'Recent' developments in low-dose radiation response

D. M. Wood, October 2017

Contents

It would be helpful for you to have read the document From radiation dose to cancer risk. There are more references for this document than for any other, partly because precisely what goes on at very low radiation doses is not fully understood in general and partly because the topic is important for those *exposed* to very low dose radiation.

Introduction

As discussed in the document above, virtually all regulations about radiation exposure are based on the 'linear no threshold' assumption: that the risk of cancer is *linearly proportional* to the radiation dose. However, the mathematical consequences of this assumption are

1. A uniform cancer risk per unit dose of radiation from very high doses (such as those experienced by survivors of the Hiroshima and Nagasaki nuclear explosions) down to unmeasurably small doses.
2. There is thus no 'safe' amount of radiation, in the sense that *any* exposure corresponds to a finite (even if extremely small) cancer risk. Unlike so-called 'deterministic effects', there is no threshold below which there are no detectable effects.

3. All that matters in radiation dose is the *total* amount of radiation you have received up to this point in your lifetime, not the *rate* (how fast or how slow) the exposure was accumulated.

However,

- Clinical radiation oncology for many decades has clearly demonstrated that a large amount of radiation delivered in many small doses is much less toxic than a single large dose. This is usually called 'dose fractionation'.
- As observed in 2000 edition of a well-known radiation biology text [1],

  > Small radiation doses seem to activate the immune response system by stimulating antigen production. This is used in radiation therapy by exposing the patient to a comparably small "pre-treatment" dose (0.5 Gy) before the large organ doses are delivered in order to hasten the recovery of the patient after the treatment.

Each observation above directly contradicts the consequences of the LNT picture, precisely because of cellular repair mechanisms mentioned briefly above.

Over the last two decades, however, it has become clear that, despite its mathematical convenience and the fact that it is satisfactory for large doses, there is no reason why this linear relation should hold (or does hold) at low doses, say at total doses of 100 mSv or less [2, 3]. As we did in the earlier document, we will define low doses[1] as those comparable to or below background radiation doses.

[1] Experts would call these 'very low doses'.

In 2005 the French National Academy of Medicine in a position paper [4] stated (as part of the executive summary

The executive summary is available in English.

> Epidemiological studies have been carried out to determine the possible carcinogenic risk of doses lower than 100 mSv, and they have not been able to detect statistically significant risks even on large cohorts or populations. Therefore, these risks are at worse low since the highest limit of the confidence interval is relatively low. It is highly unlikely that putative carcinogenic risks could be estimated or even established for such doses through case-control studies or the follow-up of cohorts. Even for several hundred thousands of subjects, the power of

> such epidemiological studies would not be sufficient to demonstrate the existence of a very small excess in cancer incidence or mortality adding to the natural cancer incidence which, in non-irradiated populations, is already very high and fluctuates according to lifestyle. Only comparisons between geographical regions with high and low natural irradiation and with similar living conditions could provide valuable information for this range of doses and dose rates. The results from the ongoing studies in Kerala (India) and China need to be carefully analyzed.

They conclude

> In conclusion, this report raises doubts on the validity of using LNT for evaluating the carcinogenic risk of low doses (< 100 mSv) and even more for very low doses (< 10 mSv). The LNT concept can be a useful pragmatic tool for assessing rules in radioprotection for doses above 10 mSv; however since it is not based on biological concepts of our current knowledge, it should not be used without precaution for assessing by extrapolation the risks associated with low and even more so, with very low doses (< 10 mSv), especially for benefit-risk assessments imposed on radiologists... The biological mechanisms are different for doses lower than a few dozen mSv and for higher doses. The eventual risks in the dose range of radiological examinations (0.1 to 5 mSv, up to 20mSv for some examinations) must be estimated taking into account radiobiological and experimental data. An empirical relationship which has been just validated for doses higher than 200 mSv may lead to an overestimation of risks (associated with doses one hundred fold lower), and this overestimation could discourage patients from undergoing useful examinations and introduce a bias in radioprotection measures against very low doses (< 10 mSv).
>
> Decision makers confronted with problems of radioactive waste or risk of contamination, should re-examine the methodology used for the evaluation of risks associated with very low doses and with doses delivered at a very low dose rate. This report confirms the inappropriateness of the collective dose concept to evaluate population irradiation risks.

