LBL-10494

CONF-

L☐ Lawrence Berkeley Laboratory
UNIVERSITY OF CALIFORNIA

MASTER

THE BEIR-III REPORT AND ITS IMPLICATIONS FOR RADIATION
PROTECTION AND PUBLIC HEALTH POLICY

J. I. Fabrikant

March 1980

Biology & Medicine Division

International
Congress
of IRPA

Jacob I. Fabrikant

The BEIR-III Report and Its Implications for Radiation

Protection and Public Health Policy   1

The BEIR-III Report and Its Implications for Radiation Protection
and Public Health Policy[1,2]

Jacob I. Fabrikant, M.D., Ph.D.[3]

Biology and Medicine Division, Lawrence Berkeley Laboratory
University of California, Berkeley[4] and Department of Radiology,
University of California School of Medicine, San Francisco,
California, U.S.A.

DISCLAIMER

INTRODUCTION

My assignment today is to try to give some sort of general
background of the implications the current Report (1) of the
Committee on the Biological Effects of Ionizing Radiation, National
Academy of Sciences-National Research Council (The BEIR-III Report)
may have on societal decision-making in the regulation of activities
concerned with the health effects of low-level radiation (Table 1,
I shall try to discuss how certain of the areas addressed by the
present BEIR Committee attempt to deal with the scientific basis
for establishing appropriate radiation protection guides, and how
the Report (1) may not necessarily serve as a comprehensive review
and evaluation of existing scientific knowledge concerning low-
level radiation exposure to human populations. Whatever I may con-
sider important in these discussions, I speak only as an individual,
and in no way do I speak for the BEIR Committee whose present
deliberations are soon to become available. It would be difficult
for me not to be somewhat biased and directed in favor of the sub-
stance of the BEIR Reports, (1-3) since as an individual I have been
sufficiently close to the ongoing scientific deliberations of agree-
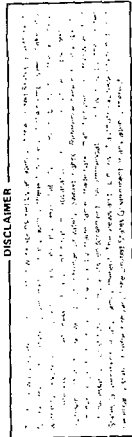ment and disagreement as they developed over the past 10 years.

I think the best thing for one to do is to discuss very briefly
why we have advisory committees on radiation, and why the BEIR

Jacob I. Fabrikant

International
Congress
of IRPA

The BEIR-III Report and Its Implications for Radiation

Protection and Public Health Policy   2

Committee, and its current Report, (1) may be somewhat different
than the others. To do this, I shall review what we know and what
we do not know about the health effects of low-level radiation,
particularly as these may highlight the controversy which has led
to scientific dispute within the Committee. Further, I shall
comment on how the risks of radiation-induced cancer in man have
been estimated, the sources of the epidemiological data, the dose-
response models used, and the uncertainties which limit precision
of estimation of excess risks from radiation. And finally, I
should like to conjecture with you on what lessons we have learned
or should have learned from the BEIR-III Committee experience, and
especially on what the implications might be of numerical risk
estimation for radiation protection and public health policy.

WHY DO WE HAVE ADVISORY COMMITTEES ON RADIATION?

For more than half a century, responsible public awareness
of the potential health effects of ionizing radiations from
medical and industrial exposure, from nuclear weapons and weapons
testing, and from the production of nuclear energy has called for
expert scientific advice and guidance. And, advisory committees
on radiation of national and international scientific composition
have for these many years met and served faithfully and effectively
to deliberate and to report on three important matters of societal
concern (Table 2): (1) to place into perspective the extent of
harm to the health of man and his decendants to be expected in the
present and in the future from those societal activities involving
ionizing radiations; (2) to develop quantitative indices of harm
based on dose-response relationships in order to provide a
scientific basis to be applied to concepts of acceptable risk and
protection of human populations exposed to radiation related
primarily to somatic and genetic risks; (3) to identify the
extent of radiation activities which could cause harm, to assess
their relative significance, and to provide a framework on how
to reduce unnecessary radiation exposure to human populations.

To a greater or lesser extent, each advisory committee on
radiation---such as the UNSCEAR, the ICRP, the NCRP, and the BEIR
Committee---have dealt extensively with these matters. But
significant differences occur in the scientific reports of these
various bodies, and we should expect differences to occur,
because of the charge, the scope, and the composition of each
Committee, and most important, public attitudes existing at the
time of the deliberations of that particular committee, and at the
time of the writing of that particular report. The BEIR Report
(1) is different; however, the main difference is not so much from
new data or new interpretations of existing data, but rather from
a philosophical approach and appraisal of existing and future
radiation protection resulting from an atmosphere of constantly
changing societal conditions and public attitudes.

WHY IS THE BEIR REPORT (1) DIFFERENT?

The Report (1) of the Committee on the Biological Effects

International
Congress
of IRPA

Jacob I. Fabrikant

The BEIR-III Report and Its Implications for Radiation

Protection and Public Health Policy   3

cf Ionizing Radiations of the National Academy of Sciences-
National Research Council is the record of the deliberations of a
standing expert scientific advisory committee (the BEIR Committee)
and deals with the scientific basis of the health effects of human
populations exposed to low levels of ionizing radiation. The
current Report (1) broadly encompasses two areas (Table 3):
(1) it reviews the current scientific knowledge---epidemiological
surveys and laboratory experiments---relevant to radiation
exposure of human populations and the delayed or late health
effects of low-level radiation; (2) it evaluates and analyzes
these late health effects---both somatic and genetic effects---in
relation to the risks from exposure to low-level radiation. The
BEIR Committee is an advisory committee to the National Academy of
Sciences-National Research Council. It presently consists of 22
members, selected for their special scientific expertise in areas
of biology, biophysics, biostatistics, epidemiology, genetics,
mathematics, medicine, physics, public health, and the radiological
sciences. The reports (1-3) of this advisory committee have, in
the past, become a reference text as a scientific basis for the
development of appropriate and practical radiation protection
standards.

     The 1972 BEIR-I Report (2) and the forthcoming BEIR-III
Report (1) differ from one or more of the other radiation advisory
committee reports of the UNSCEAR, (4,5) the ICRP, (6,7) the
NCRP, (8,9) and of the other national councils and committees,
in four important ways (Table 4):

     (1) The BEIR Report (1-3) is intended to be a readable, usable
document for all activities concerned with radiation health. The
conclusions, recommendations, and scientific appendices are pur-
posefully written in a straightforward manner, to be read and under-
stood by physicists and physicians, by congressmen and counsellors,
by unions and utilities, and by engineers and environmentalists.

