Arch Toxicol (2009) 83:203–225
DOI 10.1007/s00204-009-0412-4

REVIEW ARTICLE

The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment

Edward J. Calabrese

Received: 9 February 2009 / Accepted: 9 February 2009 / Published online: 27 February 2009

Abstract This article assesses the historical foundations of how linearity at low dose became accepted by the scientific/regulatory communities. While the threshold model was used in the 1920s/1930s in establishing radiation health standards, its foundations were challenged by the genetics community who argued that radiation induced mutations in reproductive cells followed a linear response, were cumulative and deleterious. Scientific foundations of linearity for gonadal mutations were based on non-conclusive evidence as well as not being conducted at low doses. Following years of debate, leaders in the genetics community participated in the U.S. National Academy of Sciences (NAS) (1956) Biological Effects of Atomic Radiation (BEAR) BEAR I Committee, getting their perspectives accepted, incorporating linearity for radiation-induced mutational effects in risk assessment. Overtime the concept of linearity was generalized to include somatic effects induced by radiation based on a protectionist philosophy. This affected the course of radiation-induced and later chemically-induced carcinogen risk assessment. Acceptance of linearity at low dose from chemical carcinogens was strongly influenced by the NAS Safe Drinking Water Committee report of 1977 which provided the critical guidance to the U.S. EPA to adopt linear at low dose modeling for risk assessment for chemical carcinogens with little supportive data, much of which has been either discredited or seriously weakened over the past 3 decades. Nonetheless, there has been little practical change of regulatory policy concerning carcinogen risk assessment. These observations suggest that while scientific disciplines are self correcting, that regulatory 'science' fails to display the same self-correcting mechanism despite contradictory data.

Keywords Threshold · Dose response · Risk assessment · Carcinogen · Mutagen · Mutation · Linearity · Somatic mutation hypothesis

E. J. Calabrese (✉)
Environmental Health Sciences Division,
Department of Public Health, University of Massachusetts,
Morrill I, N344, Amherst, MA 01003, USA
e-mail: edwardc@schoolph.umass.edu

Part 1: Fear of radiation-induced mutagenicity lead to linearity at low doses in risk assessment

Introduction

The acceptance of linearity at low dose for carcinogen risk assessment is the most significant risk assessment policy decision of the past century. It has had far reaching political, economic, technological and public health implications. Given the significance of this risk assessment policy, it is important to assess the historical foundations of the linearity at low dose concept and how it became accepted by the scientific community and integrated into government regulatory polices for radiation and chemical carcinogens.

Part 1 of this article will demonstrate that the linearity at low dose concept was principally developed by geneticists following the discovery of X-ray induce mutations in Drosophia by Hermann J. Muller in 1927. While the data supporting the linearity concept during this period of concept consolidation will be shown to be very limited, non-conclusive and not even remotely close to what we might call a low dose today, key researchers in the genetics community accepted this concept to be true and used it to generate concerns that exposure to radiation in medical products and atomic bomb fall-out would likely have devastating consequences on the human population. This paper is an assessment

of how this process originated and how it affected the assessment of radiation induced cancer. It will provide an evaluation of the historical foundations of radiation health standards under the leadership of the National Committee for Radiation Protection and Measurements (NCRPM) and its predecessor organization, the American X-ray and Radiation Protection Committee, with particular emphasis on the concept of the tolerance dose and its etymological offspring, the permissible dose. Within this context an assessment is provided as to how the concept of radiation-induced genetic injury was considered in the occupational health standard setting process in the time framework before and after World War II. The paper will then assess how the concern over radioactive fall-out trumped most earlier discussions of mutation and radiation health standards, making it a very high political and scientific national priority. It was within this new public crucible that the debate over low dose linearity occurred with its eventual acceptance. Part 2 of this paper assesses how the concept of linearity at low dose for chemical carcinogens became accepted into government policy and risk assessment practices. Broad and in depth evaluations of the historical foundations of the dose response relationship for chemicals and radiation have been previously published but have not focused on mutagencity (Calabrese 2004, 2005a, b, 2008; Calabrese and Baldwin 2000a, b, c, d, e).