The U.S, National Council on Radiation Protection and Measurements (NCRP) stated in NCRP Publication No. 121 "Few experimental studies and essentially no human data can be said to prove or even provide direct support for the [LNT] concept", and in NCRP Publication No.136 (NCRP-2001) stated "It is important to note that the rates of cancer in most populations exposed to low level radiation have not been found to be detectably increased, and in most cases the rates appear to be decreased."

There are other brief, excellent overviews of the current status of using the LNT hypothesis may be found [5] at

Health Physics News and on Wikipedia. As of December 2017 there are three ongoing (open) challenges filed with the Nuclear Regulatory Commission opposing continued use of the LNT model at low doses.

We will put aside the policy implications for these until after the idea of 'dose/response' curves are introduced.

Plausible expectations

A failure of LNT expectations at low doses is often introduced by a couple of observations:

1. Life on earth evolved in the presence of variable background radiation [6]. In order to reliably reproduce (and to preserve beneficial mutations) it would be crucial that there be cellular repair mechanisms for DNA damage inflicted by random background radiation. As we noted elsewhere, 'low doses' are precisely those comparable to (or less than) background radiation.

2. Clinical radiation oncology for many decades has clearly demonstrated that a large amount of radiation delivered in many small doses is much less toxic than a single large dose, in direct contradiction of the LNT picture, precisely due to such repair mechanisms.

As noted [2] by Weber and Zanzonico of the Memorial Sloan Kettering Cancer Center, "even if one concedes the validity of the LNT model, it cannot be applied reliably to individuals, but only to . . . populations sufficiently large to average out inter-individual differences in radiation sensitivity related to sex, age, diet, and other lifestyle factors and those related to intrinsic biology."

Dose response curves

The element selenium is a 'micronucrient' in the human diet, playing roles in thyroid function, immune response, and as an antioxidant. Like many substances, it is toxic at high doses and its complete absence is *also* toxic.

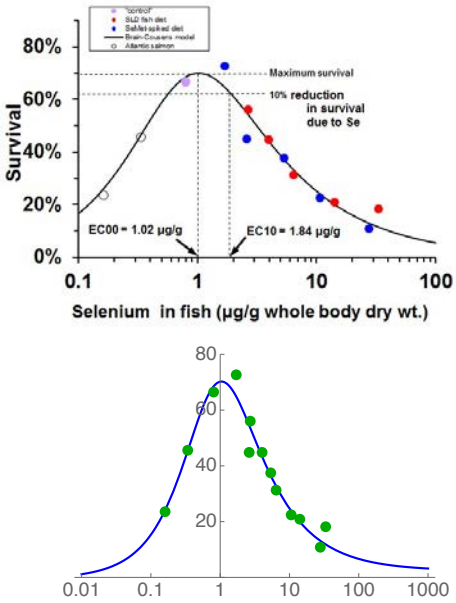

Figure 1: Dose/response curves for Se fed to juvenile fish. Data (upper) and my Brain-Cousens model fit (lower).

Fig. 1 (upper panel) from Wikipedia) shows how the survival rate of juvenile salmon after 90 days depends on the concentration of Se in their tissues. This is a particular form of a 'dose-response' curve: in this context the dose is the amount of Se in the diet (which ends up as a percentage of dry body weight) and the response is percent of fish which survive to 90 days.

It is worth noticing that (i) doses are often displayed using a 'log scale', since they can span many factors of 10, but responses generally use a linear scale (and are often displayed in percentages); (ii) although the peak is broad on a linear scale, it is well-defined, indicating a well-defined Se concentration which maximizes the survival rate (one measure of an optimum dose). The lower panel is a fit to a well known ('Brain-Cousens' [7]) mathematical form (first developed for plant growth); this is included only to show that this behavior is well parameterized mathematically (even if not fully understood).

