Canadian and A-bomb data disappears when protraction is properly addressed within the framework of multistage models.

In epidemiologic studies, exposures are often measured with error. These errors in measurement of exposure often bias the estimates of risk. Broadly speaking, two distinct types of measurement error are recognized: classical error and Berkson error. In this research we developed methods for correction of biases resulting from both types of error and illustrated the methods by application to an epidemiologic data set on radiation-induced lung cancer.

Finally, we investigated the consequences of gestational mutations on carcinogenesis. Specifically we examined the consequences of radiation-induced mutations during gestation on subsequent cancer risk, and concluded that radiation exposure to the fetus confers the largest risk of cancer when it occurs late during pregnancy.

## Highlights/Significant Findings

The analyses conducted under the auspices of this grant funding confirm the results of earlier epidemiologic analyses using conventional methods that the radiation-induced cancer risk in the Canadian cohort is considerably higher than would be predicted from the A-bomb data. In terms of mechanism, this high risk is a consequence of a promotional effect of radiation. A promotional effect of high-LET radiation has been reported by us previously. This research extends this finding to low-LET radiation, and has important consequences for the prediction of risk of exposure to protracted low-LET radiation.

## Translation of Findings

The promotional effect of low-LET radiation reported in these studies and supported by the experimental literature suggests strongly that risks from low-dose-rate protracted exposures may be higher than currently believed. The use of a constant DDREF (dose

and dose-rate effectiveness factor) is also called into question. Further analyses of epidemiologic data and large animal studies would be needed to clarify the situation.

**Outcomes/Relevance/Impact**

Risks from low-dose protracted exposure to low-LET radiation may be higher than currently believed.

**Scientific Report**

Background

The paradigm of multistage carcinogenesis is firmly established in the literature. However, conventional epidemiologic methods for data analyses do not acknowledge it. The goal of this research was to develop methods based on multistage carcinogenesis for analyses of data in radiation epidemiology.

Specific Aims

There were 5 specific aims proposed in this grant.

1. Develop models based on ideas of multistage carcinogenesis for analyses of epidemiologic data on radiation carcinogenesis with particular emphasis on incorporation of age- and time-related factors.
2. Develop methods for addressing inter-individual variations and exposure measurement errors.
3. Develop methods for analyses of case-control data.
4. Investigate the consequences of dose-protraction and dose-rate effects.
5. To analyze substantial data sets.

Procedures/Methods

The two-stage clonal expansion model, which recognizes three phases – initiation, promotion, and malignant conversion – in the carcinogenic process, was used for analyses of cohort data. The appropriate software was developed for model fitting, parameter estimation via maximum likelihood and the construction of confidence intervals. The appropriate mathematical and software development was also carried out for the investigation of exposure measurement errors and the analyses of case-control studies.

Results/Discussion/Conclusions

We use a specific form of a multistage model for carcinogenesis for the analyses of epidemiologic data on radiation carcinogenesis. Although it is not realistic to expect that every radiation-induced biological process on the pathway to cancer would be included in a biologically-based model for radiation carcinogenesis, we believe that that the major factors that shape the time-dependence of evolution of risk can be identified and quantified to the point where reasonable estimations of risk can be made. Regarding carcinogenesis, the structure of the model itself plays a role in determining the relative importance of the various processes. We show, as we had done earlier for high-LET radiation, there is evidence of an 'inverse dose-rate' or protraction effect. This result is of considerable practical importance because it suggests that protracted exposure to low-LET radiation might be greater than from acute exposure, an opinion not currently held by the radiation protection community.

This model allows also prediction of the evolution of risk over the life-time of an individual exposed to radiation. One inference is that radiation-induced initiation may not be the driving factor in the risk, but more important may be radiation-induced clonal expansion of already initiated cells. Although present throughout the length of exposure, radiation-induced initiation appears to play an important role only for cancers arising late in life, and only for those individuals who began exposure early in life. These conclusions are dependent, of course, on the hypothesis embodied in the initiation-promotion-conversion paradigm of carcinogenesis. We believe, however, that recent experimental work supports the concept of promotion by low-LET radiation.

Finally, we investigated the consequences of gestational mutations on carcinogenesis. Specifically we examined the consequences of radiation-induced mutations during gestation on subsequent cancer risk, and concluded that radiation exposure to the fetus confers the largest risk of cancer when it occurs late during pregnancy. We explored the consequences of ionizing radiation exposure during gestation on the subsequent development of colon cancer based on analysis of colon cancer incidence in the SEER data, which covers approximately 10% of the US population.

With respect to each of the specific aims for this grant listed above, we accomplished what we set out to do. For aim 3, development of methods for analyses of case-control data, we do not yet have a publication. The work was completed about the time the grant expired. We are writing up the work with support from other sources, but will acknowledge support from this grant.

**Publications**


1. Krewski D, Zielinski JM, Hazelton WD, Garner MJ, Moolgavkar SH. The use of biologically based cancer risk models in radiation epidemiology. Radiat Prot Dosimetry. 104:367-76, 2003. (Specific aims 1, 4, 5.)
2. Curtis SB, Hazelton WD, Luebeck EG, Moolgavkar SH. From mechanism to risk estimation – bridging the chasm. Advances in Space Research 34:1404-1409, 2004. (Specific aims 1, 4, 5).
3. Heidenreich WF, Luebeck EG, Moolgavkar SH. Effects of exposure uncertainties in the TSCE model and application to the Colorado miners data. Radiat Res. 161:72-81, 2004. (Specific aim 2).
4. Hazelton WD, Moolgavkar SH, Curtis SB, Zielinski JM, Ashmore JP, Krewski D. Biologically based analysis of lung cancer incidence in a large Canadian occupational cohort with low-dose ionizing radiation exposure, and comparison with Japanese atomic bomb survivors. J. Toxicol Environ Health. In Press. (Specific aim 1, 4, 5).
5. Meza R, Luebeck EG, Moolgavkar SH. Gestational mutations and carcinogenesis. Mathematical Biosciences. 197:188-210, 2005. (Specific aim 1, 4, 5).

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OMB No. 0925-0001

Department of Health and Human Services

# Final Invention Statement and Certification

*(For Grant or Award)*

DHHS Grant or Award No.: RO1 OH 07864

**A.** We hereby certify that, to the best of our knowledge and belief, all inventions are listed below which were conceived and/or first actually reduced to practice during the course of work under the above-referenced DHHS grant or award for the period

9/30/2002 *original effective date* through 9/29/2005 *date of termination*.

**B. Inventions** (Note: If no inventions have been made under the grant or award, insert the word *"NONE"* under Title below.)

| NAME OF INVENTOR | TITLE OF INVENTION | DATE REPORTED TO DHHS |
|---|---|---|
| None. | | |
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| | | |
| *(Use continuation sheet if necessary)* | | |

**C. First Signature** —The person responsible for the grant or award is required to sign (in ink). Sign in the block opposite the applicable type of grant or award.

| TYPE OF GRANT OR AWARD | WHO MUST SIGN *(title)* | SIGNATURE |
|---|---|---|
| Research Grant | Principal Investigator or Project Director | |
| Health Services Grant | Director | |
| Research Career Program Award | Awardee | |
| All other types (*specify*): | Responsible Official | |

**D. Second Signature** — This block ***must*** be signed by an official authorized to sign on behalf of the institution.

Title: SPENCER LEMONS
VICE PRESIDENT
Typed Name: INDUSTRY RELATIONS & TECHNOLOGY TRANSFER

Signature:

Date: Jan. 19, 2006

Name and Mailing Address of Institution:

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