Historical foundations of radiation health standards: before the tolerance dose

The International Committee on X-Ray and Radium Protection was established by the Second International Congress of Radiology in 1928 to advise physicians on radiation safety measures, within a non-regulatory framework. The first International Congress of Radiology met in 1925 with the goal of re-establishing lines of communication between opposing countries during World War I. Each country was to send a representative who would promote the recommendations of the International Committee in their home countries. The U.S. Bureau of Standards was asked to provide this representative, selecting Lauriston Taylor, an assistant physicist in the X-ray section of the Bureau. The leadership of the Bureau of Standards in this area would later become a political issue within the U.S. government in the 1950s, leading President Eisenhower to create the Federal Radiation Council, an organization with more direct accountability than a voluntary organization operating under the aegis of the Bureau of Standards without any legal authority over its actions and products. After the International Congress in 1928 Taylor established a national committee on radiation protection. This U.S. committee was to contribute to the international development of radiation protection standards and activities and to advance them within the U.S. Despite the fact that Taylor was a federal employee the committee was considered non-governmental and advisory to government and industry. The group was called the American X-ray and Radium Protection Committee, with the name changing two decades later following World War II to the NCRPM. Membership was based on having representatives from various relevant national organizations, consistent with the practice of the International Congress. The first full meeting of this national Committee was held on 18 September 1929. The first report of this committee was published in 1931, recommending various safety procedures and exposure monitoring activities for those who work with X-rays, such as the periodic wearing of a dental X-ray film for the qualitative estimation of exposure and the need for complete blood counts. This report did not contain an exposure standard such as the roentgen unit, but rather standards were achieved in terms of lead-equivalent insulation. Committee activities were subsequently directed toward developing a set of recommendations for working with radium within medical settings (Taylor 1971; Whittemore 1986).

When the tolerance dose concept was king

Within the context of the radium evaluation the committee determined that the best indicators of radiation effects were skin changes within the tips of the fingers, with a reddening and shiny appearance of the skin around the fingernails. An exposure of 600 r was commonly accepted as the average erythema dose, that dose producing a reddening of the skin. The number 600 r was derived from a 1927 poll of radiotherapists who gave an average erythema dose of 550 r, which was then rounded up to 600 r in order to account for background scatter radiation (Jolly 2003).

The concept of a tolerance dose was initially proposed in the U.S. by Mutscheller (1925), advocating a value of 1/100 of the erythema dose in 30 days; it was used as a means to calibrate the amount of lead shielding needed. Despite the concept of a tolerance dose, Mutscheller argued that there was no safe dose to radiation but that safety had to be weighed against the costs to achieve it. In effect, he sought a type of equilibrium in which there would be a dose to which the worker could be exposed without noticeable harm. In a practical sense a tolerance dose specifying the maximum tolerable exposure could set the minimal protection needed, thereby providing a limit on the shielding an employer would have to provide. The tolerance dose concept would go on to provide the foundation for future radiation safety standards (Taylor 1971; Whittemore 1986).

Other researchers also presented similar data during this time period (Sievert 1925; Barclay and Cox 1928). Each of the groups selected a different time interval to describe the tolerance dose. However, when normalized the derived

tolerance doses were quite similar. The derivation of the tolerance dose utilized the concept of a "safety" factor to reduce exposure via a fixed fraction below the estimated minimal toxic level.

The International Committee for Radiation Protection (ICRP) recommended a tolerance dose for occupational radiation exposure, which was officially adopted at the Stockholm Congress of 1928. This ICRP standard, which was based on Mutscheller's safety factor of 1/100 of an erythema dose, remained the principal foundation for international and U.S. prewar radiation standards (Jolly 2003). No specific numerical standard was established for exposure but guidance was provided for calculating the thickness of lead shielding used in X-ray production.

