RADIATION INDUCED CANCER IN HUMANS

A STUDY GUIDE: ISSUES & DATA ANALYSIS OF JOHN W. GOFMAN, MD, PhD

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INTRODUCTION

PURPOSE: To discuss the cancer risks associated with commonly used medical diagnostic x-ray exposures. The study of radiation induced cancer brings many groups to the table. These include the D.O.E. with interest in nuclear materials manufacturing, storage, shipping and waste management, the D.O.D. with interest in nuclear weapons manufacturing, storage, and deployment, and the nuclear power industry (GE, Westinghouse, etc.) who have major financial incentives to develop and export nuclear technologies.

The DOE and the GAO estimated in the late 1980's that nuclear site cleanup will total between 63 and 175 billion dollars [NYT-88, NYT-89]. If radiation risk estimates are increased, the cost of cleanup will increase dramatically as will the cost of radiation protection in general – recently estimated at $2000.00 per exposure rem [H.Phys1997]. The overall dollars involved are estimated to be over a trillion when plutonium trade and reactor exports are considered.

Past low radiation risk estimates & statements of threshold or even beneficial effects of irradiation have been all but discarded by most committees as new data has become available. Whether the 3 mile island & Cherobyl disasters and the subsequent decreased public tolerance for reactor construction, waste processing and storage has played a roll in data acquisition and analysis is an interesting and open question..

Agencies involved include: NCRP, BEIR, UNSCEAR, IRCP, NRC, RERC, IEA, EPA, INDEPENDENT SCIENTISTS

ORGANIZATION OF DISCUSSION

- Radiation basics: Units of radiation exposure; High vs. low LET radiation; X-ray energy content, generation;
- Biologic response to radiation: Mutagenesis; Adaptive responses
- Calculation: Radiation induced cancer rate per radiation dose.
  - Mathematics of risk: Relative vs. absolute
  - Shape of Dose-Response Curve: Linear vs. linear-quadratic vs. quadratic (Concave UP or DOWN)
  - Threshold level of low dose radiation exposure and cancer induction.
  - Risk at low doses and dose rates vs. high acute doses. [DREF's - dose rate effectiveness factor]
  - Radiosensitivity to cancer induction with respect to age and sex.
  - Duration of excess cancer risk
- Application of risks derived from one population to another population.
- Risk assessments applied to common medical X-ray exams.

[Not included is discussion of radionuclides, RBE factors for neutron and alpha emitters, etc.]

PHYSICAL DEFINITIONS AND PROPERTIES OF RADIATION:
IONIZING RADIATION DEFINITIONS:

Alpha	: Helium nuclei = 2 protons, 2 neutrons; Range in tissues 30-40 m (< sheet of paper) but intensely damaging.	[KeV-MeV]
	: Enormous collision energy deposited along short track leaving great damage to localized area (High LET).	
Beta	: Nuclear electron ejected at high speed; Range in tissues a few millimeters.	[KeV-MeV]
Neutron	: Neutral particle with high LET but not as interactive as Alpha; Produced in nuc. disint.(key to chain reactions)	[KeV-MeV]
Gamma	: Photons generated in nuclear decay; Penetrating, less interactive w/ matter (Low LET)	[KeV-MeV]
X-ray	: Photons of lower energy than gamma, generated the atomic electron cloud level;	[med=KeV]
	: Penetrate tissues similar to gamma radiation but recent evidence of 2x the risk of cancer induction over gamma.	
UV	: Photons of lower energy than X-Ray and Gamma, but ionizing level; Less penetrating than X-Ray or Gamma.	[>4.13eV]

-- Photons below ionization energy: Visible [1.77 - 4.13 eV], IR [10^{-3} eV], microwaves [10^{-5} eV], radiowaves [10^{-10} eV] --

UNITS OF RADIATION:

Based on Energy deposition per mass of target [KE= ½ mv^2 – for equal KE radiation, heavier particle moves proportionately slower]

ROENTGEN: 1 electrostatic unit of charge/0.001293 gms air (0 deg.C & 760mmHg)=83 ergs/gm air=93 ergs /gm tissue

RAD: 10^{-5} joules per gram of material irradiated = 10^2 ergs per gram = 6.24×10^{10} KeV per gram
Note – Typical biochemical bond broken by 5-7 eV and electron ionized off of hydrogen atom by 13.6eV.
1 rad of radiation = 4.59×10^{12} tissue ionizations [2.08×10^9 photons/rad x30KeV/photon/13.6eV/H-ion]
1 PA CXR (6 yo) = 15 mrad = 6.9×10^{10} tissue ionizations [3.12×10^7 photons/15mrad x30KeV/photon/13.6eV/H-ion]

REM: "Roentgen equivalent man" – RAD x RBE in human

RBE= Exp. & theoretical relative biologic effectiveness of given radiation type. [Relative to gamma: Alpha ~ 10-20x, Neutron ~1-10x, X-ray=2x]

ENERGY DEPOSITION.:

Whatever the type and/or source of radiation, when a beam passes through tissues a track of ionized atoms is generated via the stripping off of electrons from their orbits - resulting in broken chemical bonds. Those initially freed electrons then move off at high speed & collide w/ other atoms causing further ionizations. In this way a cascade of electrons (& broken bonds) percolate through the irradiated tissue until finally most of the energy is absorbed in new, often aberrant, chemical bonds. Most of the total number of X-ray photons generated by diagnostic machines are absorbed; only a small fraction are required for collision w/ the detector or film. [Note: Med. X-rays absorbed via Compton scattering &/or photoelectric effect w/ lower energy photons (mammography 25-27 KeV) absorbed predominantly by the photoelectric mechanism resulting in electrons w/ higher LET (more dangerous) than are generated by higher energy X-ray photons]. BJR89