     (2) The BEIR Report (1-3) does not set radiation standards
or public health policy. However, the Report (3) is purposefully
presented so that it will be useful to those responsible for
decision-making concerning regulatory programs and public health
policy involving radiation in the United States. There is no
intent to make the task any easier or to set a firm direction for
those decision-makers who must take into account those considera-
tions of science and technology, the relevant societal and economic
matters. and the development and execution of such regulatory pro-
grams. In this regard, the BEIR Report (3) suggests that those
responsible for setting radiation protection standards must always
take into account societal needs at that time, so that such
standards are established on levels of radiation exposure which
are not necessarily absolutely safe, but rather those which are
considered to be appropriately safe for existing circumstances at
the time to fulfill society's needs, particularly in the areas of
general population and occupational exposure from medical
radiation and nuclear energy.

International
Congress
of IRPA

Jacob I. Fabrikant

The BEIR-III Report and Its Implications for Radiation
Protection and Public Health Policy   4

(3) The experimental data and epidemiological surveys are
carefully reviewed and assessed for their value in estimating
numerical risk coefficients for the health effects in human
populations exposed to low-level radiation. Such deliberations
require scientific judgment and assumptions based on the available
epidemiological and experimental data only, and have necessarily
and understandably led to disagreement not only outside the commit-
tee room, but among committee members as well. But such dispute
and disagreement center not on the scientific facts and not on the
existing epidemiological and experimental data, but rather on the
assumptions, interpretations, and analyses of the available facts
and data. Therefore, the BEIR Report (3) uses a particularly
practical format for decision-makers, namely, the numerical risk
coefficients estimated are presented in probabilistic terms, within
most likely upper and lower boundaries, derived solely from the
scientific facts, the epidemiological data, and the scientific
hypotheses and assumptions on which they are based.

(4) The BEIR Report (1-3) addresses the continued need to
assess and evaluate the benefits from those activities involving
radiation as well as the risks. In our resource-limited society,
such benefit-risk assessment is essential for societal decision-
making for establishing appropriate and achievable radiation pro-
tection standards. Decisions can and must be made on the value
and costs of technological and societal programs for the reduction
of risk by reducing the levels of radiation exposure. This would
include societal choices centered as well on alternative methods
involving nonradiation activities available through a comparison of
the costs to human health and to the environment. (3)

WHAT ARE THE IMPORTANT BIOLOGICAL EFFECTS OF LOW-LEVEL RADIATION?

My remarks here will be restricted primarily to those delayed
or late health effects in humans following exposure to low-LET
radiation, x-rays and to gamma rays from radioactive sources, and
to a much lesser extent to high-LET neutron and alpha radiations,
since these are the ionizing radiations most often encountered in
medicine and in the nuclear industry. Briefly, low-level radiation
can affect the cells and tissues of the body in three important
ways (Table 5). First, if the macromolecular lesion occurs in
one or a few cells, such as these of the hematopoietic tissues, the
irradiated cell can occasionally transform into a cancer cell, and
after a period of time, there is an increased risk of cancer devel-
oping in the exposed individual. This biological effect is called
carcinogenesis; and the health effect, cancer. Second, if the
embryo or fetus are exposed during gestation, injury can occur to
the proliferating and differentiating cells and tissues, leading to
abnormal growth. This biological effect is called teratogenesis;
and the health effect, developmental abnormality in the newborn.
Third, if the macromolecular lesion occurs in the reproductive cell
of the testis or the ovary, the hereditary genome of the germ cell
can be altered, and the injury can be expressed in the descendants
of the exposed individual. This biological effect is called

International
Congress
of IRPA

Jacob I. Fabrikant

The BEIR-III Report and Its Implications for Radiation
Protection and Public Health Policy   5

mutagenesis; and the health effect, genetically-related ill-health.
        There are a number of other biological effects of ionizing
radiation, such as cataracts of the lens of the eye, or impairment
of fertility, but these three important late effects---carcinogene-
sis, teratogenesis and mutagenesis---stand out as those of greatest
concern. This is because a considerable amount of scientific
information is known from epidemiological studies of exposed human
populations and from laboratory animal experiments. Furthermore,
we believe that any exposure to radiation, even at very low levels
of dose, carries some risk of such deleterious effects. And, as
the dose of radiation increases above very low levels, the risk of
these deleterious health effects increases in exposed human popula-
tions. It is these latter observations that have been central to
the public concern about the potential health effects of low-level
radiation, and to the task of establishing standards for protection
of the health of exposed populations. Indeed, all reports of
expert advisory committees on radiation are in close agreement on
the broad and substantive issues of such health effects.

WHAT DO WE KNOW ABOUT THE HEALTH EFFECTS OF LOW-LEVEL RADIATION?

        A number of very important observations on the health effects
of low-level radiation have now convincingly emerged, and about
which there is firm general agreement (Table 6). These observations
are based on careful statistical evaluation of epidemiological sur-
veys of exposed human populations, in conjunction with extensive
research in laboratory animals, and on analysis of dose-response
relationships of carcinogenic, teratogenic and genetic effects,
and on known mechanisms of cell and tissue injury in vivo and
in vitro.
        1) Cancer induction is considered to be the most important
late somatic effect of low-dose ionizing radiation. Solid cancers
arising in the various organs and tissues, such as the female breast
and the thyroid gland, rather than leukemia, are the principal
late effects in indivi⁻ials exposed to radiation. The different
organs and tissues vary greatly in their relative susceptibility
to cancer induction by radiation. The most frequently occurring
radiation-induced cancer in man include, in decreasing order of
susceptibility (Table 6): the female breast; the thyroid gland,
especially in young children and in females; the hematopoietic
tissues; the lung; certain organs of the gastrointestinal tract;
and the bones. There are influences, however, of age at the time
of irradiation, of sex, and of the radiation factors and types---
LET and RBE---affecting the cancer risk.
        2) The effects on growth and development in the irradiated
embryo and fetus are related to the gestational stage at which
exposure occurs. It appears that a threshold level of radiation
dose may exist below which gross teratogenic effects will not be
observed. However, these dose levels would vary greatly depending
on the particular developmental abnormality.
        3) It has been necessary to estimate genetic risks based
mainly on laboratory mouse experiments because of the paucity of
data from exposed human populations. Our knowledge of fundamental

mechanisms of radiation injury at the genetic level is far more
complete, thereby permitting greater assurance in extrapolating
from laboratory experiments to man. Mutagenic effects are related
linearly to radiation dose, even at very low levels of exposure.
With new information on the broad spectrum and incidence of geneti-
cally-related ill-health in man, such as mental retardation and
diabetes, the risk of radiation mutagenesis in man affecting future
generations takes on new and special consideration.

