From:	Carol Marcus
To:	vietti-cook annette NRC
Cc:	CMRBARAN Resource; CHAIRMAN Resource; CMRCaputo Resource; CMRWright Resource
Subject:	[External_Sender] Addendum 11 to my petition of 2/9/15
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Attachments:	DR_Oak Har_Are continued efforts nec to reduce rad exposures_2021_19_1_1-9-2.pdf Calabrese-2021_Significance of failed historical foundation of LNT model-1.pdf

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March 2, 2021

Dear Ms. Vietti-Cook:

Attached please find two articles that I wish to add as Addendum 11 to my petition of 2/9/15 concerning the false LNT.

Sincerely,

Carol S. Marcus, Ph.D., M.D.

Commentary

Are Continued Efforts to Reduce Radiation Exposures from X-Rays Warranted?

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Abstract

There are pressures to avoid use of radiological imaging throughout all healthcare due to the notion that all radiation is carcinogenic. This perception stems from the long-standing use of the linear no-threshold (LNT) assumption of risk associated with radiation exposures. This societal perception has led to relentless efforts to avoid and reduce radiation exposures to patients at great costs. Many radiation reduction campaigns have been launched to dissuade doctors from using radiation imaging. Lower-dose imaging techniques and practices are being advocated. Alternate imaging procedures are encouraged. Are these efforts warranted? Based on recent evidence, LNT ideology is shown to be defunct for risk assessment at low-dose exposure ranges which includes X-rays and CT scans. In fact, the best evidence that was once used to support LNT ideology, including the Life Span Study data, now indicates thresholds for cancer induction are high; therefore, low-dose X-rays cannot cause harm. Current practices are safe as exposures currently encountered are orders of magnitude below threshold levels shown to be harmful. As long as imaging is medically warranted, it is shown that efforts to reduce exposures that are within background radiation levels and that are also shown to enhance health by upregulating natural adaptive protection systems are definitively wasted resources.

Keywords

X-rays, low-dose radiation, sunk-cost bias, choosing wisely, CT scan

Introduction

Throughout all healthcare there are pressures to reduce radiological imaging, as well as to reduce the exposures to ionizing radiation used when this type of imaging does occur.[1-7] Examples of these efforts include the Image Gently (children),[8] Image Wisely (adults),[9] Choosing Wisely (various disciplines),[10] and ACR Appropriateness criteria.[11] This results from the indoctrination of radiation fear (i.e. radiophobia) that was spawned since the atomic bombings of Nagasaki and Hiroshima in 1945.[12] In fact, the majority of the lay population are knowledgeable about the link between radiation and cancer and many would forgo medical imaging if it involves radiation (e.g. X-ray and CT scans).[13,14]

In 2001 there was a special issue in the American Journal of Radiology that featured several articles highlighting concerns surrounding radiation exposures to pediatric patients from CT imaging. One article in particular, Brenner et al.,[15] calculated theoretical future cancer mortality risks from childhood CT exposures. Despite the risk being shown to be small, when extrapolated throughout the pediatric population estimated to receive CT imaging annually, as expected, the number got magnified. The USA Today magazine published an article featuring the projections from Brenner's article stating: "Each year, about 1.6 million children in the USA get CT scans to the head and abdomen—and about 1,500 of these will die later in life of radiation-induced cancer, according to research out today."[16] Unfortunately, this message instilled fear but was factually an unproven hypothesis.[17]

Despite the fact that the Brenner article has been criticized for invalid use of the LNT model for low-dose radiation risk assessment as well as inappropriately extrapolating from the population down to the individual risk level,[18-20] as the saying goes, "the damage was done." Two months following the USA Today article a conference was organized to explore the "crisis" of CT imaging and radiation doses in pediatrics.[21,22]

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This conference led the medical profession to adopt ALARA "as low as reasonably achievable" as a radiation protection principle. This first "ALARA conference" led to subsequent conferences[23,24] and involved scientists, physicians, technologists, manufacturers and representatives from governmental agencies. Soon followed the creation of radiation reduction/avoidance campaigns including Image Gently for children in 2006[8] and Image Wisely for adults in 2007.[9]

The Brenner article was soon followed by the National Council on Radiation Protection and Measurements (NCRP) report 160 (2006) that showed the near doubling of public exposures to medical radiation (mostly due to CT scans).[25] Subsequently, more recent long-term studies of children cohorts who had received CT scans that showed increased cancers in adulthood emerged (e.g. Pearce et al., 2012;[26] Mathews et al., 2013[27]). These articles have been heavily criticized for suffering from "reverse causation" or how children who require CT scans in childhood are more likely (i.e. predisposed) to get more cancers than healthier children who do not get imaged.[28] Indeed, this criticism was confirmed in the study by Journey et al. who showed that while initially there was a significant correlation, after controlling for known cancer predisposing risk factors, no significant association was found in assessing cancer risk in adults who received CT scans prior to the age of 10.[29]