TRACK CALCULATION FOR TYPICAL 90 KEV X-RAY BEAM:

1 rad of low LET radiation: deposition of 10^{-5} Joules / gram of tissue = 6.24×10^{10} KeV/gm
Medical X-ray typically 90KeV peak = 30KeV average photon. [RADPRT81, RADPRT83]
→ (6.24×10^{10} KeV/gm) / (30KeV/photon) = 2.08×10^9 photons/gm
Range of 30KeV photons in tissue = 19.779μ = 1.735 cells traversed per initial photon
→ (2.08×10^9 photons/gm) x (1.735 cells traversed/photons) = 3.61×10^9 cells traversed/gm
Nucleus is ~ 0.25 of volume of cell
→ (3.61×10^9 cells traversed) x (0.25 nuclei volume / cell volume) = 9.03×10^8 nuclear volumes tracked / gm
There are 6.75×10^8 nuclei per gram of tissue
→ (9.03×10^8 nuclear vol's traversed / gm) / (6.75×10^8 nuclei./gram) = 1.3378 nuclear tracks / nucleus [at 1 rad]
→ Dose resulting in one nuclear track (on average) per initial photon = (1/1.3378) x (1 rad) = 747.5 mrad
Poisson distribution: At 750 mrad: 1 nuclear track (on average) / nucleus are actually distributed as follows:
37% will have no tracks, 37% will have single tracks, and 26% will have two or more tracks
Chem. bonds are broken by 5-7 eV collisions:For 30KeV photons: 30KeV/6eV = 5000 bonds broken/init.photon [max].
→ **Thus a typical 90 KeV diagnostic X-ray machine yielding a tissue dose of 750 mrad will generate up to ~ 5000 broken bonds in 2/3'rds (Poisson distribution) of ~ 10^9 nuclei per gram of tissue irradiated.**

BIOLOGIC EFFECTS OF LOW DOSE EXPOSURE, DNA DAMAGE → MALIGNANCY

MATH ISSUES:

Dosimetry; Linearity vs. quadratic vs. linear-quadratic;
DDREF's, Adaptation kinetics; Threshold vs. no threshold; Latency (genomic instability);
Duration of risk Relative vs. absolute; Effect of age, sex, other factors (smoking)

DNA DAMAGE:

Ionizing radiation results in the freeing of electrons from target atoms. These travel at extremely high speeds and occasionally strike a critical region of DNA and if accurate repair is ineffective, cancer is one possible result. The common DNA lesions documented can be grouped into the following: [see also Jeggo PA]

SSB:	Linear w/ dose. Unusual end groups unlike physiol. oxidation lesions* [Ward 1990]
DSB	Repair mech. error prone [GOF-90][Ward1988][Pfeiffer1998]
DNA–PROTEIN X LINKS	Error prone repair [see p3 NCRP draft]
MULTIPLY DAMAGED SITES	Error prone repair [see p3 NCRP draft]

"Ionizing radiations produce many different possible clusters of spatially adjacent damage, & analysis of track structures from different types of radiation has shown that clustered DNA damage of severity at least >/= double strand breaks can occur at biologic relevant frequencies at any dose." [Brenner & Ward 1992] Other ref's:[Goodhead 1994][Hei, et al 1997]

The susceptibility to these lesions has been found (in vitro) to depend on cell type, on cell cycle phase, etc.
Spont. rate of cell lesions ~24,000/cell/d [Helbock et al 1998]; these oxid. lesions are easily/accurately repaired [Ward 85,'95]

SUMMARY:

A 90KeV (peak) X-ray beam delivering a 750 mrad tissue dose will result in electron tracks through a large majority of cellular nuclei along the beam path (37% of nuclei w/ 1 trk.+26% nuclei w/ 2-3 trks). This causes breakage of up to 5000 bonds / ave.nucleus. The true ave. collision = 60 ev or 8-10 x that needed for simple bond breakage; the energy remaining is kinetic causing physical disruption after breakage. Repeat radiation exposures generate additive statistical risks of non-repairable or mis-repaired lesions occurring in critical DNA regions. Many studies have now demonstrated <100% DNA repair at moderate & low doses. Radiation induced cancer has been documented to follow multiple low (average of < 1 trk/nucl.) doses of medical X-ray irradiation given over time frames greater than the known DNA repair mechanisms which are completed in times of several minutes to 8 hours.

DNA DAMAGE -> GENOMIC INSTABILITY:

Mouse cells irradiated in vitro, placed into host mouse – no tumors created. If instead, post irradiated cells are grown to approx. 30 generations then injected into host animal, tumors result. This is not true for control cells not irradiated but grown in vitro in the same way.

"The loss of stability of the genome is becoming accepted as one of the most important aspects of carcinogenesis." ...

