ICRP recommendations

Consultation Comment

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The Committee for Nuclear Responsibility (CNR), a non-profit research and educational corporation in continuous operation since 1971, submits the following comments upon the "Draft Recommendations of the International Commission for Radiological Protection" (ICRP) concerning maximum annual radiation doses for workers and members of the public, and concerning release of radioactive contaminants into commerce (including foodstuffs) and into the environment.

PART ONE: Our Conclusions and Qualifications

CNR's conclusion is that the health damage from ICRP's recommendations is seriously underestimated with respect to radiation doses accumulated year after year in the annual range from 10 cSv (10 rems) down to zero, and that the recommendation for putting little or no constraint on small individual releases of radioactive material may cause irreversible harm many-fold greater than assumed. One of our chief concerns is the unevaluated risk in the ICRP Recommendations of radiation-induced coronary artery disease.

This is a well informed concern, for I (jwg) have been intimately involved with radiation health effects ever since my early work with uranium and plutonium for the Manhattan Project in 1940, subsequently as founder of (1963) and researcher at (1963-1973) the Biomedical Research Division of the Livermore National Laboratory and as Associate Director of that Laboratory (until 1969), and then as an independent researcher on radiation health effects during a very active retirement (Gofman 1976, 1979, 1981, 1985, 1988, 1990, 1992, 1994, 1996, 1998, 1999).

The present communication to the ICRP centers on the risk of radiation-induced coronary artery disease (CAD), which the ICRP draft dismisses with only four short paragraphs (pp.33-34). In Part 2 of our communication, we describe recent evidence, far more powerful than the evidence emerging from the A-Bomb Survivor Study (ABSS). The independent evidence to which we refer is provided by my own 1999 study (Gofman 1999), and shows that exposure to medical x-rays is an extremely important causal co-actor in CAD, a disease which kills as many people as all cancers combined in certain countries, such as the USA. The 1999 study benefits from the fact that I (jwg) did pioneering research (1949-1966) which helped to open up the world of the diverse serum lipoproteins and to show their connection with atherosclerosis and heart attacks. This has enabled me to propose a mechanism by which unfavorable serum lipoproteins and radiation-induced mutations intersect to cause CAD.

Over the years, my work has generally yielded higher risk estimates than concurrent publications by quasi-official authorities, such as the various ICRP, UNSCEAR, and BEIR Committees. My "dissident" views have usually arrived about a decade too early, but later have turned out to be more nearly correct than the "mainstream" views on many key radiation issues --- e.g., the probability that all forms of cancer are radiation-inducible; the reasonableness of a relative risk model; the absence of a threshold dose; the importance to health of unrepaired and misrepaired double-strand DNA breaks (chromosomal mutations); the absence of neutrons at Hiroshima; the prediction that mental retardation among *in-utero*-exposed A-bomb survivors would be manifest not just in severe degrees but also in all milder degrees too; the warning that we do not yet know enough about which disorders have an inherited predisposition to estimate the consequences of elevating human gonadal exposure to ionizing radiation by even a small amount; the warning that risk-estimates must incorporate the greater damage per cGy (rad) from low-energy photons (as in medical x-rays) than from high-energy photons (as in A-bomb radiation); the need in every epidemiological dose-response study, of disorders inducible by ionizing radiation, to match compared study-samples for accumulated exposure to medical radiation before trusting the resulting estimates of risk per dose-unit.

Now I am warning that the need, for more caution than ever before about exposures to ionizing radiation and for strict containment of radioactive contaminants, is evident from the rapidly growing confirmation that aberrations in the chromosomes and genes (including their own regulatory genes, of course) are causal co-actors in a great number of fatal and nonfatal disorders of human health --- almost certainly including coronary artery disease (Gofman 1999).

PART TWO: Radiation Induced Coronary Artery Disease

In 1999, CNR published my massive study entitled "Radiation from Medical Procedures in the Pathogenesis of Cancer and Ischemic Heart Disease: Dose-Response Studies with Physicians per 100,000 Population" (Gofman 1999). The study itself is available through the online bookseller, amazon.com, and from CNR. The 32-page executive summary, including its graphs, is available online at www.ratical.org/radiation/CNR/RMP/execsumm.html, and details of the study's method and sources are also online in Chapters Two through Five of the monograph. Additionally, comments by peer-reviewers are available online at www.ratical.org/radiation/CNR/RMP/6critiques.html.