Simultaneously, over the last 20 years the media has very successfully amplified the message of cancers being linked to essential radiological imaging.[30] Cohen for example, has presented a table featuring headlines/quotes from mainstream media outlets suggesting CT scans are associated with cancers.[17] The media's fear-mongering messaging to the public is so successful that many now fear medically warranted X-rays and CT scans; in fact, this is now a common and challenging issue among doctors attempting to deliver efficient healthcare to patients who require X-rays.[31]

The societal perception of future cancers being caused by medical imaging has led to relentless efforts to avoid and reduce radiation exposures to patients at great financial costs. As well as radiation reduction campaigns, there are pressures to use lower dose techniques and other procedures all in efforts to decrease individual exposures, as well as the endorsement to use alternate imaging methods (e.g. ultrasonography or MRI) that do not use radiation. Campaigns and agencies promulgating radiation restriction also endorse full disclosure of cancer risks and lead doctors and patients to fall prey to the sunk-cost bias when considering radiological imaging. We will discuss these key issues related to such efforts, and why these efforts waste valuable resources. We summarize these efforts into 5 main categories:

1. Promulgation of radiation reduction campaigns;
2. Endorsement of lower-dose techniques and practices;
3. Recommendation for alternative imaging;
4. Enthusiastic endorsement for informing patients of carcinogenic risks;
5. Succumbing to sunk-cost bias.

We will show that these efforts appear fruitless as they often do not reduce exposures, they are costly, they often increase radiation exposures as well as introduce other real harms. We will argue that current practices are safe as the exposures currently encountered are orders of magnitude below levels that may be harmful or carcinogenic.

Promulgation of Radiation Reduction Campaigns

There are several radiation reduction campaigns including Image Gently (children), Image Wisely (adults), and Choosing Wisely (various disciplines). As described on their corresponding websites and summarized by others,[32] multiple organizations were involved in banding together to create and launch the interdisciplinary message that pervades throughout all healthcare; that is, to avoid and minimize patient radiation exposures due to future cancer risks.

The main problem with these campaigns is that there is no evidence that low-dose radiation as given by X-rays and CT scans induce cancers.[29,33-35] In fact, there is evidence to the contrary, low-dose radiation exposures lowers cancer incidence[36,37] and extends cancer latency period.[38,39] The studies that have claimed that cancers are caused by radiological imaging are either theoretical LNT-based projections (e.g. Brenner et al. 2001[15]/Brenner and Hall, 2007[40]) which are falsehood,[34,41,42] or studies that have follow-up with cohorts who were imaged in their childhood that suffer from "reverse causation"[28] (e.g. Pearce et al.;[26] Mathews et al.[27]) because healthy children do not need CT scans![35] In fact, Shibata et al. state that because they determined children who required CT scans had 13x the rate of congenital anomalies, "the population of children undergoing CT is completely different from that not undergoing CT. The 2 groups should not be compared."[35]

The historic evidence that has always been touted as the main source or "proof" that radiation causes cancer is the Life Span Study (LSS) data.[43] In 2012, however, Ozasa et al.[44] reported an update that upon correction for background cancer incidence by Doss,[45,46] clearly shows a non-linear or quadratic dose-response curve; that is hormesis (Figure 1). The threshold shown by Doss is at 700 mGy. Thus, the LSS does not support the LNT ideology. Cuttler as well has re-analyzed data from UNSCEAR (1958) and determined the threshold for leukemia (Figure 2), the cancer that would first occur after a pathologic radiation dose was higher than anticipated at 1100 mGy (95% CI 530-2600 mGy).[47,48] As Oakley and Harrison recently stated: "even considering the lower threshold dose of 700 mGy, this represents about 2 to 3 orders of magnitude greater than the amount of radiation given from medical X-rays."[31]

Decades of radiobiological research on animals and humans show that on the molecular, cellular and whole-body levels there are effects that occur that are not consistent with LNT ideology.[49-51] In fact, there are many adaptive defense mechanisms that get initiated and/or upregulated upon low-dose radiation stimulation such as DNA repair systems, programed cell