"One of the hallmarks of the cancer cell is the inherent instability of the genome." [Morgan 1966 p247 and p254].
Other ref's:[Nowell 976][Cheng1993][Kadhim1992,1994,1995][Holmberg1994][Marder1993][Mendonca1993][Kronenberg1994][Ullrich1998]

"... Instead, initiation [of cancer] more likely appears to be an event that increases the genomic instability of the cells of subsequent rounds of cell division." [BEIR V p138]

MONOCLONAL SOLID TUMOR ORIGIN:

Evidence is now quite strong that all cancers are monoclonal in origin – i.e. one transformed cell is the initial cause of all cancers. [Wainscoat & Frey 1990][Worsham et al 1996][Nowell 1976][Noguchi 1992][Fialkow 1976, 1984][Arnold et al 1983][Cleary et al 1988] [Levy et al 1977][Minden et al 1985][Evans 1979] [Lloyd 1988]

DISEASES ASSOCIATED WITH INABILITY TO REPAIR DNA LESIONS

There are a variety of enzymes responsible for DNA lesion repair. Several diseases are associated with increased cancer risk and are known to have poorly functioning DNA repair systems
[Borek1983][Chan1987][Willis1987][Cleaver1968][Hecht1987][Khan SG1998][Kikpi MO][Groisman1999][Becker1998]

e.g.	**DISEASE**	**ENZYME SYSTEM**
	Ataxia Telangiectasia Synd.	Double Strand DNA break repair mechanism defect
	Coccayne's Synd.	TCR (transcription coupled repair enzyme)[Cooper et al 1997]
	Nonpolyposis Colorectal CA	Mismatch repair enzyme system
	Blooms syndrome	DNA ligase repair enzyme defect
	Xeroderma pigmentosum	DNA excision repair mechanism defect
	Hepatitis B	Hepatitis B Virus X protein interferes w/ DNA repair mechanism -> hepatic CA.

RELATIVE (MULTIPLICATIVE) RISK

Many studies have now convincingly shown that cancer incidence each year post-irradiation increases at a rate related to the spontaneous cancer rate, specific for age & population. E.g.: if colon cancer incidence rates increase each year through life then in an irradiated group, the incidence rate will increase faster than the control, non irradiated group. The higher rate is equal to a multiplier of the spontaneous rate; this is what is meant by relative risk increase following irradiation.

For radiation-induced cancer, relative risk analysis is the accepted mathematical model. [GOF-81,90][BEIR-V][NCRP98], etc.

SHAPE OF DOSE : RESPONSE RELATIVE RISK CURVE

This is a debated issue. Some studies are consistent with a linear dose-response curve [RERF91][RERF92], whereas other studies are consistent with supralinear responses (larger effect at low doses than at high doses) [GOF-81,90]. This remains an open question. In terms of age at exposure, the data is clear that relative risk is much higher at younger ages at irradiation. [Gof-Tam '69,'70][NCRP98][BEIR V]

[Most reasonable to consider dose-response curve as either linear or supralinear (convex up);exercise due caution until more is known.

NO-THRESHOLD FOR RADIATION INDUCED CANCER

Most radiation researchers agree that based on current data there is likely to be no low-dose threshold for cancer. Unlike chemical toxins which when given in sufficiently low doses are detoxified or removed before damage is done, radiation is delivered on the cellular level by high speed electrons that literally crash through the cellular machinery. Many of the lesions that occur are repaired by cellular mechanisms (estimated repair events number 10,000 –24,000 / cell per day). If, however, a high speed electron, set in motion by a medical X-ray photon, collides with a critical portion of DNA and repair systems are unable to properly undo the damage, a malignancy may result. [UNSCEAR 1993 Rpt, p.634, para.74][NCRP98 draft rpt]

Furthermore, even if it is postulated that double track events are required for misrepair -- at <u>any dose,</u> the Poisson distribution insures that some nuclei are hit by more than 1 track at a dose that is calculated to deliver an average of much less than or equal to one track through an average nucleus [i.e. <<750mrad]. As one single track can damage the DNA, there is no theoretical threshold of risk – i.e. As the dose decreases, the only change is in the number of targets struck but at any dose at least one target may be hit and may then generate a lesion leading to malignancy.

With reference to adaptive effects, experimental evidence suggests that at least 500 mrad is required and that this results in only a 50% reduction in lesions. Repair mechanisms are therefore unable to <u>fully</u> protect at any dose level. Thus, there is no theoretical basis for belief in a threshold dose below which no sustained damage could occur. [NCRP98]

DURATION OF INCREASE IN EXCESS RELATIVE RISK AFTER RADIATION EXPOSURE

Several studies, including those listed in this paper continue to demonstrate that radiation induced excess cancer rates continue for at least 40 years after exposure and perhaps for a lifetime. The A-Bomb survivors, now 54 years after their exposure, continue to show excess cancer rates. A-Bomb survivors have also been shown to continue to carry chromosome abnormalities for at least 40 years after the exposure with dose dependent numbers of abnormalities documented. [GOF-81 ->A-Bomb data, Hempleman 1975, Shore 1977, Boice-Monson 1977, etc.]

The peak incidence rate for solid cancers (non-hematologic) appears to occur at 30-40 years post irradiation. [GOF-90] *"In contrast to the rates for leukemia & bone cancer, the rates for most other cancers appear to have remained in excess for as long as most exposed populations have been followed" [BEIR V p52]*

<u>A possible explanation for ~ 10 year latencies seen for solid tumors:</u> A single cell is critically irradiated, resulting in genomic instability. Assuming no immune killing effects, after >30 gen.'s the cell mass = 10^9 (1gm) -10^{12} (1 kg) cells. With immune killing and suppression there would be long cancer latencies & incidence durations from the initial damage.