WHAT DO WE NOT KNOW ABOUT THE HEALTH EFFECTS OF LOW-LEVEL RADIATION?

In spite of a remarkable understanding of the health effects
in exposed human populations, there is still a considerable amount
we do not know about the potential health hazards of low-level
radiation (Table 7):
   1. We do not know what the health effects are at dose rates
as low as a few hundred millirem per year. It is probable that
if any health effects do occur, they will be masked by environ-
mental or other competing factors that produce similar effects.
   2. The vast epidemiological data on exposed human populations
are nevertheless highly uncertain in regard to the forms of the
dose-response relationships for radiation-induced cancer in man.
This is especially the case for low-level radiation. Therefore,
it has been necessary to estimate human cancer risk at low doses
primarily from observations at relatively high doses, frequently
greater than 100 rads and more. However, it is not known whether
the cancer incidence observed at high dose levels also applies to
cancer induction at low dose levels.
   3. We have no reliable method at the present time of estimat-
ing the repair of injured cells and tissues of the body exposed to
very low doses and dose rates. And further, we do not know how to
identify those persons who may be particularly susceptible to
radiation injury.
   4. Analyses of the numerous epidemiological surveys of
irradiated populations exposed in the past demonstrate that we
have very limited information on the precise radiation doses
absorbed by the tissues and organs. Furthermore, we do not know
the complete cancer incidence in each study population, since new
cases of cancer continue to appear with the passing of time.
Accordingly, any estimation of excess cancer risk based on such
limited dose-response information must necessarily be incomplete,
until the entire study population has died from natural causes.
   5. We do now know the role of competing environmental and
other host factors---biological, chemical, or physical factors---
existing at the time of exposure, or following exposure, which may
influence and affect the carcinogenic, teratogenic, or genetic
effects of low-level radiation.

WHAT ARE THE UNCERTAINTIES IN THE DOSE-RESPONSE RELATIONSHIPS FOR RADIATION-INDUCED CANCER?

The present BEIR-III Committee, in its earliest deliberations,
recognized that there was great uncertainty in regard to the shapes

of the dose-response curves for cancer induction by radiation
in humans, and this was especially the case at low levels of
dose. Estimates of excess cancer risk at low doses appear to
depend more on what is assumed about the mathematical form of the
dose-response function than on the available epidemiological data.
Accordingly, in estimating the excess cancer risk from low-dose
low-LET radiation, the BEIR-III Committee chose to use a linear-
quadratic dose-response model felt to be consistent with epidemi-
iological and radiobiological data in preference to more extreme
dose-response models. In this regard, the current BEIR-III
Report[1] differs substantially from the 1972 BEIR-I Report[2]. I
should like to examine the deliberations of this decision more
closely.

In recent years, a general hypothesis for estimation of
excess cancer risk in irradiated human populations, based on
theoretical considerations, extensive experimental animal studies
and epidemiological surveys, suggests that complex dose-response
relationships between radiation dose and observed cancer inci-
dence[10-15]. Perhaps the most widely accepted model for cancer
induction by radiation, based on the available information and
consistent with both knowledge and theory, takes the complex
linear-quadratic form: $I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2)\exp(-\beta_1 D - \beta_2 D^2)$,
where I is the cancer incidence in the irradiated population at
radiation dose D in rad, and α_0, α_1, α_2, β_1 and β_2 are non-
negative constants (Figure 1). The multicomponent dose-response
curve contains (1) an initial upward-curving linear and quadratic
functions of dose which represents the process of cancer induc-
tion by radiation; and (2) a modifying exponential function of
dose which represents the competing effect of cell killing at
high doses. α_0 is the ordinate intercept at 0 dose, and defines
the natural incidence of cancer in the population. α_1 is the
initial slope at 0 dose, and defines the linear component in the
low dose range. α_2 is the curvature near 0 dose, and defines
the upward-curving quadratic function of dose. β_1 and β_2 are
the slopes of the downward-curving function in the high dose
range, and define the cell killing function.

Analysis of a large number of dose-incidence curves for
cancer induction in irradiated populations, both in humans and
in animals, has demonstrated that for different radiation-
induced cancers only certain of the parameter values of these
constants can be theoretically determined. However, the extent
of the variations in the shapes of the dose-response curve does
not permit direct determination from the data of any of these
parameter values with precision, or of assuming their values,
or of assuming any fixed relationship between two or more of
these parameters. In the case of the epidemiological surveys
of irradiated human populations, this complex multicomponent
general dose-response form cannot be universally applied.
Therefore, it has become necessary to simplify the model by
reducing the number of parameters which would have the least
effect on the form of the dose-response relationship in the
dose range of low-level radiation. Such simpler models, with
increasing complexity, include the linear, quadratic, linear-

quadratic, and finally, the multicomponent linear-quadratic form
with an exponential modifier (Figure 2).

The BEIR-III Committee recognized three compelling situations
which seriously limit precise numerical estimation of the excess
cancer risk of low-level radiation in human populations (Table 8).
(1) We lack an understanding of the fundamental mechanisms of can-
cer induction by radiation in man. (2) The dose-response infor-
mation from human data is highly uncertain, particularly at low
levels of dose. (3) Experimental and theoretical considerations
suggest that various and different mathematical forms of dose-
response relationships may exist for different radiation-induced
cancers in exposed human populations. Nevertheless, these limita-
tions do not relieve decision-makers of the responsibility for
determining public health policy based on appropriate radiation
protection standards. Accordingly, not only did the BEIR-III
Committee consider it essential that quantitative risk estimation
be determined, based on the available epidemiological and radio-
biological data, but that in addition, it was equally essential
that precise explanations and qualifications of the assumptions
and procedures involved in the determination of such risk esti-
mates are to be provided. This has been done explicitly in the
current BEIR-III Report[1] containing the estimates of excess cancer
risk. The Committee recognized that some experimental and human
data, as well as theoretical considerations, suggest that for
exposure to low-LET radiation, such as x-rays and gamma rays, at
low doses, the linear model probably leads to overestimates of
the risk of most radiation-induced cancers in man, but that the
model can be used to define the upper limits of risk. Similarly,
the Committee believes that the quadratic model may be used to
define the lower limits of risk from low-dose low-LET radiation.
For exposure to high-LET radiation, such as neutrons and alpha
particles, linear risk estimates for low doses are less likely
to overestimate risk and may, in fact, underestimate risk.