If you were to approach the problem knowing only about selenium toxicity [8] and moved along the dose/response from the high-dose end, you would probably be stunned to see discover that there was an optimum amount of Se (not equal to zero) in the diet. In December 2017 a European nutrition journal article [9] shows that, based on a meta-analysis (a quantitative overview of existing published work rather than new clinical or experimental evidence), cheese in the diet protects human beings (most clearly, women) against cardiovascular disease.

Fig. 2 shows (redrawn from the article) the relative risk (beginning at 1 with no cheese consumption) of cardiovascular disease as a function of daily cheese consumption. The minimum relative risk (about 0.84) occurs at a daily intake of about 35 g/day (about 1.2 oz): this much reduces your risk of CVD by about 16% (or from 9% to 22%, including confidence intervals). Cheese is high in calcium, vitamins, minerals, proteins, and conjugated linoleic acid (believed to inhibit the progression of atherosclerosis—the deposition of fatty plaques espe-

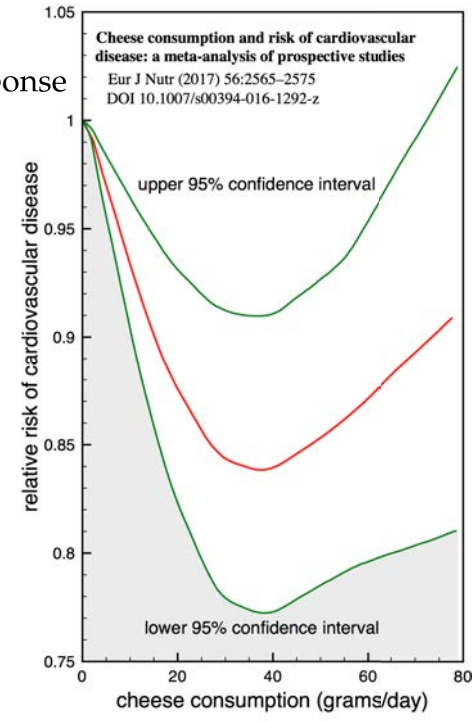

Figure 2: Relative risk ('response') of cardiovascular disease due to daily intake of cheese (dose) [9]

"A prospective cohort study is a longitudinal cohort study that follows over time a group of similar individuals (cohorts) who differ with respect to certain factors under study, to determine how these factors affect rates of a certain outcome."–Wikipedia.

cially on coronary artery walls), but it also contains a lot of saturated fatty acids. There is even no clear evidence that high-fat cheese is harmful in any way. The protective effect of a substance which is toxic to an organism at high doses is generally termed *hormesis*, or a *hormetic response*.

Radiation hormesis

A (now strident) subgroup of radiation biologists and epidemiologists strongly support the idea of *radiation hormesis*, closely related to the 'evolutionary' topic of 'adaptive response'. This paradigm, following on the existence of cellular repair mechanisms that of necessity exist[10], for supporters imply that small doses of radiation

- 'Prime' the immune system
- Trigger cellular DNA repair mechanisms
- Trigger cell apoptosis ("suicide") of already damaged cells
- As a result, actually can *protect* organisms or tissues from radiation damage and cancer.

The journal *Dose-Response* is a the publication of choice for members of the International Hormesis Society [11]. SARI (Scientists for Accurate Radiation Information) [12] intends to counter radiological misinformation and espouses radiation hormesis. Web sites which reflect a pro-hormesis bias for flagrantly commercial reasons include radiation-hormesis.com and Nighthawk Minerals (search for the phrase "hormesis + healing" for more). Remember that in the 1920s radium was similarly touted as a panacea before the 'Radium Girls' scandal of the late 1920s.

Examples?