EFFECT OF AGE AND SEX ON RADIATION SENSITIVITY – CANCER INDUCTION

Gofman's findings (A-Bomb study as well as meta-analysis of multiple studies):

RELATIVE RADIATION-INDUCED CANCER RATES PER DOSE

Age (yr)	Male	Female	
1	1.01	1.02	
5	1.11	1.16	<|
10	1.38	1.52	<|
15	2.80	3.18	|
20	3.14	3.64	|
30	3.68	4.17	|------
40	8.44	9.31	
50	210.89	213.98	
55	307.53	306.88	

2. Several studies [eg. RERF91a, see refs] have also shown that children are more radiation sensitive than are adults. This increased sensitivity follows the relative risk model, i.e. after irradiation in childhood, the risk of cancer induction 20-40 years later is higher than if the same irradiation occurred in adulthood with cancers detected 20-40 years later in older age.

Although risk per dose is proportionately higher as age decreases, overall risk from medical diagnostic X-rays works out to be highest at ages between 5-10 years, as between these years the entrance dose grows faster than the relative risk of cancer falls as the child ages.

ORGAN SPECIFIC CANCER RATES FOLLOW RELATIVE RISK MODEL

Organs that have the highest malignant transformation potential include: mouth, chest, abdomen, Pelvis.

Several studies: [eg. RERF90a, RERF94] have demonstrated that radiation induced excess cancer risk is related to the baseline risk rate (organ specific relative risk). If a particular organ is more likely to generate a cancer than another organ, when both are exposed to the same radiation dose, the increase in cancer rates of each will be proportional to the respective organ specific unexposed, spontaneous cancer rate.

BIOLOGIC EFFECTS OF LOW DOSE EXPOSURE, ADAPTIVE RESPONSE – "DDREFS"

HISTORY:

There has been a question as to whether a difference exists in cancer induction risk from acute delivery of a low radiation dose compared with fractionated, low delivery rate of a low total radiation dose.

With animal based evidence only, a mathematical construct, "Dose and Dose Rate Effectiveness Factor" (DDREF) was created in the mid 1970's [UNSCEAR-77]. The logic for its initial use has been sited over the past 20 years despite increasingly conflicting human data.

The current NCRP DRAFT (NCRP-98) report on Low Dose Radiation Effects makes a very strong case against the use of DDREF's or any other method that yields a non linear curve with lower effects at low doses. In fact there is now data suggesting a supralinear response with higher radiation induced cancer rates from low doses than from high dose exposure. [GOF-81, GOF-90]. In reference to low dose rate effects, there is a paucity of data to date. [Little 1999][Brenner 1999]

BEIR-V CONFLICTING REFERENCES:

"In spite of evidence that the molecular lesions which give rise to somatic and genetic damage can be repaired to a considerable degree, the new data do not contradict the hypothesis, at least with respect to cancer induction and hereditary genetic effects, that the frequency of such effects increases with low-level radiation as a linear, non-threshold function of the dose." [pg 4.] but then on pg.6: *"For low LET radiation, accumulation of the same dose over weeks or months, however, is expected to reduce the lifetime risk appreciably, possibly by a factor of 2 or more."*

"For most other cancers in the LSS (A-Bomb Life Span Study), the quadratic contribution is nearly zero, and the estimated DREF's are near unity. Nevertheless, the committee judged that some account should be taken of dose rate effects and in chapter 1 suggests a range of dose rate reduction factors that may be acceptable." (pg.17) [see Tbl 1-4

"Summary of Dose Rate Effectiveness Factors for Low-LET Radiation" and on page 22: *"There are scant human data that allow an estimate of the dose-rate effectiveness factor (DREF)"*

MOST RECENT NCRP DRAFT REPORT

"At the outset, it must be noted that radiation imparts its energy to living matter through a stochastic process, such that a single ionizing track has a finite probability of depositing enough energy in traversing a cell to damage a critical molecular target within the cell, such as DNA. Furthermore, the various types of DNA damage that are known to result from irradiation appear to increase linearly with the dose in low-to-intermediate dose range. Also, although most such DNA damage is reparable to varying degrees, some types of lesions – namely, double-strand breaks and multiply damaged sites – are often repaired through a process that is error-prone. Because of the vast number of target cells, vanishingly small frequencies of non-lethal, unrepaired or misrepaired lesions can nevertheless result in a finite number of cells undergoing a cancer-initiating event, even at low doses." [NCRP-Oct.98 p228]

"Those lesions in DNA that remain unrepaired or are misrepaired may be expressed initially in the form of mutations, the frequency of which increases with the dose of radiation over the dose range in which the effects are amenable to measurement. Although the shape of the dose-response curve varies, depending on the LET of the radiation, the dose rate, the type of mutation, and other variables, it is noteworthy that mutation of types implicated in carcinogenesis – namely, point mutations and partial deletion mutations – have been observed to be inducible at relatively low doses, with apparently linear – nonthreshold dose-response relationships in various kinds of cells." … AND … pg. 229 *"Thus, the data imply that traversal of the cell nucleus by a single low-LET radiation track may occasionally suffice to cause a chromosome aberration."*

Referring to a graph of excess relative risks established for solid tumor incidences, researchers at RERF stated*: "…clearly indicate that only LDEF [DDREF] values near 1 are consistent with the shape of the dose-response curve for solid tumor incidence. This suggests that a linear model provides a good description of these data and that no low-dose correction is needed."* [RERF Update 4(3):5-6,1992]

SUMMARY: Human data (& logic) are consistent w/ a linear dose-response curve at low doses & dose rates w/ some data consistent w/ supralinearity – i.e higher risks per rad at lower doses and/or dose rates than high and/or acute doses.