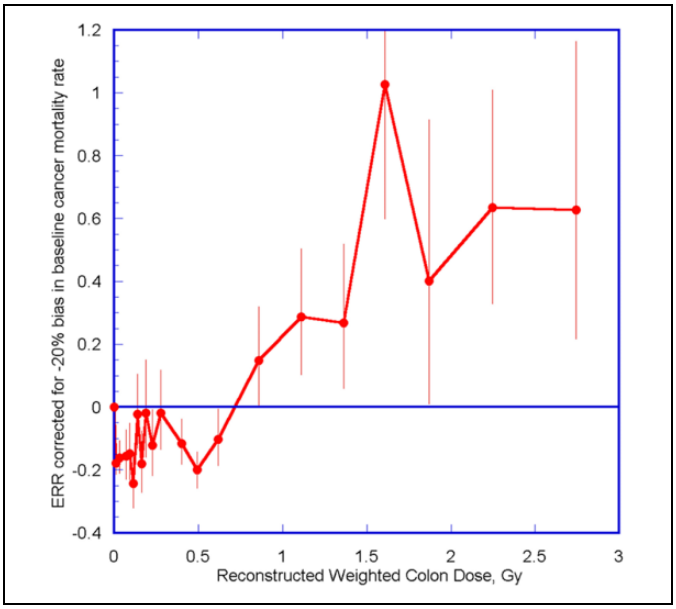

Figure 1. Excess relative risk (ERR) correcting for a 20% bias in baseline cancer mortality rate for all solid cancers in atomic bomb survivors from the original data from Ozasa et al.[44] Error bars represent 95% confidence intervals. Threshold is at about 0.7 Gy (700 mGy).[45,46]

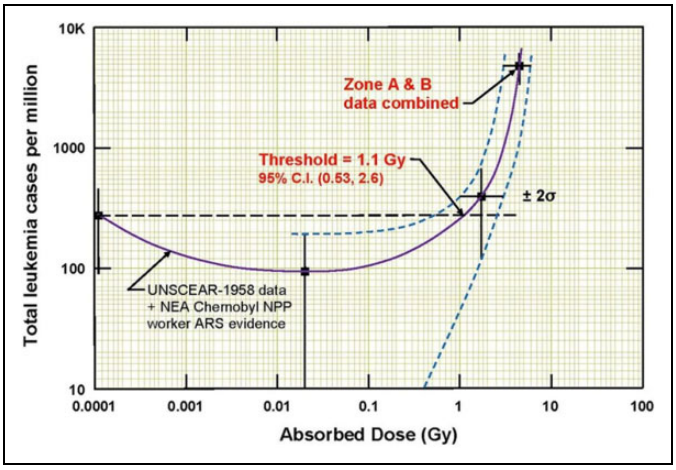

Figure 2. 1958 UNSCEAR data indicates a threshold of about 1.1 Gy (1100 mGy; assuming RBE = 1) for radiogenic leukemia in 95,819 persons exposed to A-bomb radiation from Hiroshima.[48]

death, cell cycle delay, cellular senescence, adaptive memory, bystander effects (exposed cells communicate to non-exposed cells), epigenetics, immune stimulation and tumor suppression.[52,53] These innate adaptive responses are very efficient and effective (Figure 3).[54-56] This is how low-dose irradiation (LDI) therapy works.[57] Many human diseases can be successfully treated by LDI therapy including inflammatory conditions, infections and cancers.[57-59] In fact, "LDIR therapy is expected to decrease the risk of cancer because it stimulates the immune system to destroy cancer cells more effectively than it would without the LDIR stimulation."[57]

The most current radiobiological data shows low-dose radiation exposures decrease cancers and the most current LSS analyses show high thresholds for harm and invalidates the LNT for use in risk assessment from low exposures as from X-rays and CT scans.

Endorsement of Lower-Dose Techniques and Practices

Lower-dose techniques include reducing image parameters or customizing image parameters to the size of the patient, particularly in accommodating children for CT scans. Use of patient shielding to "protect" the gonads or thyroid is another common practice. Other practices include triaging patients to non-radiation tests such as MRI, or opting to skip radiological testing without an alternative test. Each of these practice deviations resulting from the attempt to avoid radiation exposures may present harms in different ways.

Lower-dose techniques imply adjusting radiation exposure parameters to lower the overall dose while attempting to capture an image that retains high diagnostic quality. The balancing of image quality with lowest feasible exposure settings presents challenges and often results in retakes—this obviously doubles the exposure![34] The outcome of a retake, of course, results in self-defeat for LNT advocates attempting to reduce radiation exposures, but in actuality only translates into wasted time and resources according to the current reality of radiation hormesis from low-doses. Alternatively, if an image is considered 'satisfactory' when parameters were purposefully lowered to reduce the exposure, and under traditional circumstances (not considering radiation exposure) would normally warrant a re-take, then the chance of a missed diagnosis occurs. Missing a diagnosis can be more actually harmful than the imagined harm from the extra radiation exposure resulting from ensuring an adequate image.[60-62] As has been stated: "Missing a diagnosis due to poor image quality resulting from suboptimal imaging parameters in the attempt to reduce patient exposures by an infinitesimal amount is practically negligent."[34]

Practices encouraged to further reduce radiation exposures includes use of gonadal shielding. Shielding however, is often poorly placed leading to re-takes.[34] Further, if enough of the automatic exposure control photo timing cells are covered, it has been shown to increase the radiation output from 63% to 147%.[63] This has led McKenney et al. to state that gonadal shielding is nothing more than "good intentions."[63] Shielding cannot prevent internal scatter from the anatomy sought for examination; thus, many have questioned its further use,[64-66] and this includes the American Association of Physicists in Medicine who recommend its discontinuation.[66] Thus, efforts to reduce exposures by lowering exposure parameters and using shielding often result in repeated imaging as well as increased exposures, which of course is only a significant concern to those adhering to LNT and ALARA principles.