1. Radon and protection against lung cancer

   U.S. residential limits on radon appear to have been established by downward extrapolation of cancer risks seen for underground miners exposed to much higher levels of radon using the LNT description. The now-deceased physicist Bernard L. Cohen published in 2002 an article [13] examining (based on the known carcinogenicity of radon gas) a famous article in which he examined the normalized cancer mortality rate around the U.S. as the household radon concentration increased (Fig. 3). The purple line shows the expected cancer death rate increase expected on the basis of the (then used version of) LNT data. Astonishingly, his

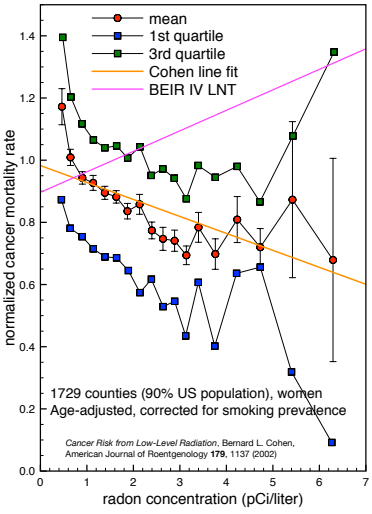

Figure 3: Cancer mortality rate for U.S. women (adjusted for smoking and age) replotted from Cohen[13].

(orange) curve of best fit showed a clear *decline* of the death rate with radon concentration, 'as if' the radon exposure protected women (and men too) from lung cancer due to radon.

A fairly recent study by a biostatistician [14] examined 200 lung cancer cases (and about 400 control patients) matched for age and gender and controlled for smoking history. Household radon levels (not total radon exposure) were monitored via etch-track detectors (such as are used in radon 'test kits') or other detectors. Only 15 out of 200 lung cancer cases had never smoked; cancer risk due to smoking was enhanced by factors of from 11 to 68 depending on number of 'pack-years' smoked. Despite the profound effects of smoking on lung cancer rates, it appears clear that for radon levels up to 545 $\mathrm{Bq\,m^{-3}}$ of air (or, in units more familiar in the US for radon levels, up to 14.7 pCi/l, the presence of radon (^{222}Rn is the α emitting isotope) in household air is *protective* against lung cancer. See also [15].

2. The Taiwan ^{60}Co incident

   Another well-known example cited by radiation hormesis proponents concerns a large cohort of people living in residential (1700 apartments!), school, and industrial buildings in Taiwan inadvertently constructed with steel contaminated by several ^{60}Co (which is an emitter of very penetrating γ rays with a half-life of 5.27 years) sources. Some rates of radiation exposure are estimated [16] to have reached 270 µSv per hour, considered a low dose rate. A 2006 report [16] followed 7271 for 16 years on average and found an slightly elevated cancer risks (standardized incidence ratios of 1.2-7.4 for leukemias in men and 1.0-5.7 for solid cancers in women), but with a small sample size.[2] More can be found at [18].

   However, a slightly later article [19] in the journal *Dose-Response* estimate a 0.4 Sv average dose and found that "... the incidence of cancer deaths in this population was greatly reduced—to about 3 per cent of the inci-

Around Rocky Flats, the background inside my house is about 0.16 µSv $\mathrm{h^{-1}}$, thus considered a *very low* dose rate.

[2] A 'standardized incidence ratio' (SIR) is [17] "... an estimate of the occurrence of cancer in a population relative to what might be expected if the population had the same cancer experience as some larger comparison population designated as "normal" or average.".

dence of spontaneous cancer death in the general Taiwan public. In addition, the incidence of congenital malformations was also reduce–do about 7 per cent of the incidence in the general public." Their results are shown in Fig. 4. There has been a major suppression of radiation deaths.

Finally, in a 2017 follow-up [20] Hsieh *et al.* found for a nominal 100 mSv dose a 'hazard ratio' of 1.04-1.28 (90 % confidence interval) for an increased risk of leukemia, 1.05-1.20 for breast cancers, and 1.0-1.08 for all cancers; women under age 20 at the time of exposure had a breast cancer HR of 1.14-1.60. These data indicate that the initial data grossly overestimated the cancer rate, after 30 years the increased risk was relatively slight, and it leaves the *Dose-Response* article in limbo.