WHAT IS THE CONTROVERSY OVER LOW-LEVEL RADIATION?

The estimation of the cancer risk of exposure to low-level
radiation is said to be clouded by scientific dispute. In par-
ticular, there appears to be disagreement among some scientists
as to the effects of very low levels of radiation, even as low
as our natural radiation background. While there is no precise
definition of low-level exposure, most scientists would generally
agree that low-level radiation is that which falls within the
dose range considered permissible for occupational exposure.
According to accepted standards (16),5 rem per year to the whole
body would be an allowable upper limit of low-level radiation
dose for the individual radiation worker.

In this context, and with this as the boundary condition for
occupational exposure, then it could very well be concluded that
most of the estimated delayed cancer deaths which may be associ-
ated with a so-called hypothetical nuclear reactor accident, for
example, are therefore considered by some scientists to be caused
by exposures well below the allowable occupational limits.

Furthermore, if it is assumed that <u>any</u> extra radiation above
natural background, however small, causes additional cancer, then
if millions of people are exposed, some extra cancers will inevi-
tably result. Other scientists strongly dispute this, and firmly
believe that low-level radiation is nowhere near as dangerous as
their adversarial colleagues would insist. Central to this dis-
pute, it must be remembered that cancers induced by radiation are
indistinguishable from those occurring naturally; hence, their
existence can be inferred only on the basis of a statistical excess
above the natural incidence. Since such health effects, if any,
are so rarely seen under low-level radiation because the exposures
are so small, the issue of this dispute may never be resolved--it
may be beyond the abilities of science and mathematics to decipher.
     It is just this type of controversy that was at the root of
the division within the present BEIR-III Committee. There is little
doubt that the Committee's most difficult task has been to estimate
the carcinogenic risk of low-dose low-LET whole-body radiation.
Here, emphasis was placed almost entirely on the human epidemio-
logical studies, since it was felt that little information from
animal studies could be applied directly to man. Therefore, as the
earlier 1972 BEIR-I Report (2) had done, some members of the present
BEIR-III Committee chose it necessary to adopt a linear hypothesis
of dose-response to estimate the cancer risk at very low-level
radiation exposure where no human epidemiological data are avail-
able. Here, it was assumed the same proportional risks are present
at low levels as at high levels of radiation. This position implies
that even very small doses of radiation are carcinogenic, a find-
ing that could force the Environmental Protection Agency to adopt
stricter health standards to protect against occupational and
general population exposure. Other members of the Committee do not
accept this position, and believe this is an alarmist approach.
When there is no human epidemiological evidence at low doses, these
scientists prefer to assume that the risks of causing cancer are
proportionally lower.
     Let us look at some of the problems. In its deliberations,
the present BEIR-III Committee concluded two important points: (1)
It is not yet possible to make precise low-dose estimates for can-
cer induction by radiation because the level of risk is so low it
cannot be observed directly. (2) There is great uncertainty as
to the dose-response function most appropriate for interpolating
in the low-dose region. In studies of exposed animal and human
populations, the shape of a dose-response relationship at low doses
may be practically impossible to ascertain statistically. This is
because the population sample sizes required to estimate or test
a small absolute cancer excess are extremely large; specifically,
the required sample sizes are approximately inversely proportional
to the square of the excess. For example, if the excess is truly
proportional to dose, and if 1,000 exposed and 1,000 control per-
sons are required in each group to test the cancer excess ade-
quately at 100 rads, then about 100,000 in each group are required
at 10 rads, and about 10,000,000 in each group are required at one
rad. Thus, it appears that experimental evidence and theoretical
considerations are more likely than empirical data to guide the
choice of a dose-response function. In this dilemma and after much

disagreement among some of its members, the present BEIR-III Commit-
tee chose to adopt as a working model for low-LET radiation and car-
cinogenesis the linear-quadratic dose-response form with an expo-
nential term to account for the frequently observed turndown of
the curve in the high-dose region. However, in applying this multi-
component model, only certain of its derivatives, including the
linear, linear-quadratic, and pure quadratic, could prove practical.
     It should be remembered that in the 1972 BEIR-I Report
cancer risk estimates for whole-body radiation exposure were derived
from linear model average excess cancer risk per rad observed at
doses generally of a hundred or more rads. These estimates have
been generally criticized on the grounds that the increment in can-
cer risk per rad may well depend on dose and that the true risk
at low doses may therefore be lower or higher than the linear
model predicts (9). In animal experiments, it has been shown, often
with considerable statistical precision, that the dose-response
curve for radiation-induced cancer can have a variety of shapes.
As a general rule, the curve has a positive curvature for low-LET
radiation, i.e., the slope of the curve increases with increasing
dose. However, at high doses, the slope often decreases and may
even become negative. Dose-response curves may also vary with the
kind of cancer, with animal species, and with dose rate. On the
basis of the experimental evidence and current microdosimetric
theory, therefore, the present BEIR-III Committee could quite rea-
sonably adopt as the basis for its consideration of dose-response
models the linear-quadratic form with an exponential term for a
negative slope in the high dose region.
     On the other hand, the Committee recognized that for the most
part, the available human data from the vast body of epidemiologi-
cal studies fail to suggest any specific dose-response model, and
are not sufficiently reliable to discriminate among a priori models
suggested by the experimental and theoretical work. However, there
appears to be certain exceptions; for example, cancer of the skin
is not observed at low radiation doses (17), and dose-response rela-
tionships observed in the Nagasaki leukemia data appear to have
positive curvature (18). The incidence of breast cancer seems to be
adequately described by a linear dose-response model (11,19)
(Figure 3).
     In attempts to apply derivatives of the multicomponent linear-
quadratic model to the human data, simplification was required to
obtain statistically stable risk estimates in many cases. It is
now well known that members of the BEIR-III Committee were divided
on this matter; some members of the Committee strongly favor the
linear model, others favor the quadratic form. A further modifi-
cation of the linear-quadratic form was assumed with the linear and
quadratic components to be equivalent at some dose, which is con-
sistent with epidemiological data and radiobiological evidence,
and avoids dependence on either of the extreme forms (14,15).