Another practice of avoiding radiation is the triaging of patients to non-ionizing radiation imaging such as MRI

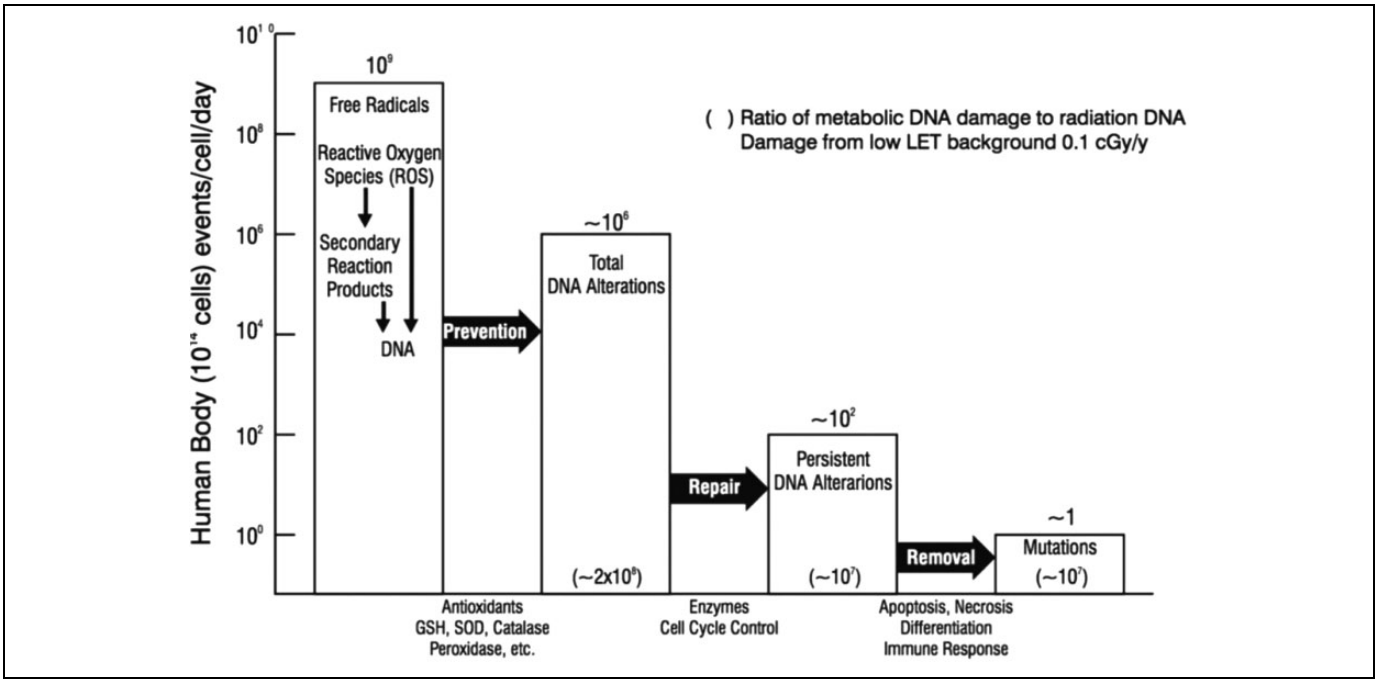

Figure 3. The adaptive response systems (aka DNA damage-control biosystem) very efficiently prevents, repairs, or removes virtually all DNA alterations from mostly natural metabolic processes (e.g. breathing air).[54]

(we discuss in next section), or to "opt out" of radiological imaging without an alternative test and to monitor the patient which leads to "watch and wait" practice. This type of practice obviously leads to increasing patient anxiety as they do not get a definitive diagnosis, but also adds liability concerns for the physician. Often the patient gets admitted for surveillance which adds risks of nosocomial infections and hospital error; in fact, it is much riskier to be admitted to the hospital than to get an X-ray.[67] Often taking an image also decreases hospital admittances and unnecessary surgeries.[34]