The first report on radiation standards published by the NCRPM was in 1931 and designated as the National Bureau of Standards Handbook 15. The report was principally based on the 1928 ICRP recommendations. It contained shielding tables but no tolerance dose/exposure standard. By 1934, when the NCRPM issued its second report (NBS Handbook 18) several important new developments occurred. Most notably, this report offered a specific radiation exposure standard, in effect, the first attempt to develop an explicit tolerance dose (Whittemore 1986). This effort was lead by Professor G. Failla who developed data at Columbia University Medical School on occupational radium exposures that could be safely tolerated, using skin and blood changes as biological markers. The findings indicated that 0.6 r/month would be a safe dose. This exposure rate was one-thousandth of the 600 r value, and was believed by Failla to be a dose to which workers could be continuously exposed for a number of years without safety concerns, especially since it had a tenfold larger safety factor than the Mutscheller recommendation. This information, which was provided to the Committee in 1932, was based on the belief that there is a balance between injury and tissue repair (Whittemore 1986). The assumption of an equilibrium between injury and repair suggested that there was a biological threshold of radiation which could be safely absorbed/administered for an indefinite time. Even though the Committee accepted the basic clinical findings of Failla and the safety factor concept, they settled on a higher tolerance dose, that is, use of a lower safety factor. The report stated that a safe whole body exposure is 0.1 r/day for hard X-rays, and could be used to guide radium protection practices. The dose of 0.1 r/day was the result of a somewhat crudely conservative rounding down of the figure based on the work of Mutscheller nearly a decade earlier (Jolly 2003).

In the time between when the radium report was finalized and when it was printed, the Committee adopted the concept of a "tolerance dose", it being the first major concept change in the Committee's approach to radiation safety. In fact, the adoption of a tolerance dose of 0.1 r/day for X-rays and gamma rays was inserted into the preface (Whittemore 1986). The 0.1 r/day rate was proposed since it was consistent with other national values such as Germany (Taylor 1971).

In the U.S., the Committee was using the term tolerance dose in correspondence and discussion but up to 1933 it had not been used in any formal reports (Whittemore 1986). However, the tolerance dose was adopted in 1933 but it was not widely seen until the publication of a revised handbook 3 years later, the delay being related to the unfunded nature of the voluntary activity of the Committee. According to Whittemore (1986), the underlying assumption of the tolerance dose was that ionization was proportional to biological effect. The Committee archives indicate that their concept of tolerance dose was one in which any harm that might occur from exposures below the tolerance level was acceptable (i.e. tolerable), and not that such effects were nonexistent. Nonetheless, the use of a specific numerical limit was frequently interpreted to mean that there was a threshold of radiation exposure below which no harm occurred, even though the tolerance dose did not equal threshold dose in the view of the Committee. While the respective publications on X-ray and radium protection marked the completion of the specific goals for which the Committee was originally formed, it did not disband but continued to respond to questions from the public and government (Whittemore 1986).

Radiation-induced mutation: the key discovery for the eventual acceptance of low dose linearity

The concept of low dose linearity for radiation-induced mutations developed relatively soon after the report by Muller (1927) in *Science* that X-ray treatment profoundly increased the occurrence of sex-linked mutations in *Drosophila*. Follow up studies were published by several investigators (i.e. Hanson, Oliver) working under the direction of Muller and several others (e.g. Stadler). While it is generally believed that Muller did not adequately address the concept of the dose response in his initial work, a closer look reveals that he did consider the issue. In his historic study Muller initially experimented with the heterozygous sc v f × bb strain of *Drosophila* females and homozygous sc v f males. In this experiment dose was based on the differing time periods (12, 24, 36, 48 min) during which the flies were exposed to X-rays. Doses resulting from 36 to 48 min duration were generally high enough to cause sterility in a high percentage (70–80%) of the males. While there was only one mutant observed at the lowest dose, the mutation rate markedly increased at the next highest dose and continued to progressively increase with the duration of exposure. While Muller did not replicate this experiment,

he re-ran the same experimental concept this time using his C1B technique which was more sensitive than the other model. In this second experiment, he opted to use only the 24 and 48 min exposure durations/doses. Based on the data presented, a non-linear dose response occurred in his first experiment with the four doses whereas there was little capacity to assess dose response with only two doses in the second experiment; in this case there was a dose response proportionality seen for the two doses but it also was not linear with Muller characterizing the increase a being close to the $\sqrt{2}$ rather than a doubling (twofold increase) (Muller 1928). Thus, in the 1927 and 1928 papers Muller did not claim a direct linear relationship but rather a curvilinear one that was yielding a relationship that was most likely a response being related to the square root of the X-ray energy absorbed. Muller (1927) went on to discuss some biological implications of the lack of a linear relationship. He then emphasized the need for additional research to assess the nature of the dose response for a wide range of doses.