WHAT ARE THE UNCERTAINTIES IN ESTIMATION OF THE CARCINOGENIC RISK
IN MAN OF LOW-LEVEL RADIATION?

     The quantitative estimation of the carcinogenic risk of low-

dose, low-LET radiation is subject to numerous uncertainties (Table
9). The greatest of these concerns the shape of the dose-response
curve. Others include the length of the latent period, the RBE for
fast neutrons and alpha radiation relative to gamma and x-radiation,
the period during which the radiation risk is expressed, the model
used in projecting risk beyond the period of observation, the effect
of dose rate or dose fractionation, and the influence of differences
in the natural incidence of specific types of cancer. In addition,
uncertainties are introduced by the biological risk characteristics
of humans, e.g., the effect of age at irradiation, the influence
of any disease for which the radiation was given therapeutically,
and the influence of length of observation or follow-up. The col-
lective influence of these uncertainties is such as to deny great
credibility to any estimates of human cancer risk that can be made
for low-dose, low-LET radiation. It is for these reasons, the pre-
sent BEIR-III Committee has placed more emphasis on the methods of
risk estimation than on any numerical estimates derived thereby.

WHAT ARE THE SOURCES OF EPIDEMIOLOGICAL DATA FOR THE ESTIMATION OF EXCESS CANCER RISK IN EXPOSED HUMAN POPULATIONS?

The tissues and organs involved in radiation-induced cancer
in man about which we have the most reliable epidemiological data
from a variety of sources from which corroborative risk estimates
have been obtained include the bone marrow, the thyroid, the breast,
and the lung. The data on bone and the digestive organs are, at
best, preliminary, and do not approach the precision of the others.
In several of these tissues and organs, risk estimates are obtained
from very different epidemiological surveys, some followed for over
25 years, and with adequate control groups. There is impressive
agreement when one considers the lack of precision inherent in
the statistical analyses of the case-finding and cohort study popu-
lations, variability in ascertainment and clinical periods of
observation, age, sex and racial structure, and different dose
levels, and constraints on data from control groups.

By far, the most reliable and consistent data have been those
of the risk of leukemia, which come from the Japanese A-bomb sur-
vivors (18), the ankylosing spondylitis patients treated with x-
ray therapy in England and Wales (20,21), the metropathia patients
treated with radiotherapy for benign uterine bleeding (22), and the
tinea capitis patients treated with radiation for ringworm of the
scalp (23,24)(Table 10). There is evidence of an age-dependence and
a dose-dependence, a relatively short latent period of a matter of
a few years, and a relatively short period of expression, some 10
years. This cancer is uniformly fatal.

The data available on thyroid cancer are more complex; the
surveys include the large series of children treated to the neck
and mediastinum for enlarged thymus (25), children treated to the
scalp for tinea capitis (23,24), and the Japanese A-bomb survivors (18)
and Marshall Islanders (26) exposed to nuclear explosions (Table 10).
Here, there is an age-dependence and sex-dependence--children
and females appear more sensitive. Although the induction rate is
high, the latent period is relatively short, and it is probable

that no increased risk will be found in future follow-up. In addition, most tumors are either thyroid nodules, or benign or treatable tumors, and only about 5% of the radiation-induced thyroid tumors are fatal.

In very recent years, much information has become available on radiation-induced breast cancer in women (13,19) (Table 11). The surveys include primarily women with tuberculosis who received frequent fluoroscopic examinations for artificial pneumothorax (27), post-partum mastitis patients treated with radiotherapy (28), and the Japanese A-bomb survivors in Hiroshima and Nagasaki (18). Here, there is an age- and dose-dependency, as well as a sex-dependency, and the latent period is long, some 20 to 30 years. Perhaps about half of these neoplasms are fatal.

Another relatively sensitive tissue, and a complex one as regards radiation dose involving parameters of the special physical and biological characteristics of the radiation quality, is the epithelial tissue of the bronchus and lung (Table 11). The information from the Japanese A-bomb survivors (18), and uranium miners in the United States and Canada (29,30), and the ankylosing spondylitis patients in England and Wales (20,21) provide reliable risk estimates of lung cancer exposed persons. There is some evidence of age-dependence from the Japanese experience and a relatively long latent period. This cancer is uniformly fatal.

The lifetime risk of radiation-induced bone sarcoma (Table 11), based primarily on radium and thorium patients who had received the radioactive substances for medical treatment, or ingested them in the course of their occupations (31,32) is low. For all other tumors arising in various organs and tissues of the body, values are extremely crude and preliminary estimates.

There is now a large amount of epidemiological information from various comprehensive surveys from a variety of sources; the most extensive, perhaps, include the Japanese A-bomb survivors (18), the patients treated to the spine for ankylosing spondylitis (20,21), the metropathia patients (22) and the early radiologists (33). These data indicate that leukemia is now no longer the major cancer induced by radiation, and that solid cancers are exceeding the relative incidence of radiation leukemia by a factor as high as 5[5]. That is, in view of the long latent periods for certain solid cancers to become manifest, it can be estimated that perhaps after some 30 years following radiation exposure, the risk of excess solid cancers may prove to be many times the risk of excess leukemia. These estimates remain very crude, since they do not take into account the obvious lack of precision of certain of the epidemiological studies, particularly as regards radiation dose distribution, ascertainment, latency periods, and other important physical and biological parameters. The BEIR (1,2), the UNSCEAR (4,5) and the ICRP (6,7) Reports have estimated the risk from whole-body exposure in different ways and based primarily on the studies of the Japanese A-bomb survivors (18), and to a much lesser extent, from data on the ankylosing spondylitis patients (20,21), the metropathia patients (22), the tinea patients (23,24), and similar epidemiological surveys carefully followed, many of which now have adequate control study populations, a very crude figure of the total lifetime

excess absolute risk of radiation-induced cancer deaths can be
derived. This figure for all malignancies from low-LET radiation,
i.e., x-rays and gamma rays, delivered at low doses would be an
overestimate of the true risk. The actual figure may be much lower
in terms of excess cancer cases per million persons exposed per rad
total lifetime risk, a large fraction of which would not necessarily
be fatal (1,5). Any such estimated figure remains very unreliable, but
it does provide a very rough figure for comparison with other esti-
mates of avoidable risks, or voluntary risks, encountered in every-
day life.

WHAT ARE THE RISK ESTIMATES OF RADIATION-INDUCED CANCER IN MAN?