Recommendation for Alternative Imaging

Traditional alternatives to X-ray imaging (X-ray/CT scans) typically include the use of ultrasonography (US) or magnetic resonance imaging (MRI).[68] Often a doctor reluctant to order an X-ray or a patient resistant to receive one will lead to the choice of an alternate test that may be inferior as opposed to the traditional and common triage of X-ray/CT use which would provide the best and most direct assessment method (e.g. CT for abdominal obstruction, head trauma etc.). This is a dangerous practice as it may lead to a missed diagnosis or misdiagnosis, either of which may result in more actual harm than the imaginary risk from an X-ray[34,60,61]

Risks have been compared to hypothetical future cancers from X-rays to more immediate acute risks from mismanaging common medical emergency scenarios. Brody and Guillerman discuss the fact that CT scans are often taken on patients with life-threatening diseases; thus, they often would not live long enough to suffer from the development of cancers thought to be attributed to low-dose imaging.[67] In fact, based on the LNT hypothesis, the risk of death from a future cancer from a single CT image is predicted to be 1 in 4000[67] and the likelihood of diagnosing an acute clinically important traumatic brain injury (ci-TBI) on CT after following appropriate clinical decision rules for a head-injured pediatric patient is 1-8%.[69] Thus, the image should indisputably be taken.

The example above shows that to *not* perform a CT scan in the relatively common clinical scenario of a child reporting with head injury resulted in a risk that is between 40-320 times *more* dangerous than simply taking the scan as ci-TBIs such as an intracranial hemorrhage (i.e. brain bleed) can cause rapid death such as in the case of Bryan Salinas.[70] This 2-year old boy fell out of a window hitting his head, the family rushed him to the hospital, but after examination the doctor refused imaging and sent him home with a clean bill of health despite the fact he was vomiting. The boy died a few hours later from a massive brain bleed that would have been easily detected by CT, and timely imaging would have led to life-saving emergency surgery. It is assumed the scan was not pursued as the doctor was following a pediatric clinical decision rule algorithm (that emergency physicians are expected to follow) that aims to identify those children not at risk of ci-TBI for the purpose of avoiding CT scans and "risks of radiation-induced malignancy" that is universally assumed according to the prevailing LNT notion.[71]

Another issue with using MRI over radiological imaging is that although MRI does not expose the patient to ionizing radiation, MRI is much more expensive. More judicious use of X-ray is actually advocated in certain clinical scenarios[72,73] as the economic cost savings can be substantial. Kim et al. for example, found that triage to routine X-ray imaging versus

advanced imaging (CT or MRI) resulted in less use of the more costly advanced imaging. They found that although their program incurred $109,720 from additional consultations and X-rays, it saved over $2 million by avoiding advanced imaging. When the authors extrapolated the findings from their study site of Toronto Western hospital to the greater province of Ontario, they estimated an annual savings of $25 million by implementing a policy of routine initial X-ray use.[73]

Use of MRI also introduces other harms much more risky than low-dose radiation exposures—that are not actually harmful. For example, MRI often requires use of sedation for children, seniors and others who cannot lie still. Performing MRI exams often requires Gadolinium, a contrast agent that is toxic and can adversely affect some patients, particularly those with kidney issues. These examples illustrate potential real risks that are definitively more harmful than the imagined risks hypothetically attributed to low-dose radiation exposures. Regarding infants, there is consensus that anaesthetic medications may cause neurological injury. Jevtovic-Todorovic et al. found that infants undergoing sedation had developmental delay or behavioral problems up to 4 times greater than a control group.[74]

Newer "micro-dose" radiological imaging techniques are being developed. This includes the slot-scanning device or slit-beam digital radiography system (EOS Imaging®, Paris, France) which is an x-ray technology that allows simultaneous acquisition of coronal and lateral images of the entire body in a natural, erect position, and is also capable of performing three-dimensional reconstructions from these images.[75] It is primarily used in the evaluation of scoliosis, but can be used for any spinal condition to assess spinopelvic biomechanical parameters such as sagittal and coronal balance. This technology is not yet widely available, is expensive and has not been shown to be cost-effective;[76] due to these reasons it is doubtful it will replace traditional radiography.[42] The pursuit of this type of technology, however useful, should not be for reasons of "less radiation exposure,"[75] but for the technological superiority for biomechanical analysis.