Muller encouraged Oliver and Hanson, who were working in his laboratory, to follow up on the dose response question. In the case of Oliver he extended the doses to five and explored a lower dose range, including 3.5, 7.0, 14 min., 28 and 56 min (Oliver 1930, 1931). At the lowest dose tested, the occurrence of mutant lethals was 5.7-fold greater than the control values. Nonetheless, there was a generally linear response across the range of doses studied. The lowest dose tested was still quite high, being the equivalent of 275 r. These findings, which were obtained using the C1B method, were not fully consistent with the earlier C1B experimental data of Muller but more substantial, having explored a lower dose range.

In the case of Hanson the research used the C1B method with exposure to radium. In several studies Hanson did the equivalent of a dose times time ($D \times T$) experiment and found a constant outcome, supporting what he called a proportionality function. In several cases a "dose response" was explored to a limited extent via the use of two doses. In each case a linear appearing relationship occurred (Hanson and Heys 1929). In one case using radium a large number of doses were employed with a generally linear relationship being exhibited. However, even at low dose the absolute exposure levels were quite high. Other researchers have also explored the dosage issue in the years immediately after the 1927 report of Muller. Weinstein (1928), using the same methods of Muller and his C1B strain, did not show a proportionality response using two doses (24 and 48 min). In the case of Stadler (1930) with barley seed germination he claimed a linear dose response using with X-rays. This study, which used 15 doses of X-rays over a 15-fold dose range (2–30 min exposures), failed to show the linearity at the low doses. The findings would be more supportive of a threshold. The author acknowledged this observation but discounted it because "in other experiments with low dosage mutations have been found". However, no data were presented or reference cited that would permit an evaluation of this statement.

In the case of studies that addressed the shape of the dose response, the issue was not experimentally resolved by the early 1930s. The fact is that Muller's landmark papers did not support this relationship; this was also the case for the follow up studies by Weinstein and Stadler, who employed a 15 dose study. The strongest study supporting linearity was by Oliver (1930) using 5 doses. This was a stronger study than that of Weinstein but can not be directly compared to the first Muller experiment with a different fly model and the work of Stadler with plants. Even in the case of the Oliver study the lowest dose tested was very high (i.e. 275 r). Other research showing a $D \times T$ equals a constant response was not designed to test the nature of the dose response but dose equivalency, yet it was used to imply support for the linear interpretation. Despite such limited data and lack of overall consistent findings (Table 1) Muller nonetheless surprisingly and incorrectly firmly concluded that mutation frequency "is exactly proportional to the energy of the dosage absorbed. There is, then, no trace of a critical or threshold dosage beneath which the treatment is too dilute to work" (Muller 1930). According to his biographer Elof Carlson (1981), Muller maintained this same perspective nearly a decade later in this report to the Medical Research Council of Great Britain. Yet one has to wonder what Muller actually believed based on a letter to Robley Evans, an MIT professor criticizing the low dose linearity hypothesis. In his letter to Evans in 1949, Muller stated that "many of the quantities are only very roughly known even for *Drosophila*, and we are admittedly extrapolating too far in applying this to man, but it is all we can do in our present state of ignorance and we must meanwhile remain on the safe side." Such a comment strongly suggests that Muller was guided more by a precautionary public health philosophy rather than the science with respect to the extrapolation of his findings for various types of extrapolations including across species and from high to low dose. It is interesting to note that in his book on the history of genetics, Sturtevant (1965) also supported the linearity interpretation of Muller citing the research of Oliver, Standler and Hanson/Feys, neglecting the even stronger evidence of a lack of linearity and failing to address the extremely high doses used by these early investigators.