The chief sources of epidemiological data used in the current
BEIR-III Report (1) are the Japanese populations exposed to whole-body
irradiation in Hiroshima and Nagasaki, patients with ankylosing
spondylitis and other patients who were exposed to partial body
irradiation therapeutically, or to diagnostic x-rays and various
occupationally exposed populations, such as uranium miners and
radium dial painters. Most epidemiological data do not systemati-
cally cover the range of low to moderate radiation doses for which
the Japanese atomic bomb survivor data appear to be fairly reliable.
Analysis in terms of dose-response therefore rely greatly on the
Japanese data. The substantial neutron component of dose in Hiro-
shima and its correlation with gamma dose limit the value of the
more numerous Hiroshima data to the estimation of cancer risk from
low-LET radiation. The Nagasaki data, for which the neutron com-
ponent of dose is small, are less reliable for doses below 100 rads.
For its _illustrative computations_ of the lifetime risk from
whole-body exposure, the present BEIR-III Committee chose three
exposure situations for low-dose, low-LET radiation:
(1) a single exposure of a representative (life-table) popula-
tion to 10 rads;
(2) a continuous, lifetime exposure of a representative (life-
table) population to 1 rad per year; and
(3) an exposure to 1 rad per year over several age intervals
exemplifying conditions of occupational exposure.
The three exposure situations were not chosen to reflect any circum-
stances that would normally occur, but embrace the areas of concern--
general population and occupational exposure and single and continu-
ous exposure. These were substantially different from the exposure
situation chosen for illustrative computation by the 1972 BEIR-I
Committee, where 100 mrem per year was selected.
Below these dose levels chosen for the current report, the
uncertainties of extrapolation of risk to very low levels were
strongly felt by some members of the present Committee to be too
great to justify risk estimation. The selected annual exposure,
although only one-fifth the maximal permissible dose for occupational
exposure, is nevertheless consistent with occupational exposures in
the nuclear industry. The U.S. 1969-1971 life-table was used as the
basis for the calculations, and all results are expressed in terms
of excess cancers per million persons throughout their lifetime after
exposure. The expression time was taken as 25 years for leukemia
and the remaining years of life for other cancers. Separate estimates

were made for cancer mortality and for cancer incidence.

The resulting cancer mortality risk estimates for all forms
of cancer differ by as much as an order of magnitude. The uncer-
tainty derives chiefly from the range of dose-response models used,
from the alternative absolute and relative projection models, and
from the sampling variation in the source data. The lowest esti-
mates are derived from the pure quadratic model; the highest, from
the linear model. The linear-quadratic model provides estimates
intermediate between these two extremes.

In the absence of any increased radiation exposure, among one
million persons of life-table age and sex composition in the United
States, about 164,000 persons would be expected to die from cancer,
according to present cancer mortality rates. For a situation in
which these one million persons are exposed to a single dose
increment of 10 rads of low-LET radiation, the linear-quadratic
model predicts increases of about 0.5% and 1.5% over the normal
expectation of cancer mortality, according to the projection model.

For continuous lifetime exposure to 1 rad per year, the
increase in cancer mortality, according to the linear-quadratic
model, ranges from about 3% to 8% over the normal expectation, de-
pending on the projection model.

To compare these estimates with those of the 1972 BEIR-I
Report (2) and the 1977 UNSCEAR Report (5), it was convenient to express
them as cancer deaths per million persons per rad of continuous
lifetime exposure. For continuous lifetime exposure to 1 rad per
year the linear-quadratic dose-response model for low-LET radia-
tion yielded estimates some 25% to 50% below the comparable linear
estimates in the 1972 BEIR-I Report (2), depending on the projection
model. Although the present BEIR-III Report (1) uses much more scien-
tific information not available for the earlier 1972 report, the
differences mainly reflect changes in the assumptions made by the
two BEIR Committees almost a decade apart. The present Committee
preferred a linear-quadratic, rather than linear, dose-response
model for low-LET radiation, and preferred not to assume a fixed
relationship between the effects of high-LET and low-LET radia-
tion. The present risk estimates do not, as in the 1972 BEIR-I
Report (2), carry through to the end of life very high relative-risk
coefficients obtained with respect to childhood cancers induced
in utero by radiation. The present BEIR-III risk estimates do not
differ appreciably from those in the 1977 UNSCEAR Report

Cancer-incidence risk estimates were less firm than mortality
estimates. The present BEIR-III Committee used a variety of dose-
response models and several data sources. The dose-response models
produced estimates that differed by more than an order of magnitude,
whereas the different data sources gave broadly similar results.
For the linear-quadratic model and for continuous lifetime exposure
to 1 rad per year, for example, the increased risks expressed as
percent of the normal incidence of cancer in males were about 2% to
6%, depending on the projection model. Risks for females were sub-
stantially higher than those for males, due primarily to the rela-
tive importance of radiation-induced thyroid and breast cancer.

Estimates of excess risk for individual organs and tissues
depend in large part on partial-body irradiation and use a wider

variety of data sources. Except for leukemia and bone cancer,
estimates for individual sites of cancer were made only on the
basis of the linear model and were stated in terms of excess cancer
cases per year per million persons exposed per rad. For leukemia,
the linear-quadratic model yielded about 1.0 to 1.4 excess leukemia
cases (or deaths) per year per million persons exposed per rad, for
females and males, respectively. For solid cancers, linear-model
estimates were, for example: for thyroid in males, about 2, and
in females, about 6; for female breast, about 6; and for lung,
about 3.5 to 4. These risk coefficients derive largely from epi-
demiologic data in which exposure was at high doses, and these
values may, in some cases, overestimate risk at low doses.

WHAT ARE THE IMPLICATIONS OF NUMERICAL RISK ESTIMATION FOR
RADIATION PROTECTION AND PUBLIC HEALTH POLICY?