Enthusiastic Endorsement for Informing Patients of Carcinogenic Risks

LNT supporters disseminating doom and gloom projections of the "public health time bomb" of future cancers from medical imaging enthusiastically endorse full disclosure for informing the patient of the dangers of radiation exposures of medically warranted and often life-saving medical imaging.[77]

There is nothing wrong with informed consent; however, how is one to discuss (supposed) risks from medical imaging when it is a highly debated issue and when there is not only a lack of sufficient evidence of harm, but evidence of no harm, and moreover, evidence of benefits (beyond the benefits due to diagnostics)? The fact is doctors are not taught about the biphasic dose-response model that more accurately describes radiation effects versus the traditional LNT model that now many consider defunct as applied to low-doses as from X-rays and CT scans.[34,36,37,41,42,57,60-62,78,79] Cuttler states "Physicians are not taught the experience of the last 120 years that low doses of radiation stimulate the protection systems, including the immune system, which involve more than 150 genes."[57]

There are serious issues related to communicating hypothetical risks about radiological imaging to patients. First, the doctor is not adequately trained in having this dialogue. Second, it is argued that it may be inconceivable for a patient to understand this complex topic.[19] Third, when informed of cancer risks from medical imaging, many patients may raise concerns and even refuse consent.[13,14,30] This increased resistance caused by the doctor initiating questionable dialogue obviously results in constraining practice and for this reason patient resistance to receive radiological imaging has been termed a front-line health worker "crisis."[34]

Ironically, as discussed by Harvey et al. true informed consent over X-rays is circuitous. They state "To be truthful and not misleading—fundamental principles of informed consent—a practitioner would have to state that there is an unproved possibility that the CT study could increase the risk for cancer and then state that there is an unproved possibility that it may not affect, or may even decrease, the risk for cancer."[80] The fact is, real informed consent is not truly achievable relative to the low-dose radiation exposures from medical imaging.[81,82] Although Harvey et al.[80] makes the case for informed consent over radiological imaging to be circuitous, we contend that actually it is not, not because there is a lack of evidence suggesting X-rays are harmful, but because there is a large evidence-base showing low-dose radiation exposures are healthful (e.g. prevents cancers).[36-39,52-57,59,83]

Although there is a push for "shared decision-making" versus traditional informed consent,[81,82] involving the patient in the decision process over warranted medical imaging will continue to constrain practice which the doctor has little time for. Due to the uncertainty around projecting hypothetical harms from X-rays there are also those who push for not disclosing radiation risks.[84] In the larger picture, and considering the evidence of the lack of harm and even increased health effects from low-doses, we argue that non-disclosure of hypothetical (i.e. imagined) risks are the most ethical and evidence-based approach that also frees physicians from difficult discussions they are not well trained for.

Succumbing to the Sunk-Cost Bias

Pandharipande et al. conducted a survey of 578 radiologists about imaging decisions based on knowledge of patient exposure histories.[85] They found that 92% of the respondents would incorporate a patient's past radiation exposure history (e.g. number of CT scans experienced) into the decision process for ordering a current radiological exam and the author's suggested that this may "lead to undesirable effects on decision making regarding the use of imaging."[85] This is alarming and shows that those in charge of medical management succumb to the "sunk-cost bias."

The sunk-cost bias is a human tendency to want to mitigate or make up for past events, in this case past X-rays and CT

scans, by altering future actions (e.g. not taking an X-ray).[86] Eisenberg et al.[87] illustrated how it is easy to fall prey to the sunk-cost bias by describing 2 patients, A and B. Both patients are male and 35 years of age, and report to the emergency with possible appendicitis. Patient A is otherwise healthy with no past X-rays. Patient B has a history of testicular cancer and has received 20 past abdominopelvic CT scans for cancer treatment and surveillance. When weighing the risks and benefits it is an easy decision to order a CT for patient A, but much more difficult to justify ordering a CT for patient B.[36] In reality sunk costs (previous X-rays) should not influence the calculation of future risks or benefits and therefore, "performing CT in patient A but not patient B is illogical."[87] Thus, falling prey to the sunk-cost is a bias stemming from the falsehood of LNT ideology.

There have been movements to sync patient exposure histories as a part of image ordering software.[88,89] Although arming the physician with a more accurate knowledge of a patient's exposure history, this would exacerbate considerations of risks, and would skew clinical judgement towards succumbing to the sunk-cost bias. In reality, integrated patient exposure histories should play no part in current practice of considering X-ray/CT exams; it should always be based on the clinical scenario, the best evidence, the clinician experience and the patient needs.

Conclusions

We have shown that radiation reduction campaigns, advocating lower-dose techniques and practices, using alternative imaging, endorsing full informed consent and falling prey to the sunk-cost bias are all potentially harmful. These efforts do not necessarily reduce patient radiation exposures as intended by LNT advocates, but deprives the patient of radiation doses that could enhance their health, not compromise it. Many of these efforts actually cause harms by unintended consequences such as presenting a new risk (e.g. sedation for MRI) that may introduce real harms not just hypothetical harms. All these efforts cost greatly and do not accomplish their intended purpose of decreasing future cancers since X-rays and CT scans cannot cause cancers as they prevent them.