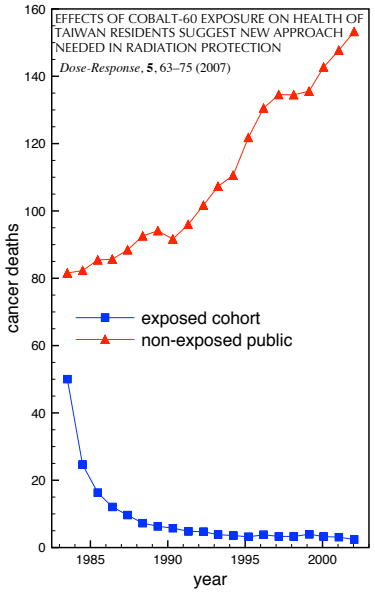

Figure 4: Cancer mortality among Taiwanese cohort exposed to low dose ^{60}Co γ rays; replotted from [19].

A 'hazard ratio' is essentially identical to a standardized incidence ratio—see above.

Current status

Savage criticism of the linear no threshold description and those who first advocated its use, and exuberant defense of radiation hormesis is most closely associated in the United States with Prof. Edward Calabrese of the University of Massachusetts, Amherst. Its supporters are more common in the countries of the former Soviet Union and Japan.

An early review [21] discusses some of the policy implications were hormetic response adopted for low doses of many toxins.

> The hormetic perspective also turns upside down the strategies and tactics used for risk communication of toxic substances for the public. For the past 30 years, regulatory and/or public-health agencies in many countries have 'educated'–and in the process frightened–the public to expect that there may be no safe exposure level to many toxic agents, especially carcinogens such as radiation and dioxins. If the hormetic perspective were accepted, the risk-assessment message would have to change completely. . . It would certainly be resisted by many regulatory and public-health agencies as an industrial-influenced, self-serving scheme that could lead to less costly, less protective clean-up standards, reminiscent of attempts by early opponents of hormesis to link it with homeopathy. . .

More radical thinking is embodied in more recent work, as radiation hormesis proponents have become more adamant about the need for change in regulating low-dose dose exposure to radiation. Beagles have born a heavy burden since the 1950s in assessing the radiological effects of, for example, $^{239}PuO_2$ (the same chemical compound which occurs around Rocky Flats). In a conference proceeding from 2015, J. M. Cuttler and L. Feinenegen note in a commentary on the beagle work [23]

> Lung cancer is the leading cancer killer in the United States. The studies on inhaled plutonium dioxide suggest that the incidence of spontaneously-occurring lung tumors could be significantly reduced by low-dose alpha-radiation, such as from a single inhalation of $^{239}PuO_2$, as a prophylaxis. Because the amount of plutonium is infinitesimally small, plutonium [chemical–Ed.] toxicity is of no concern in this context.

A very reasonable review as of 2012 exists [22] on a website whose very name provokes suspicion (in me, at least).

At this point there are many 'examples' of radiation hormesis, but it important to note that many remain unconvinced about its generality. Thayer *et al* [24] in 2005 gave a detailed critique of the hormesis model up to that point, citing the example of alcohol, which appears to reduce the risk of coronary heart disease at low dose (and obviously causes problems at high dose), but has not been found safe for pregnant women. Morgan and Bair [25] and Beyea [26] have attempted to refute some of the more incendiary claims of criminal intent by those who first established the linear no-threshold description. A very recent survey [27] characterizes the ongoing as debate as characterized by "much heat and little light". Some recent overviews include [6] and the 2016 article *Epidemiology without biology: false paradigms, unfounded assumptions, and specious statistics in radiation science* [28] which is worth reading not only to see the hormesis arguments but also to read two critical commentaries (and the authors' rebuttal).

Some objections to radiation hormesis work include

- 'Cherry picking' of data[3]
- Sloppiness about statistical niceties like robust confi-

[3] This means selecting data that agrees with one's biases.

dence intervals, fits which include error bars, etc.

- Overstatements about the frequency of hormesis in dose/response curves and the conclusion that it is an adaptive (in the sense of evolution) phenomenon.