CRITICAL ANALYSIS AND CRITICISM OF BEIR V METHODOLOGIES

John Gofman, MD, PHD [GOF-90][GOF-96]

PROCEDURES THAT DIRECTLY UNDERESTIMATE RISK

1. Reliance on animal data

The BEIR V report (p.22) states: "There are scant human data that allow an estimate of the dose-rate effectiveness factor." In its Executive Summary, however, the committee recommends use of a DREF (Dose and Dose Rate Effectiveness Factors) of at least two for environmental and occupational exposures with the evidence based largely on animal model experiments. This is the opposite of a conservative approach – that is, if one assumes that the data base (animal) is questionable, one should not decrease the assessed risk assessment applied to people. (DREF's lower the calculated radiation risk, based on the rate that doses are delivered – assuming that more slowly over time are less risky. The human data suggesting this is very unconvincing.

Waldren C, et al; "Measurement of low levels of x-ray mutagenesis in relation to human disease"; Proc Natl Acad Sci USA 83: 4839-44 (1986)

Found that conventional methods for measuring mutagenesis in mammalian cells seriously underestimated the contribution of radiation to cancer and genetic diseases. They found a 200 fold higher mutation frequency in the 0-50rad range then some previous conventional studies had found. They also found the curve of dose:mutation to be supra-linear.

Little, JB; "Low-Dose Radiation Effects: Interactions and Synergism"; Health Phys 59: 49-56 (1990)

Found significant differences with regard to inhibitory effects of DMSO, dose response and the effects of changes in dose-rate for radiogenic induction of mutations in rodent, compared with human cells. He found reduced effects in rodent cells when the dose was delivered at low rates but at high total doses, but did not find these effects in human cells between doses of 0-250rads. Thus the use of rodent cells to infer human cellular response is questionable.

Carnes BA, Fritz TE; "Responses of the beagle to protracted irradiation"; Rad Res 128:125-32 (1991)

378 beagle dogs with accumulated doses between 450 and 3000 rads at varying rates between 3.8 and 26.3 rads/day showed no relationship between tumor mortality and dose rate but a clear linear relation with accumulated dose.

2. Discarding data

The BEIR V report also discards data with little scientific basis for doing so. For example, a.) cancer deaths in A-bomb survivors over 75 years old are discarded owing to uncertainties of proper ascertainment of cause of death and b) breast cancer rates following fluoroscopic irradiation in women with tuberculosis were 6x higher in the Nova Scotia group than in another Canadian study group – they therefore chose to discard that data: "Within the Canada-TB cohort, the estimated risk per Gray for women treated in Nova Scotia was about six times that for women treated in other provinces. This difference is highly significant ($p<0.001$) … the higher risk observed among Nova Scotia women is not attributable to non-linearities in the dose response. Since there is currently no explanation for thedifference within the Canadian-TB cohort and since the Committee was generally interested in low dose effects, it was decided to use the data on the Canadian-TB cohort without the Nova Scotia women, as the basis for risk estimates in the parallel analysis" [BEIR-V p255][see also GOF-96]

CRITICISMS OF RERF - IMPROPER HANDLING OF A-BOMB DATA
[1986 REFR COHORT CHANGES DISPUTED]

IMPROPER, NONBLINDED ALTERATION OF DOSE GROUP COHORTS:

After the 1982 analysis, RERF shifted thousands of people from one cohort to another in developing the new dosimetry. Those who worked on revising the dosimetry had knowledge of expected results therefore the change did not occur under blinded conditions. In addition, in 1986 RERF added 11,393 Nagasaki survivors who were exposed at a distance of 2500 to 9999 meters from the hypocenter and for whom complete follow-up during 1950 - 1982 was available. These 11,393 people were assigned to the 0 dose group to increase the precision of the background mortality rate estimates and consequently the excess risk estimates in Nagasaki. Again this was done in a non-blinded fashion. In 1987 the cohort was changed from 91,231 to 75,991 with 15,240 persons moved into suspension as the corrections made from the T65DR dosimetry to the DS86 dosimetry was not possible given a lack of relevant information. (This is 31% of the Hiroshima Dose-Group 2 cohorts!). The remaining 75,991 was denoted as the DS86 cohort group. Because of this nonblinded alteration of dosimetry and cohort status, Gofman chose to analyze the available data of all survivors through 1982 (37 years after the bombings) for analysis in his 1990 report.

COHORTS IMPROPERLY CONFIGURED – NOT AGE (ATB) AND SEX MATCHED

Therefore even without irradiation, risk of cancer and leukemia are different for these groups. The Gofman analysis removes this bias by reconfiguration of cohorts of dose groups. In the Gofman analysis, the only variable is therefore irradiation dose.

Raw RERF data is not properly normalized for age & sex (groups must be equal to properly evaluate rad effect)

Age Normalization:

* RERF Ref. grps 1+2 used as model for all other dose grps (male & female) using ratio of each age band : total
* From Table 11-D rows 17-21: Age bands 1-5 -- ratios: 0.180, 0.193, 0.241, 0.230, 0.156 respectively are used
  (Total # in each dose band) x (Approp. ratio above). Enter # as the norm'ed # in each age band for that dose.
* Recalc. Observations: (Norm'ed # people / raw # people) x (raw observed #) = Norm'ed observations.
* Recalc. Total observations for each dose group.