Although the typical contemplation in choosing to take a radiologic medical image is the weighing of the benefit-to-risk trade-off, as in "does the benefits of the exam outweigh the risk of the exam?" (risk referring to assumed carcinogenic risks), we argue that this traditional risk trade-off notion is false. Since low-dose ionizing radiation enhances health, there is no benefit-to-risk trade-off from the traditional LNT standpoint. The only realistic trade-off is whether the image is worth the investment of resources sacrificed to take the image (e.g. costs).

Once the best evidence that was used to support LNT ideology, the Life Span Study data, now indicates that thresholds for cancer induction are quite high (Figures 1; 2), and that exposures to low-dose X-rays do not cause harm. Current practices are safe as exposures currently encountered are on orders of magnitude below threshold levels that have been shown to be harmful. We have shown efforts to reduce exposures that are within background radiation levels that are also shown to enhance health by upregulating natural adaptive protection systems are definitively wasted resources. In the modern evidence-based era, these fruitless radiation reduction efforts need to stop as they are neither evidence-based nor effective, but do constrain practice and cause harm.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: P.A.O. is a paid research consultant for CBP NonProfit, Inc.; D.E.H. teaches spine rehabilitation methods and sells products to physicians for patient care that require radiography for biomechanical analysis.

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The significance of the failed historical foundation of linear non-threshold model for cancer risk assessment

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Abstract: The linear non-threshold (LNT) single-hit (SH) dose response model for cancer risk assessment is assessed with respect to its historical foundations. This paper examines and summarises how mistakes, ideological biases, and scientific misconduct by key scientists affected the acceptance, validity, and application of the LNT single-hit model for cancer risk assessment. This analysis concludes that the LNT single-hit model was inappropriately adopted for governmental risk assessment, regulatory policy and practices, and for risk communication.

Keywords: dose response; linear dose response; cancer risk assessment; mutation; history of science; threshold dose response; Manhattan Project; National Academy of Sciences.

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Biographical notes: Edward J. Calabrese is a professor of toxicology within the School of Public Health at the University of Massachusetts at Amherst. He has published over 900 articles in the peer-reviewed literature. Over the past 30 years he has investigated in depth the nature of the dose response in the low dose zone, with the overall findings supporting the conclusion that the hormetic-biphasic dose response is fundamental to biology with widespread public health and medical applications. This long-standing interest in hormesis lead him to explore in considerable depth the historical foundations of the LNT dose response model resulting in major new revelations that are summarised in this issue of the journal.

This paper is a revised version of a paper entitled 'The historical foundations of the linear non-threshold dose response model for cancer risk assessment' presented at the 'XVIII PTBR National Meeting Satellite Symposium. Applications of low radiation doses in medical diagnosis and therapy', Jan Kochanowski University, Institute of Chemistry, Kielce, Poland, 17 September 2019.

The LNT model for cancer risk assessment emerged from the firm belief and assertion of the U.S. radiation genetics community of the 1930–1970s period (Calabrese, 2019a). This community built their beliefs on the conclusion of Muller (1927) that the induced transgenerational phenotypic changes in *Drosophila* via the use of high doses of X-rays he produced in his Nobel Prize research were due to gene mutation. Following the subsequent research of two students who showed that X-rays induced similar 'gene' mutations in a linear fashion, but also at very high doses, Muller claimed the existence of the Proportionality Rule, asserting that the dose response for X-ray induced gene mutation was linear down to a single ionisation (Calabrese, 2017c, 2019a). Some five years later a team of prominent physicists and radiation geneticists integrated target theory with Muller's findings, creating the single-hit LNT model, providing a mechanism for the LNT model/Proportionality Rule (Timofeeff-Ressovsky et al., 1935). These actions would culminate in the recommendation of the U.S. National Academy of Sciences, Biological Effects of Atomic Radiation I (NAS BEAR I), Genetics Panel recommendation, some two decades later, of a switch from a threshold dose response to the LNT model based on the radiation geneticist mantra that all induced gene mutations were cumulative, non-repairable, irreversible, and displayed a linear dose response (Anonymous, 1956). This recommendation inspired the National Committee on Radiation Protection and Measurements (NCRPM) (1960) to generalise this recommendation for germ cells to somatic cells two years later, applying it to cancer risk assessment. It was this sequence of events that propelled the LNT cancer risk assessment model into the public health arena, transforming the fields of environmental health, food safety, radiation health, and occupational health.

The 1956 NAS BEAR I Genetics Panel recommendation was embraced by the Biological Effects of Ionising Radiation (BEIR) 1972 Committee, which based their LNT belief on mega-mouse studies of William Russell at Oak Ridge National Laboratory. The BEIR 1972 Committee was officially charged with offering guidance/recommendations to the fledgling United States Environmental Protection Agency (U.S. EPA) which was created in 1970. In 1975, U.S. EPA adopted the U.S. BEIR LNT recommendation, noting that it was based on the research of Russell. The findings of Russell provided a beacon of scientific reliability as it was founded on such a massive amount of data derived from nearly two million mice and had a mechanistic basis (Calabrese, 2017a, 2017b). This scientific foundation of Russell was acknowledged by EPA as critical since the capacity of epidemiological research to clarify the nature of the dose response in the low dose zone is limited, not being able to adequately detect and resolve radiation risks below 100 mSv due to numerous methodological problems, uncertainties and variations in risk factors within human populations.