The present BEIR-III Committee has not highlighted any contro-
versy over the health effects of low-level radiation. In its eval-
uation of the experimental data and epidemiological surveys, the
Committee has carefully reviewed and assessed the value of all the
available scientific evidence for estimating numerical risk coef-
ficients for the health hazards to human populations exposed to
low levels of ionizing radiation. Such devices require scientific
judgment and assumptions based on the available data only, and has
led to disagreement not only outside the committee room but among
committee members as well. But such disagreement centers not on
the scientific facts or the epidemiological data, but rather on
the assumptions and interpretations of the available facts and
data.
The present scientific evidence and the interpretation of
available human data can draw very few firm conclusions on which
to base scientific public health policy for protection standards
for low-level radiation. However, based on the radiation risk
estimates derived, any lack of precision does not minimize either
the need for setting public health policy standards nor the conclu-
sion that such risks are extremely small when compared with those
available from alternative options, and those normally accepted by
society as the hazards of everyday life. When compared with the
benefits that society has established as goals derived from the
necessary activities of energy production and medical care, it is
apparent that society must establish appropriate standards and
seek appropriate controlling procedures which continue to assure
that its needs and services are being met with the lowest possible
risks.
In a third of a century of inquiry, embodying among the most
extensive and comprehensive scientific efforts on the health ef-
fects of an environmental agent, certain practical information neces-
sary for determination of radiation protection standards for public
health policy is still lacking, and may remain so. It is now
assumed that exposure to radiation at low levels of dose carries
some risk of deleterious effects. However, how low this level may
be, or the probability, or magnitude of the risk, still are not
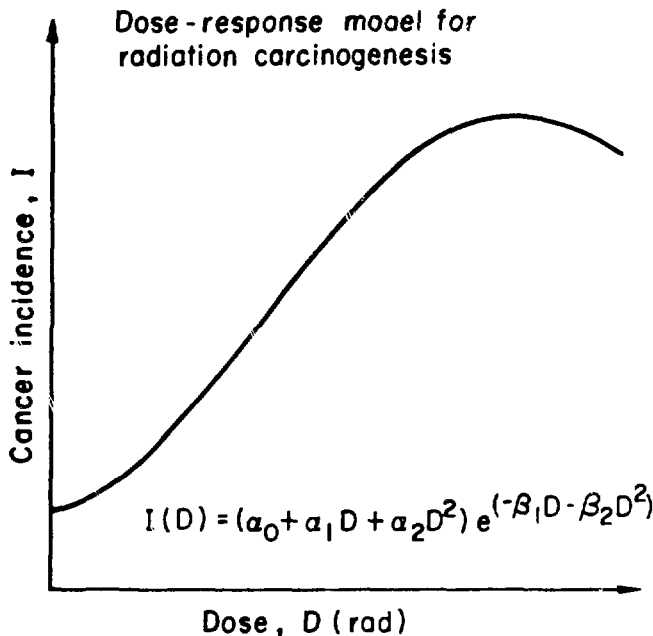known. Our best scientific knowledge and our best scientific

advice are essential for the protection of the public health, for
the effective application of new technologies in medicine and
industry, and for guidance in the production of nuclear energy.
Man cannot dispense with those activities which inevitably involve
exposure to low levels of ionizing radiation in medicine, where he
readily recognizes some degree of risk to health, however small,
exists. In the evaluation of such risks from radiation in all
other societal activities involving ionizing radiation, including
nuclear energy, as is done in medicine, it is also necessary to
limit the radiation exposure to a level at which the risk is
acceptable both to the individual and to society.
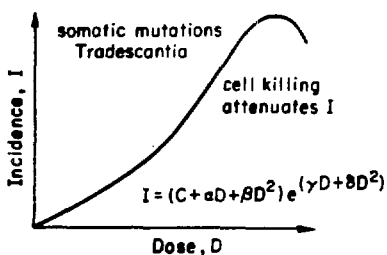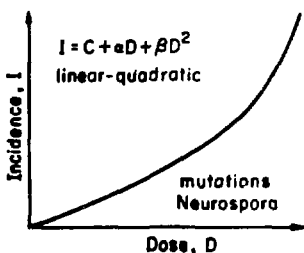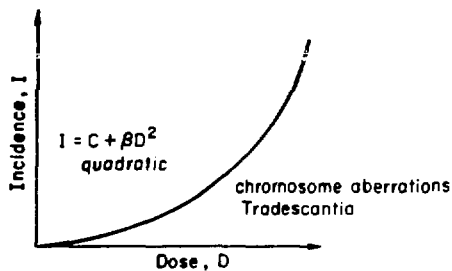
Acknowledgements

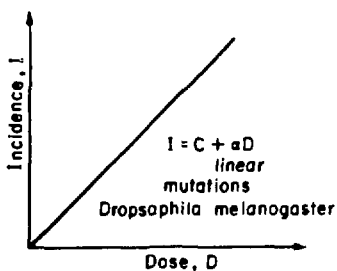## Mailing Address

Jacob I. Fabrikant, M.D., Ph.D., Donner Laboratory
University of California, Berkeley, California 94720 U.S.A.

Dose - response model for
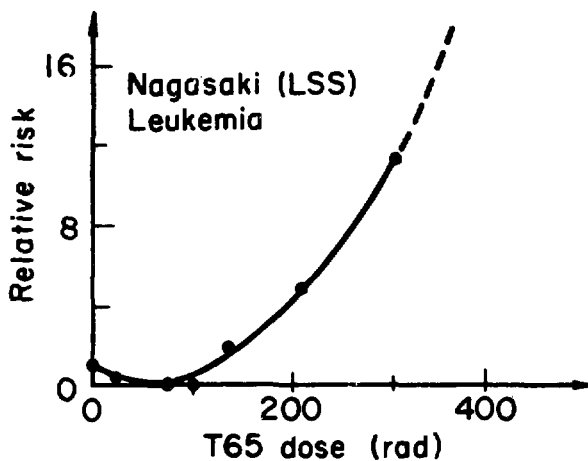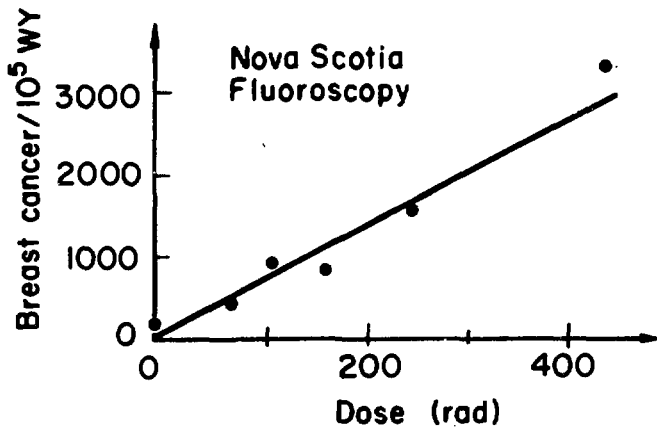radiation carcinogenesis