While the genetics community was nearly unanimous in their belief of low dose linearity for genetic injury, Singleton of the Brookhaven National Laboratory was one who questioned the linearity hypothesis. He reported a non-linear relationship between mutation rate and dose rate, with

Table 1 Dose response mutagenicity data at the time of linearity concept consolidation (Circa 1927–1934)

Reference		# Doses		
Supportive of linearity				
Oliver (1930)	*Drosophila*	5 doses	X-ray	Lowest dose 275 r
Hanson and Heys (1932)	*Drosophila*	2 doses	Radium	Lowest dose 6,315 r
Hanson et al. (1931)	*Drosophila*	13 doses	X-ray	Lowest dose 445 r
Timofeeff-Ressovsky et al. (1935)	*Drosophila*	5 doses	X-ray	Lowest dose 1,400 r
Timofeeff-Ressovsky et al. (1935)	*Drosophila*	5 doses	X-ray	Lowest dose 1,400 r
Not supportive of linearity				
Muller (1927, 1928) (Exp 1)	*Drosophila*	4 doses	X-ray	
Muller (1927, 1928) (Exp 2)	*Drosophila*	2 doses	X-ray	
Weinstein (1928)	*Drosophila*	2 doses	X-ray	
Hanson (1928)	*Drosophila*	2 doses	X-ray	
Hanson and Heys (1929)	*Drosophila*	2 doses	X-ray	
Stadler (1930)	Barley	15 doses	X-ray	
Serebrousky and Dubinin (1930)	*Drosophila*	3 doses	X-ray	

disproportional increases at higher doses. These data suggested the need for more than one ionization to produce a detectable effect (i.e. mutation), thus challenging the linearity at low dose concept (Singleton 1954a, b; Richter and Singleton 1955). In fact, 17 April 1955 an article in the New York Times provided the opportunity to challenge the warning of Sturtevant concerning genetic damage. Singleton stated that "there probably is a safe level of radiation, below which no genetic changes occur." According to Jolly (2003), the findings of Singleton, a well accomplished genetic researcher, were generally ignored because they were in conflict with the dominant intellectual paradigm of low dose linearity.

From tolerance to permissible dose: incorporating genetic hazards into risk assessment

In 1932, Failla prepared a memorandum to the committee in which he referred to Muller's (1927) historic paper which demonstrated that X-rays induced mutations in fruit flies. Despite the fact that X-rays were shown to cause mutations at high doses, Failla did not respond to the mutation data with particular concern at this time, suggesting low doses radiation may even be essential for life. In contrast, an unnamed committee member wrote to Taylor in 1935 suggesting a reduction in the tolerance dose from 0.1 to 0.05 r/day, based on acceptance of the cumulative nature of radiation induced genetic effects received over a very long period of time. It was thought that this letter may have come from Newell who made this identical suggestion to the committee in 1940 (Whittemore 1986).

The findings that were discussed related to the effects of X-rays on fruit flies and their extrapolation to humans. However, there was no clear consensus on how to use this new information. At the December 1938 meeting of the Committee, it was proposed to amend the paragraph on tolerance dose to read "The generally accepted tolerance dosage is taken as 10^{-5} r/s for 7 h a day. Geneticists pointed out that because of the cumulative effect of X-rays the tolerance dose should not exceed 10^{-6} r/s (Whittemore 1986, see footnote 300)". The committee then suggested several practical ways in which this change in tolerance dose could be achieved via workplace and engineering modifications. By December 1940, the proposal was modified to where there was now sufficient agreement that it could be brought to the entire Committee. The minutes of that meeting reveal that Newell made the proposal to change the tolerance dose to the 10^{-6} r/s. The committee wrote that "it was decided to include a paragraph explaining the reason for the lower tolerance dose, pointing out that under the old concept we were concerned only with injury to the bone marrow, whereas today there is sufficient evidence for us to be concerned about genetic injuries" (Whittemore 1986, see footnote 305).