Remarkably, all the turmoil has re-focused interest on a number of sites around the world which have 'high natural background' radiation levels (see the chart of doses produced by the DOE for examples); for recent reviews, see [29] and [30]. Möller and Mousseau review [6] and conclude that "Our findings are clearly inconsistent with a general role for hormesis in adaptation to elevated levels of natural background radiation."

Why amend the linear no-threshold description?

Some of the arguments made by advocates of radiation hormesis include

1. Fear of cancer may cause individuals to choose to postpone or forego medical diagnostic procedures which involve ionizing radiation (X-rays, CT scans, cardiac diagnostics involving short-lived radiopharmaceuticals, etc.) because of overestimates of cancer risks due to use of the LNT criteria
2. Policy based on unreasonable fear of radiation can be more damaging than the radiation itself.

There have been reports [31] of abortions in Belarus and Russia after the Chernobyl nuclear incident. About 1600 people–mostly elderly who were deprived of routine health care or succumbed to hypothermia or dehydration–died during the evacuation around the Fukushima power plants in 2011 Wikipedia. Had fear of radiation exposure been relaxed (see the New York Times article *When radiation isn't the real risk*) somewhat to reflect reduced cancer risks, a less frantic evacuation could have saved hundreds of lives. As the article observes "By avoiding what would have been an average cumulative exposure of 16 millisieverts, the number of cancer deaths prevented was perhaps 160, or 10 percent of the total who died in the evacuation itself".

Overall, I find the arguments that hormetic response exists logically appealing, but this doesn't mean it can be used as a predictive tool.

What good would adopting a radiation hormesis picture do?

Here are some points to consider

- What do proponents of radiation hormesis suggest we replace the LNT hypothesis with? The LNT is both simple and explicit; no one can currently say for sure what the dose/response curve to radiation looks like.

I would guess that there *is* no universal curve: each sort of tissue or cell organelle would have its own curve as its own cellular repair mechanisms turn on and then are overwhelmed as the dose rate increases.

- Why should we do it *now*? Precisely what happens at very low dose is not extremely well understood for human beings. The low-dose region is plausibly where individual sensitivities (as opposed to statistical outcomes) to carcinogens may become important, but almost all studies group participants into large groups based on dose, thus smoothing over this issue. With the cancellation in 2016 of the DOE's Low Dose Program we are forced back to epidemiology to decide.
- The main price paid for using the linear no-threshold model is a possibly significant overestimate of cancers for low doses. At least this is an error on the side of caution.

The probable future

As we have seen, the 'linear no threshold' description of the dose/response curve for radiation/cancer is extremely convenient (and a reasonable description for high doses) because distinct sources of ionizing radiation (*e.g.*, background, medical imagery such as CT scans and dental X-rays) can be simply added. It is therefore very probable that the LNT description will *continue* to be used for the medium future (I'd say, decades) until a clear, predictive understanding of human cancer response to low-dose radiation emerges.

I don't think this will happen anytime soon. Despite the clamor by radiation hormesis advocates to immediately abandon LNT for low-dose radiation exposure, the inertia and intrinsic conservatism of the medical community (including radiation oncologists, the host of imaging technologies which depend on ionizing radiation, etc) is extremely likely to oppose any rapid change in regulations.

Takeaway messages

- Relatively little reliable is known about cancer rates for humans exposed to doses below about 0.100 Gy. International and U.S. agencies recommend *against* using the 'linear, no-threshold' description of cancer rates, though most do not say what to replace it with!
- Thus for low-dose radiation exposure, the linear, no-threshold assumption has been relegated to a *regulatory* status, easy to use but not accurate.

- There is some evidence that low doses of radiation are *beneficial*, a manifestation of principle called 'radiation hormesis'.
- No one should be surprised if *observed* cancer rates for low-dose radiation exposure (comparable to background radiation rates, such as occur around inside the Rocky Flats National Wildlife Refuge) fall below (possibly well below) what is predicted on the basis of the LNT description, such as is used by the Department of Energy's Office of Legacy Management in monitoring the Refuge. (Remember: everything outside the Refuge was certified as suitable for ordinary use long ago.)

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