Sex Normalization:

* Use ratio found in reference group 1+2 (Tables 11-B,D Col's F where M/F = 27585/38443 = 0.717556)
* Find total people in dose group – eg. Grp.1: (15,406 M + 21,767 F = 37,173).
* Let F = age and sex norm'ed #females in Grp.1. Then 0.717556 x F is age and sex normed #males in Grp1
* F + 0.717556*F = 37,173 which is equiv. To 1.717556 * F = 37,173. Therefore F = 37,173/1.71756.
* M=37,173 – F or M=37,173 – 37,173/1.71756 = 15,530.02 persons to enter into row 11G, Col.F (Row132)
* Using same calculation, enter norm'ed numbers for each dose group after which all dose groups are norm'ed.
* Recalc. Observations: (Norm'ed # people / raw # people) x (raw observed #) – Norm'ed observations.

DS86 DOSIMETRY

Several dosimetry systems since the A-Bomb study began in 1950 as new information has been discovered. These include: T57D, T65D, T65DR and the current DS86 dosimetry systems. The new dosimetry was introduced simultaneous to the breaking of the initial cohort groups within the ongoing RERF study population.

There are many variables in considering true exposure: not an exact system.
* Gamma vs. Neutron exposures: U235 in Hiroshima (10% neutron), Pu239 in Nagasaki (nearly all gamma).
* Neutron RBE, Activation nuclide generation and exposure, neutron and gamma shielding and capture, etc.
* Fallout and environmental exposure after the initial (less than 1 microsecond) gamma and neutron flux.

APPLICATION OF DATA TAKEN FROM STUDY POPULATION TO US POPULATION [GOF-90]

There is debate about the transfer of information from, for example, A-Bomb survivors to a mixed US population. In Japan there is a higher rate of stomach cancer than in the U.S. and in the U.S. there is a higher rate of breast cancer than in Japan.

It has been argued that using the relative risk method and A-Bomb data could therefore inflate the projected risk of stomach cancer and underestimate the risk of breast cancer in a mixed exposure in the U.S.

ESTIMATE OF ONGOING RADIATION INDUCED CANCER FOR U.S. POPULATION (GOF-90; 25-15)

In the U.S.: approx. 22% die of cancer = 2,200 cancer deaths / 10,000 people
From GOF-90, pg25-15 26 cancer deaths / 10,000 people per rem of full body exposure

60 year dose accumulation calculation:

SOURCE (BEIR V Tbl 1-3)	**ANNUAL DOSE (rems)**	**60 YEAR DOSE (rems)**	**LIFETIME FATAL CA/10^4 PERSON*REMS**
RADON	0.200	12.00	312
OTHER NATURAL	0.094	5.64	147
MED X-RAYS	0.039	2.34	61
ALL OTHER	0.024	1.44	37
TOTAL CA death/10^4	**0.357**	**21.42**	**557**

As 2,200 cancer deaths per 10,000 in US, 557 / 2,200 = 25.3% of US Cancer death is caused by radiation exposure.

CANCER RATES PER 10,000 PER RAD ORGAN DOSE – U.S. POPULATION [GOF-85][GOF-90]

ORGAN [M]	0	1	5	10	15	20	25	30	35	40	45	50	55
Oral	13.34	13.17	12.01	9.66	4.78	4.24	4.22	3.64	2.60	1.57	0.69	0.063	0.043
Eyes	0.67	0.66	0.60	0.49	0.24	0.21	0.21	0.18	0.13	0.08	0.03	0.003	0.002
CNS	4.91	4.85	4.42	3.56	1.76	1.56	1.55	1.34	0.95	0.58	0.25	0.023	0.016
Esophag.	4.63	4.57	4.17	3.36	1.66	1.47	1.46	1.26	0.90	0.55	0.24	0.022	0.015
Stomach	10.46	10.33	9.41	7.59	3.74	3.33	3.31	2.85	2.03	1.24	0.54	0.050	0.034
S.Intest.	0.89	0.88	0.80	0.65	0.32	0.28	0.28	0.24	0.17	0.11	0.05	0.004	0.003
L.Intest.	26.88	26.55	24.18	19.50	9.62	8.56	8.50	7.31	5.23	3.19	1.39	0.13	0.087
Rectum	14.17	14.00	12.75	10.28	5.07	4.51	4.48	3.86	2.76	1.68	0.73	0.070	0.046
Liver	4.17	4.11	3.75	3.02	1.49	1.33	1.32	1.13	0.81	0.49	0.22	0.02	0.014
Panc.	9.35	9.23	8.41	6.78	3.34	2.98	2.96	2.54	1.82	1.11	0.48	0.040	0.030
Dig-msc	0.97	0.95	0.87	0.70	0.35	0.31	0.31	0.27	0.19	0.11	0.05	0.005	0.003
Lungs/br	11.55	11.41	10.39	8.38	4.13	3.68	3.65	3.14	2.25	1.37	0.60	0.055	0.038
Larynx	6.72	6.63	6.04	4.87	2.40	2.14	2.12	1.83	1.31	0.80	0.35	0.032	0.022
Pul-misc	1.49	1.47	1.34	1.08	0.53	0.47	0.47	0.40	0.29	0.18	0.080	0.007	0.005
Breasts	0.67	0.66	0.60	0.49	0.24	0.21	0.21	0.18	0.13	0.080	0.030	0.003	0.002
Bladder	19.35	19.11	17.41	14.04	6.92	6.16	6.12	5.26	3.76	2.29	1.00	0.092	0.063
Kidney	7.83	7.73	7.05	5.68	2.80	2.49	2.48	2.13	1.52	0.93	0.40	0.037	0.025
Prostate	49.16	48.55	44.23	35.67	17.58	15.65	15.55	13.37	9.56	5.83	2.54	0.230	0.160
Genitals	3.73	3.68	3.35	2.71	1.33	1.19	1.18	1.01	0.72	0.44	0.19	0.018	0.012
Thyroid	1.94	1.91	1.74	1.41	0.69	0.62	0.61	0.53	0.38	0.23	0.10	0.009	0.006
End.misc.	0.37	0.37	0.34	0.27	0.13	0.12	0.12	0.10	0.07	0.044	0.019	0.002	0.001
Bld/lym.	15.51	15.33	13.95	11.25	5.55	4.93	4.90	4.22	3.01	1.83	0.80	0.074	0.050
Bone	0.82	0.81	0.74	0.60	0.29	0.26	0.26	0.22	0.16	0.10	0.04	0.004	0.003
Skin	5.15	5.09	4.64	3.74	1.84	1.64	1.63	1.40	1.00	0.61	0.27	0.024	0.017
Con.Tis.	1.87	1.84	1.68	1.35	0.67	0.59	0.59	0.51	0.36	0.22	0.10	0.009	0.006
Other	10.83	10.70	9.75	7.86	3.87	3.45	3.43	2.95	2.11	1.28	0.56	0.051	0.035
TOTAL	227.43	224.59	204.62	164.99	81.34	72.38	71.92	61.87	44.22	26.94	11.75	1.077	0.738