The 'acceptance' of LNT therefore was based on the findings and intellectual leadership of Muller and the radiation geneticist research community along with a transition to a mammalian model based on the Russell findings. The epidemiological literature was consistent with the LNT model at high doses but could not resolve the central issue of the nature of the dose response at low doses. This has been the LNT cancer risk assessment foundation for the past nearly half century. In fact, the NCRPM (1960) acknowledged that the LNT cancer risk assessment model was not based on a sound scientific foundation in contrast to the assertive position of the BEAR I Genetics Panel (Calabrese, 2019a). The NCRPM (1960) acknowledged that there are unresolved

uncertainties at low dose, basing their LNT recommendation/endorsement on their version of the 'Precautionary Principle'. This uncertainty was also clearly asserted by the BEAR 1960 Genetics and Medical Panels in separate statements. Yet, when the EPA (see Calabrese, 2017b, 2019a) adopted the LNT from the BEIR (1972) committee, the BEIR (1972) report only recounted the unequivocal recommendation of the BEAR I Genetics Panel (1956) (Calabrese, 2019b), ignoring the uncertainty statements of the NCRPM and the two BEAR 1960 Panels.

Thus, the fledgling EPA, without acknowledging the scientific weaknesses of the LNT model, moved forward with bureaucratic certainty, applying the LNT for ionising radiation and chemical carcinogens, giving the public false impressions of precise cancer estimates such as a dose causing a risk of $1/10^6$, that could never be studied nor verified.

Over the past ten years numerous papers have revealed many previously unknown details of the Muller-BEAR I and II and BEIR I era. These revelations have shown that:

- Muller (1927) did not induce gene mutations in his 1927 major paper – but principally modest to mostly massive gene deletions (Calabrese, 2017c).
- The single-hit LNT model was based on the false assumption of gene mutations induced by ionising radiation at high doses (Calabrese, 2017c).
- The Manhattan Project genetics research at the University of Rochester with the leadership of Curt Stern has now been shown to have been presented in a deliberately deceptive manner to support LNT (Calabrese, 2011a, 2012).
- Muller was deceptive in his Nobel Prize lecture, asserting that the threshold concept had no scientific standing and should be replaced by LNT, knowing all the while, that the Caspari and Stern (1948) study at the University of Rochester supported a threshold (Calabrese, 2011b). The new gold standard of BEIR I (1972) that was based on the massive experiments of William Russell was challenged Paul Selby who found major errors some 20 years later in Russell's control group, forcing the Russells to increase its control group mutation value by 120% changing the linear estimate to a threshold response (Calabrese, 2017a, b).

The point of this LNT recapitulation is to raise the philosophical, yet practical question, of what happens to a science hypothesis that becomes the basis for national and international regulation when its scientific basis is no longer reliable? Yet, the scientific culture, all the way from study design, to testing, to biostatistical modelling, to cost-benefit and the overwhelming precautionary principle concerns, were based on false certitudes that created a broad and deep series of societal actions.

The question arises concerning what to think and do when the basis of a fundamental societal scientific belief becomes discredited. How should society continue to think about the issue of cancer risk assessment in light of these current developments? A simple common sense solution, that is, that lower exposure almost always makes sense, is type of personalised precautionary principle. This approach is the equivalent of choosing caution over risk taking. While this may appear to be good advice for members of the general public, what posture should regulatory agencies take? In today's world, such agencies should strive for greater transparency. They should share with the public what these new revelations concerning cancer risk assessment are and mean for regulatory

agencies, the public health, the risk communication message for the media, school systems and the public. To date, regulatory agencies appear to have ignored these scientific developments and have seemingly doubled down on their assertions to support LNT, holding to a belief without a credible history and scientific foundation. While this position may seem to work, in the end, it can't. Why? The challenge will be factual. The EPA adopted the LNT in the mid-1970s, applying it to all sorts of regulations, claiming that 80% of human cancers were related to environment. Now 50 years later, with numerous strict and enforceable standards for carcinogens long in place, such regulations have not affected the tumour incidence (Calabrese, 2019c). Thus, after such a long period of time and with trillions of dollars spent to reduce such risks, the EPA actions have been a dismal public health failure. EPA's predictive models and other methods of assessment have been in serious error. This development calls for a serious re-evaluation of the nature of the cancer risk assessment process, with the goal of deriving regulations that are finally based on sound science and a proper understanding of the cancer causation.

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