Cancer incidence, I

$$I(D) = (\alpha_0 + \alpha_1 D + \alpha_2 D^2) e^{(-\beta_1 D - \beta_2 D^2)}$$

Dose, D (rad)

XBL791-3029

SHAPES OF DOSE RESPONSE CURVES

Incidence, I

$I = C + \alpha D$
linear
mutations
Dropsophila melanogaster

Dose, D

Incidence, I

$I = C + \beta D^2$
quadratic

chromosome aberrations
Tradescantia

Dose, D

Incidence, I

$I = C + \alpha D + \beta D^2$
linear-quadratic

mutations
Neurospora

Dose, D

Incidence, I

somatic mutations
Tradescantia

cell killing
attenuates I

$$I = (C + \alpha D + \beta D^2) e^{(\gamma D + \delta D^2)}$$

Dose, D

XBL7812-12392

XBL801-3027

REFERENCES

1. National Academy of Sciences-National Research Council. (1980.
    To be published): Advisory Committee on the Biological Effects
    of Ionizing Radiations. The Effects on Populations of Exposure
    to Low Levels of Ionizing Radiation. Washington, D.C.
2. National Academy of Sciences-National Research Council. (1972):
    Advisory Committee on the Biological Effects of Ionizing Radia-
    tions. The Effects on Populations of Exposure to Low Levels of
    Ionizing Radiation. Washington, D.C.
3. National Academy of Sciences-National Research Council. (1977):
    Advisory Committee on the Biological Effects of Ionizing Radia-
    tions. Considerations of Health Benefit-Cost Analysis for Acti-
    vities Involving Ionizing Radiation Exposure and Alternatives.
    Washington, D.C.
4. United Nations Scientific Committee on the Effects of Atomic
    Radiation. (1972): Ionizing Radiation: Levels and Effects.
    New York.
5. United Nations Scientific Committee on the Effects of Atomic
    Radiation. (1977): Sources and Effects of Ionizing Radiation.
    New York.
6. International Commission on Radiological Protection. (1966):
    The Evaluation of Risks from Radiation. ICRP Publication 8.
    Pergamon Press, Oxford.
7. International Commission on Radiological Protection. (1977):
    Recommendations of the International Commission on Radiological
    Protection. ICRP Publication 26. Pergamon Press, Oxford.
8. National Council on Radiation Protection and Measurements.
    (1971): NCRP Report No. 39. Basic Radiation Protection
    Criteria. Washington, D.C.
9. National Council on Radiation Protection and Measurements.
    (1975): NCRP Report No. 43. Review of the Current State of
    Radiation Protection Philosophy. Washington, D.C.
10. Brown, J.M. (1976): Health Phys., 31, 231.
11. Brown, J.M. (1977): Radiation Res., 71, 34.
12. Upton, A.C. (1977): Radiation Res., 71, 51.
13. Upton, A.C., Beebe, G.W., Browr, J.M., Quimby, E.H., and
    Shellabarger, C. (1977): J. Natl. Cancer Inst., 59, 480.
14. Fabrikant, J.I. (1979): (In) Epidemiology Studies of Low-Level
    Radiation Exposure. Report LBL-8667, p. 1, University of Cali-
    fornia, Berkeley.
15. Fabrikant, J.I. (1980. To be published): (In) Nuclear Reactor
    Safety: A Current Perspective. Science.
16. International Commission on Radiological Protection. (1970):
    Protection Against Ionizing Radiation from External Sources,
    ICRP Publication 15. Pergamon Press, Oxford, 1973. Data for
    Protection Against Ionizing Radiation from External Sources:
    Supplement to ICRP Publication 15. ICRP Publication 21.
    Pergamon Press, Oxford.
17. Shore, R.E., Albert, R.E. and Pasternack, B. (1976): Arch.
    Environment. Health, 31, 21.
18. Beebe, G.W., Kato, H. and Land, C.E. (1977): Life Span Study
    Report 8. Radiation Effects Research Foundation Technical Report
    RERF TR 1-77. National Academy of Sciences, Washington, D.C.

19. Mole, R.H. (1978): Brit. J. Radiol., 51, 401.
20. Court-Brown, W.M. and Doll, R. (1965): Brit. Med. J.,
    2, 1327.
21. Smith, P.G. and Doll, R. (In press): (In) International Sym-
    posium on the Late Biological Effects of Ionizing Radiation,
    IAEA-SM-224/771, Vienna.
22. Smith, P.G. and Doll, R. (1976): Brit. J. Radiol. 49, 223.
23. Shore, R.E., Albert, R.E. and Pasternack, B.S. (1976): Arch.
    Environ. Health 31, 21.
24. Modan, B., Baidatz, D., Mart, H., Steinitz, R., and Levin, S.G.
    (1974): Lancet 1, 277.
25. Hempelmann, L.H., Hall, W.J., Phillips, M., Cooper, R.A.,
    and Ames, W.R. (1975): J. Natl. Cancer Inst. 55, 519.
26. Conard, R.A. (1977): (In) DeGroot, L.J., ed. Radiation-
    Associated Thyroid Carcinoma, p. 241, Academic Press, New York.
27. Myrden, J.A. and Quinlan, J.J. (1974): Ann. Roy. Coll.
    Physicians Can. 7, 45.
28. Hempelmann, L.H., Kowaluk, E., Mansur, P.S., Pasternack, B.S.,
    Albert, R.E. and Haughie, G.E. (1977): J. Natl. Cancer Inst.
    59, 813.
29. (1976): Health Effects of Alpha-Emitting Particles in the
    Respiratory Tract. Report of ad hoc Committee on "Hot Particles"
    of the Advisory Committee on the Biological Effects of Ionizing
    Radiations. Washington, D.C.
30. Ham, J.M. (1976): Report of the Royal Commission on the Health
    and Safety of Workers in Mines. Ministry of the Attorney
    General, Province of Ontario.
31. Mays, C.W. and Spiess, H. (1978): (In) Miller, W.A. and Ebert,
    H.G., eds. Biological Effects of ^{224}Ra. Benefit and Risk of
    Therapeutic Application, p. 168, Nyhoff Medical, The Hague.
32. Rowland, R.E. and Stehney, A.F. (1977): (In) Argonne National
    Laboratory Report ANL-77-65, Part II, 206, Argonne, Illinois.
33. Matanoski, G.N., Seltzer, R., Sartwell, P.E., Diamond, E.L. and
    Elliott, E.A. (1975): Amer. J. Epid. 101, 119.