ORGAN [F]	0	1	5	10	15	20	25	30	35	40	45	50	55
Oral	6.22	6.07	5.34	4.11	1.96	1.72	1.7	1.5	1.08	0.68	0.302	0.029	0.020
Eyes	0.72	0.71	0.62	0.48	0.23	0.20	0.20	0.17	0.12	0.08	0.035	0.004	0.002
CNS	4.32	4.22	3.71	2.85	1.36	1.19	1.17	1.04	0.74	0.46	0.21	0.02	0.014
Esophag.	2.14	2.09	1.84	1.41	0.67	0.59	0.58	0.51	0.37	0.23	0.10	0.01	0.007
Stomach	7.39	7.21	6.34	4.87	2.32	2.03	2.01	1.77	1.27	0.79	0.36	0.035	0.024
S.Intest.	0.82	0.80	0.70	0.54	0.26	0.23	0.22	0.20	0.14	0.090	0.040	0.004	0.003
L.Intest.	35.26	34.40	30.26	23.25	11.09	9.69	9.57	8.46	6.04	3.79	1.71	0.160	0.110
Rectum	13.12	12.80	11.26	8.65	4.13	3.61	3.56	3.15	2.25	1.41	0.63	0.061	0.043
Liver	4.92	4.80	4.22	3.25	1.55	1.35	1.34	1.18	0.84	0.53	0.24	0.023	0.016
Panc.	9.40	9.18	8.07	6.20	2.96	2.58	2.55	2.26	1.61	1.01	0.45	0.044	0.031
Dig-misc	1.15	1.13	0.99	0.76	0.36	0.32	0.31	0.28	0.20	1.12	0.056	0.005	0.004
Lungs/br	8.10	7.90	6.95	5.34	2.55	2.23	2.20	1.94	1.39	0.87	0.39	0.038	0.026
Larynx	1.39	1.36	1.19	0.92	0.44	0.38	0.38	0.33	0.24	0.15	0.067	0.007	0.005
Pul-misc	0.82	0.80	0.70	0.54	0.26	0.23	0.22	0.20	0.14	0.088	0.040	0.004	0.003
Breasts	88.49	86.34	75.92	58.34	27.83	24.32	24.02	21.24	15.16	9.50	4.28	0.410	0.290
Bladder	7.80	7.61	6.69	5.14	2.45	2.14	2.12	1.87	1.31	0.84	0.38	0.036	0.025
Kidney	5.24	5.11	4.49	3.45	1.65	1.44	1.42	1.26	0.90	0.56	0.250	0.024	0.017
Uterous	44.23	43.16	37.95	29.16	13.91	12.16	12.00	10.61	7.57	4.75	2.14	0.211	0.143
Ovaries	13.95	13.62	11.97	9.20	4.39	3.84	3.79	3.35	2.39	1.50	0.67	0.065	0.045
Gen-misc	3.67	3.60	3.19	2.43	1.16	1.01	1.00	0.89	0.63	0.40	0.18	0.017	0.012
Thyroid	5.37	5.20	4.58	3.52	1.68	1.47	1.45	1.28	0.91	0.57	0.26	0.025	0.017

End.misc.	**0.33**	**0.32**	**0.28**	**0.22**	**0.10**	**0.09**	**0.09**	**0.08**	**0.056**	**0.035**	**0.016**	**.002**	**0.001**
Bld/lym	**15.08**	**14.71**	**12.93**	**9.94**	**4.74**	**4.14**	**4.09**	**3.62**	**2.58**	**1.62**	**0.73**	**0.07**	**0.049**
Bone	**8.23**	**8.03**	**7.05**	**5.42**	**2.59**	**2.26**	**2.24**	**1.98**	**1.40**	**0.89**	**0.40**	**0.039**	**0.026**
Skin	**5.92**	**5.78**	**5.06**	**3.90**	**1.86**	**1.63**	**1.61**	**1.42**	**1.01**	**0.64**	**0.29**	**0.028**	**0.019**
Con.Tiss.	**1.65**	**1.61**	**1.41**	**1.09**	**0.52**	**0.45**	**0.45**	**0.40**	**0.28**	**0.18**	**0.08**	**0.008**	**0.005**
Other	**11.93**	**11.64**	**10.24**	**7.86**	**3.75**	**3.28**	**3.24**	**2.86**	**2.04**	**1.28**	**0.58**	**0.056**	**0.039**
TOTAL	**300.05**	**292.81**	**257.48**	**197.85**	**94.39**	**82.50**	**81.47**	**72.03**	**51.41**	**32.25**	**14.516**	**1.399**	**0.972**