Part 2-a: Extremely Strong Dose-Response between Radiation and Coronary Artery Disease

This 1999 study , "RMP" for short, uncovers extremely strong, positive, linear dose-responses (R-squared for males is 0.95; for females, 0.87) between cumulative x-ray exposure in the USA by census divisions and age-adjusted mortality rates in 1950 from ischemic heart disease, also known as coronary artery disease (CAD). These correlations are far stronger than any relationship uncovered by the Atomic Bomb Survivor Study (ABSS) between bomb radiation and either CAD or cancer.

Moreover, extrapolation from the RMP study's remarkably strong dose-responses produces the estimate that, in 1950, medical x-rays were a necessary causal co-actor in 79% of the male age-adjusted mortality rate from CAD, and in 97% of the corresponding female rate. The RMP study yields very important information about a controllable cause of a disease which accounts for as much mortality as all cancers combined in the USA.

Part 2-b: How Can Radiation Cause Coronary Artery Disease?

How can radiation be a causal co-actor in production of CAD? I have proposed that there are great similarities with radiation's causal co-action in producing cancer.

Carcinogenic mutations, acquired after conception, are regarded almost universally as a necessary (but not sufficient) co-actor in the evolution of malignant tumors. The correlations uncovered in RMP very strongly indicate that some of the mutations occurring in coronary arteries must be atherogenic, conferring upon the mutant cell both proliferative advantage (resulting in a clone of mutant cells, a localized mini-tumor) and the consequential dysfunctions required for evolution of a fatal atherosclerotic plaque.

My Unified Model, of atherogenesis and acute CAD events, unites the newly uncovered correlations (between x-rays and CAD) with much earlier observations, that unfavorable concentrations of certain plasma lipoproteins are causal co-actors in these afflictions (for instance, Gofman 1949, 1950a, 1950b, 1954, 1959, 1966).

I propose that an atherosclerotic plaque arises and evolves in an arterial wall where non-inherited mutations have produced a clone of dysfunctional cells (probably smooth muscle cells, possibly endothelial or other cells) which mishandle certain kinds of plasma lipoproteins. Because these cells have a proliferative advantage, they gradually dominate a patch of otherwise normal arterial intima.

In the absence of interference by the dysfunctional clone, plasma lipoproteins would pass harmlessly out of the arterial intima, as they do elsewhere in the arteries, in massive amounts throughout a lifetime. However, the result of localized incomplete egress by the lipoproteins from the intima, where they have no physiological function, is gradual accumulation there of an unwanted substance --- a "foreign body." Activation of the inflammatory and immune responses ensues. Smooth muscle cells deposit collagen and other fibers, to sequester the accumulating lipid pool, which is highly thrombogenic (Fuster 1994; Libby 1995), and to keep repairing the containment "edifice," including the fibrous cap. Macrophages and T-cells arrive in abundance. Gradually debris (sometimes including cholesterol crystals and calcium) accumulates in the lesion's core. Some advanced plaques become vascularized.

What evolves at a particular location is a lesion (plaque) humming with activities. The really dangerous plaques are those whose particular gene-based dysfunctions result in an edifice having a weak fibrous cap, which ultimately fails to separate the lesion's thrombogenic lipid core from the arterial lumen. For instance, if the particular gene-based dysfunctions of an atherosclerotic mini-tumor include production by the smooth muscle cells of defective collagen unable to build a strong fibrous cap, or if they include inappropriate activation of the enzymes which destroy the cap's collagen fibers, the lesion's protective fibrous cap is vulnerable to erosion or rupture, even if the lesion is only mildly stenotic. It is now clear that the mildly stenotic lesions are very often the ones which rupture and cause CAD death (Libby 1995).

Because x-ray induced mutations occur at random locations within a cell's DNA, atherogenic clones (mini-tumors) differ in their specific types and degrees of dysfunction and menace --- as do malignant solid tumors.

Elsewhere, others have puzzled over the fact that atherosclerotic plaques are localized and surrounded by normal intimal tissue in most patients. Is it so surprising? The same observation is true for solid cancers. And we propose that the explanation is the same for both diseases. Acquired mutations, unlike inherited mutations, occur in a limited number of cells. Only a few cells acquire the kinds of mutations which, with the help of co-actors, will produce atherosclerosis in blood vessels or cancer in other tissues.

The mutation hypothesis of atherogenesis naturally includes the potential for genomic instability, meaning a high and sometimes accelerating rate of additional gene aberrations generated "spontaneously" by the cell's own mutated DNA. This would be another similarity with carcinogenesis, because many (not all) cancer biologists regard genomic instability as a key characteristic of cancer (Nowell 1976; Morgan 1996).