This recommended value became known and discussed before the formal publication of the official committee report, being cited in professional journals (Cowie and Scheele 1941) and generating letters to Taylor from representatives of interested professional societies, such as the Radium Society (Whittemore 1986). Despite the fact that the decision to support the change had been made at a meeting of the committee, a key member of the committee had not attended the meeting, being unaware of the change. Thus, in June 1941 Failla wrote to Taylor expressing his disapproval of the decision and the scientific and technical reasons supporting his position, including his view of the

implications of the Muller mutagenicity data. While Failla appreciated the logic of the decision to reduce the tolerance dose, he was opposed to lowering it for genetic reasons. He believed that the current tolerance dose provided adequate protection from genetic damage. He specifically wrote that: "To be sure, the smaller the dose the less the genetic damage but the possible damage from 0.1 r/day is so slight that one can just as well stop at this point" (Whittemore 1986, see footnote 320). Failla was not challenging a linear/non-threshold perspective but the practically of detection).

Failla was principally concerned with the likelihood that as soon as genetic hazards became the basis for setting the tolerance dose, there would be no logical or natural stopping point short of zero. He continued by stating that: "if we bring in the genetic criteria then there is no limit at all and 0.02 r/day is just as arbitrary as 0.1 r/day." (Whittemore 1986, footnote 321). Failla may have been motivated by the fact that he oversaw radium cancer treatment at Columbia University and he believed that the new proposal would seriously affect the capacity of such treatments to be continued. This is because the technician literally had to hold a vial of radium via tweezers adjacent to the location of the tumor for prolonged periods (Whittemore 1986).

Failla challenged the committee decision by demanding proof that radiation exposure at the tolerance dose caused genetic damage in people. He specifically stated that: "I should like to see that evidence members of the Committee have in support of the new tolerance dose. I do not know of anything in the published literature which warrants the change." (Whittemore 1986, see footnote 327). In so doing, Failla shifted the burden of proof in the debate. This issue came to a head in the 29 September 1941 meeting of the Committee in Cincinnati, Ohio. While there were many issues that related to the proposed change in the tolerance dose, including legal, administration and personnel, the scientific debate focused on the uncertainty of extrapolating from fruit flies to humans and the further uncertainty over possible genetic effects seen after several generations. As for the shape of the dose response, the members agreed that no natural threshold had yet been demonstrated for mutations. In fact, they believed that Muller's research suggested the possibility of there being no threshold. The committee acknowledged that it was possible that no dose was safe from genetic injury. However, this specific point was turned around to favor the Failla position. "With regard to the genetic effects of X-rays, it was agreed that genetic effects of some order are produced from any size dose, and therefore there is a valid question as to whether a further factor of 10 is vitally important from a genetic point of view." (Whittemore 1986, see footnote 371).

It was proposed that the Committee take cognizance of the fact that genetic injury has no threshold of safety, thus placing this type of injury in a class apart from those in which a safe dosage exists. This situation was agreeable to the Committee which accepted the perspective being offered by the genetics community, that no tolerance dose exists for radiation-induced mutation. The bottom line was that the Committee simply did not have the data to justify reducing the tolerance dose. Thus, the committee revised its decision, with Failla prevailing. However, as one might suspect, there was some concern that they would be viewed as ignoring Muller's warnings. So they decided to replace the term tolerance dose with a new concept called the maximum permissible dose. It was felt that the term tolerance dose was generally thought to be one which could be tolerated without any damage; this was not believed to be the case with genetic damage, which was assumed to be cumulative. The committee thought that a dose that could be "permitted" could still injure, but only to an "acceptable" degree. It was recommended therefore that in the future the term 'permissible dose' be employed. It was to be a term that was not necessarily completely safe but one that also considered practical features. Whether the public or professionals actually appreciated the important differences between a tolerance dose and a maximally permissible dose is not clear, but it was an important change for the committee. According to Whittemore (1986), the name change was principally cosmetic as it was generally believed that a quasi-governmental recommended exposure standard, what ever the name, was a "safe" level of exposure, even if this is not what the committee intended. It should be noted that even though the committee had decided to drop the term "tolerance dose" and refer only to "permissible dose", this change in terminology was not formally published. This failure to publish the change in terminology would lead to a new debate over such terminology concerns immediately following WWII.