CONCLUSIONS

DEMONSTRATION OF ASSUMPTIONS -- CALCULATION OF STUDY CONSERVATIVE VALUES APPLICABLE TO DIAGNOSTIC X-RAYS USED IN MEDICAL PRACTICE (See: CONV.TBL-1)

STUDY	CA DEATHS PER 10^4 P*R	REMOVE DDREF'S	RERF UNDERDX. FACTOR = x 1.23	X-RAY=2x GAMMA RISK [Correction:gamma->X-ray]		BEST EST. CA DEATH PER 10^4 P*R
GOF-81	37.30	37.30	37.30	[1.50x]	=	**55.95**
GOF-90	25.60	25.60	25.60	[1.00x]	=	**51.20**
BEIR V	3.475	6.95	8.55	[1.86x]	=	**16.24**
EPA-94	5.100	10.20	10.20	[2.00x]	=	**20.40**
UNSCEAR	4.835	9.67	11.89	[2.00x]	=	**23.78**
ICRP	4.450	9.90	19.80	[2.00x]	=	**39.60**

THE DIAGNOSTIC X-RAY RISK TABLES FOLLOWING BASED ON: <u>37.30 FATAL CA/10^4 PERSON*RAD</u> [GOF-85]

- Diagnostic X-rays increase a patients lifetime risk of cancer – the risk is quantifiable and has been quantified.
- There is no threshold of risk with respect to diagnostic X-rays or any other type of ionizing radiation.
- Most conservative model of risk: supralinear at low doses; certainly no less than linear dose - response.
- Malignant transformation is related to high speed electron tracks through cell nuclei resulting in ionization of portions of the DNA strands and subsequent misrepair of those strands. If the wrong portion of the molecule is damaged, malignancy can be the result.
- Radiation risk is additive with respect to total lifetime dose & multiplicative with respect to risk of cancer induction [(excess risk) x (unexposed cancer rate)] i.e. relative risk model is consistent with data.

Metaphor: blindfolded person firing gun in random directions from 1000 yds away; target at 1000 yds distant is unlikely to be struck over 1 minute if the gun is fired at a 1x / min. rate. If, however, the target remains in place for several years, or if the gun is fired at a very rapid rate, the statistical risk becomes quite high that eventually, the target will be struck. Thus, exposure risk is independent of rate and is additive with respect to total exposure.

- Dose to peak effect = 40 years after latency of 10-12 years for solid cancers and for leukemia peak effect = 7-10years.
- Duration of increased relative risk of cancer appears to be lifelong and follows the relative risk model
- Cancer risk is dependent on age at irradiation, sex and baseline organ specific cancer rates.
- Medical X-rays are twice as damaging to biologic systems as are gamma rays produced by radionuclides
- Minimum risk est. for mixed U.S. pop. from gamma:1 extra cancer fatality / 268 - 2878 people irradiated w/ 1 rad.
- Conservative risk est. " " U.S. pop. from X-rays: 1 extra cancer fatality / 179 - 616 people irradiated w/ 1 rad.
- <u>The diagnostic X-ray risk table to follow is based on:1 extra cancer fatality / 268 people irradiated w/ 1 rad</u>

SUMMARY:

Exercise caution with x-rays, consider the organ dose & risk/benefits to pt. This diagnostic tool is not without significant risk of lifetime cancer induction. As information is available, we are obligated to obtain informed consent for any radiological procedure (w/ the understanding that full risk table accuracy must be given as a range of as much as 10x less risk than these tables state based on lowest risk assumptions of BEIR V.

It is better to err on the side of conservatism & safety than to use risk assessments influenced by financial considerations of nuclear clean-up, worker safety, plutonium trade & nuclear technology export.

Read radiation studies with care, common pitfalls include: small sample sizes, dosimetry errors (look for true organ doses), not controlling for sex & age at exposure, not calculating lifetime effect (ie. limited follow-up), and failing to analyze confounding variables (typical of environmental studies).

---- CONVERSION TABLE I ----

GAMMA DOSE DATA VS. X-RAY DATA IN EACH STUDY → GENERATE CONVERSION RISK TO X-RAY

(Where orthovoltage X-rays are considered to have approximately 2x cancer induction risk over gamma photons)

BEIR-V: [BEIR-V ppg 182-188]	A-Bomb Cohort approx. 93% of study	**93.2 % x factor of 2 = 1.864x**
GOF-90:	A-Bomb Cohort	**100 % x factor of 2 = 2.00x**
GOF-81:	A-Bomb Cohort approx. 75% of study	**~75 % x factor of 2 = 1.50x**
EPA-94:	A-Bomb Cohort	**100 % x factor of 2 = 2.00x**
ICRP:	A-Bomb Cohort	**100 % x factor of 2 = 2.00x**
UNSCEAR:	A-Bomb Cohort	**100 % x factor of 2 = 2.00x**

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