The conclusion, that radiation-induced mutations can be atherogenic as well as carcinogenic, is certainly consistent with the fact that ionizing radiation is a proven human mutagen and carcinogen, and with the fact that in the RMP study the strong positive linear dose-responses for cancer and for CAD age-adjusted 1950 mortality (versus accumulated x-ray exposure) very closely resemble each other. The RMP study explored beyond cancer and CAD. It is notable that dose-responses in the RMP study for noncancer nonCAD age-adjusted 1950 mortality (versus x-ray exposure) show either no slope at all or show a significant negative linear slope --- the opposite direction from the dose-responses for CAD and for cancer. These two diseases select themselves out from the other major causes of death in 1950 ---

because acquired mutations are very important causal co-actors in each.

Part 2-c: A Weak and a Strong Study on Radiation-Induced Coronary Artery Disease

The ICRP (p.33-34) mistakenly asserts (a) that "the strongest evidence" so far for radiation induction of coronary artery disease at doses below 50 cSv arises from the 2003 analysis of the A-Bomb Survivors Study or ABSS, (b) that the shape of the dose-response is unclear below 50 cSv in that study, and (c) that only "subclinical inflammation" has been suggested as the explanation of the observations.

By contrast, the RMP study has produced far stronger evidence than does the ABSS. The strength of the dose-responses is spectacular. Such correlations do not happen by accident.

Correlations alone can never prove causation, of course, but they are certainly given great weight by users of the ABSS, including the ICRP. Nonetheless, it is also possible that the true cause of a correlation is some unidentified agent which is not equally present in all the dose-groups.

Several such potential confounders in the ABSS are absent from the RMP study. For example, most of the approximately 100,000 participants in the ABSS not only received one acute exposure to bomb-radiation in 1945, but they also accumulated acute partial-body exposures to medical x-rays both before and after 1945.

Unless it can be established, somehow, that all the compared dose-groups in the ABSS have accumulated equal x-ray doses, the findings of the ABSS are compromised to an unknowable degree. By contrast, across the approximately 100 million participants "enrolled" in the RMP study, none of the dose-groups received any acute exposures to bomb-radiation which could augment in unequal amounts their doses from medical x-rays, because they received no bomb exposure at all.

In 1998, a report on the ABSS acknowledged the problem of medical x-rays among the ABSS participants. In its Chapter 3, Kato, Russell, and Kodama state that by 1982, "The doses from diagnostic x-ray examinations had already become significantly great contaminants of the radiation doses from the atomic bombs" (Kato 1998, p.51). And the x-ray doses keep growing.

They also report analyses indicating that, "Numerous atomic bomb survivors have received medical radiation doses which are comparable with their atomic bomb radiation doses" (Kato 1998, p.67). And Kato's dose-comparison ignores the well-known findings that medical x-rays are about 4-fold more mutagenic per cGy (rad) than a-bomb radiation (Gofman 1999, Chapter 2, Part 7; ICRP 2005 Recommendations, Section 3.4.1) --- which means that the accumulated medical doses, to the extent that they have been reasonably reconstructed, far exceed the bomb doses in "numerous" cases. This makes it essential to have accurate matching of the ABSS dose-groups for accumulated medical x-ray doses. Please see further discussion in Part 3.

Besides medical radiation, the ABSS incorporates several other potential confounders which are absent from the RMP study. For example, because the RMP study is confined to

age-adjusted CAD mortality in 1950, the RMP study is not "muddied" by the full impact of cigarettes, whose use peaked for males in 1963 in the USA (Gofman 1999, Chapter 48). Nor do the RMP study's 1950 age-adjusted CAD mortality rates incorporate consequences from use of chest radiation for cancer therapy and use of chemotherapy --- another mutagen --- because such practices were almost nonexistent before 1950 (Gofman 1999, Chapter 68).

We recommend that the ICRP and other such groups carefully consider the RMP study before issuing any radiation guidelines in 2005. The consequences of effective doses of radiation up to a few cSv (rems) each year, upon causation of such an important disease, should certainly not be excluded from the estimated "detriment." The proposed exclusion in the ICRP 2005 Recommendations (p.34) is unacceptable and will surely end up creating a false sense of safety.

PART THREE: Risk-Values Rendered Untrustworthy by Unevaluated Medical X-rays

Contamination, of virtually all dose-response studies which attempt to identify and quantify causal agents in the etiology of CAD and cancer, has resulted from unevaluated and unmatched accumulated exposures to medical x-rays. With respect to studies of ionizing radiation, such contamination renders the ICRP's estimates of risk per dose-unit inherently untrustworthy.

If either the accumulated doses or the mutagenic power of medical x-rays were negligible, such contamination could be neglected, as are so many variables in epidemiological studies. But both the accumulated doses and the mutagenic power of medical x-rays are far from negligible. In many radiation studies, the "background" dose of accumulated x-ray doses is probably dominant.

This is impossible to ascertain. In all the developed countries, medical x-rays have been very widely used ever since the year 1900 (Gofman 1996, especially Chapters 31, 32, 33), but entrance doses were not measured, and still are far too rarely measured. In the United States, medical x-rays were very liberally given to children until about 1960 (Gofman 1996 throughout), and even during the 1980s, patients below age 45 received a large share of the total estimated number of x-ray procedures (Gofman 1999, Chapter 2, Part 3f). There is probably not one single person in the United States who knows his or her accumulated lifetime organ doses from medical x-rays. For many organs, such doses will far exceed the lifetime accumulated doses from natural background radiation (Gofman 1999, Appendix K).

For instance, up until the 1970s, prenatal irradiation during the mother's pelvimetry occurred in approximately one birth in every 14; the retroactively estimated fetal doses ranged between one and three cGy or rads (Gofman 1996, Chapter 12). Medical fluoroscopy was frequently and widely used starting in the 1920s; around 1950, the average fluoroscopy exam delivered an estimated skin dose of 65 Roentgens, or approximately 65 cGy or rads (Moeller 1953, pp.58-59; more context in Gofman 1999, Appendix K); more recent medical practice uses fluoroscopy of various duration and cumulative dose to guide catheters and many types of surgical procedures. CT scans, introduced in the 1970s in Japan as well as the USA, have typically delivered over 2 cGy or rads of dose to internal organs, per exposure; many exams require two exposures --- with and without a contrast medium --- and dose-levels vary from one facility to another.

Part 3-a: Permanent Large Uncertainties about Anyone's Accumulated X-ray Doses

The A-Bomb Survivor Study (ABSS), on which I (jwg) relied for so many years to calculate risk/cGy estimates, is badly contaminated by accumulated doses from medical x-rays. Somewhat heroic efforts in Japan to "reconstruct" x-ray doses for a subcohort of 15,000 ABSS participants (in the Adult Health Study) are necessarily unreliable. For example, surveys in several nations show that doses used for equivalent films vary by factors of 3 due to variation in film-processing methods, that doses vary in a fluoroscopic examination by factors of 10 or more due to variation in dose delivered per minute and number of minutes consumed, and that doses vary for a many reasons by additional factors of 2 or more for any procedure on patients of equal size (details in Gofman 1985, Chapter 16; Gofman 1996, Chapter 48; UNSCEAR 1993, p.243; and elsewhere).

Most dose-response studies do not even attempt to evaluate accumulated x-rays doses. Those that do make the attempt cannot eliminate the inherent and large uncertainty in the individual estimates assigned to each participant. The result is that the menace, of seriously unmatched accumulated x-ray doses among the compared groups, may be present in most studies, and cannot be ruled out of any study. However, the RMP study was designed to minimize the problem of never-measured x-ray doses.

Part 3-b: How Unmatched X-ray Doses Affect Risk-Estimates by ICRP and Others

What are some of the ways in which serious errors in risk-estimates can result from unmatched accumulated x-ray doses? These ways do not differ from inability to match study samples for non-x-ray variables --- for instance, for cigarette smoking. Some of them are demonstrated and depicted in Gofman 1999, Chapter 5 and Appendix L.

The direction of the error depends on how the unequal accumulated x-ray doses are distributed among the dose-groups, of course.

For instance, mismatched dose-groups can, in the most extreme cases, alter a truly positive dose-response to appear as a negative one. Or vice versa (Gofman 1999, Chapter 5). They can alter a truly positive linear dose-response to appear as a supralinear dose-response, or as a concave upward dose-response, or as a hormetic dose-response (Gofman 1999, Appendix L), or as a threshold dose-response, or as a flat "correlation absent" dose-response.

They can change the slope of a truly positive linear dose-response (change the increase in effect per unit increase in cause). And they can increase the scatter around a dose-response curve and thus lower its statistical significance and reliability.

Part 3-c: Conclusion about Neglect of Accumulated X-ray Doses

There is no doubt that the menace of dose-cohorts, unmatched for accumulated x-ray organ-doses in the ABSS, should warn everyone to reduce the trust commonly placed in quantitative risk-estimates derived from the ABSS --- as are most of the ICRP guidelines.

And this menace is not limited to the ABSS or to other dose-response studies of the effects from just ionizing radiation. For instance, it is a hazard in dose-response studies of any

suspected causal co-actor (e.g., any mutagen, or diet, smoking, non-ionizing radiation) in mortality from coronary artery disease or cancer.

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