Post World War II: genetic concerns becoming the driving factor

The Committee did not function during World War II but reconvened soon after, acquiring the name NCRPM. In late 1946, the NCRPM created two new subcommittees, one to develop a permissible dose for external radiation and the other to derive permissible doses for radioactive emitters within the body. While the Committee did not place a high priority on addressing concerns with genetic effects prior to the war, it did so in 1947 as it was pressured by a principal funding source, the U.S. Atomic Energy Commission (AEC), to take action. In fact, the AEC requested that the NCRPM add a geneticist to the committee, specially suggesting the recent Nobel Prize winner, Hermann Muller. According to Whittemore (1986), the long term political implications of an explicit consideration of genetic hazard were probably not appreciated in 1947 since exposure stan-

dards were occupational exposure limits, rather than public health standards.

In the 1947 draft report, Failla decided that the term tolerance dose should be replaced by the term permissible dose, thereby revisiting the pre-WWII position that had been agreed upon but never formalized and published in the open literature. He asserted that the tolerance dose concept was based on two questionable assumptions. The first being that the tolerance dose concept assumes the existence of a threshold dose below which no injury is caused by radiation (it is odd that he asserted this as nearly a decade before his NCRPM committee had a much more flexible toxicological interpretation of the Tolerance Dose concept as noted above.). The second assumption is that there is no accumulation of injury even after many years of exposure. That is, it assumes there is no cumulative effect. In fact, Failla noted that experiments with animal models revealed that "there is no threshold dose or recovery in the case of certain genetic changes induced by radiation." (Whittemore 1986, see footnote 245). This led him to conclude that 'it has been recognized for some years that the concepts of tolerance dose and tolerance dose rate should be abandoned." (Whittemore 1986, see footnote 246). Rejecting the threshold concept for genetic effects, Failla stated further that "it is sounder to assume that some damage may result from exposure to ionizing radiation no matter how low the single or daily dose may be" (Whittemore 1986, see footnote 247).

Failla believed that a change in terminology would represent a shift in toxicological assumptions: that is, the maximum permissible dose would indicate the likelihood of some, but presumably, negligible injury rather than the assumption of no injury which was inherently assumed with the tolerance dose concept. The term negligible injury (e.g. one adverse effect/illness per population unit per lifetime) was not defined. Taylor forwarded the report of Failla to the AEC, with the standard unchanged despite the change in terminology with no evidence that Muller ever reviewed this preliminary report despite his membership on the committee (Whittemore 1986). Thus, early in 1948 the NCRPM reaffirmed the current limit of 0.1 r/day, within the framework of a permissible dose rather than as a tolerance dose. Less than a year latter the dose would be decreased to 0.3 rem/week, a change that occurred as an agreement amongst the U.S., Canada and Great Britain (Taylor 1971). This was a change for which the NCRPM, while conceptually agreeing to, needed to develop a supportive scientific rationale. The justification of the change in exposure standard as occurred in 1948 would not be published for 6 years, with 1954 being the official year of its reporting. The delay in the finalization has been credited to a combination of institutional factors, intellectual disputes and personality conflicts (Whittemore 1986). Strange as it may seem, the change in standard, while not official for six years, was readily leaked and a widely adopted, thus taking pressure off the Committee for finalization. This process also clearly reflected the limitation of a voluntary activity with no public accountability.

As noted above the NCRPM had long been aware of the fact that radiation exposure had the potential to cause mutation. In fact, just prior to the war, the Committee had for a brief period lowered the tolerance dose for genetic reasons. However, the only record of this temporary lowering of the tolerance dose were articles published in 1941 (Cowie and Scheele 1941; Henshaw 1941). This was the recommended standard that was opposed by Failla and the committee later reversed. When the new committee "found" these articles in the early 1950s, it was remembered more as a "misprint", than evidence of a policy shift. But in the post war era there was a new focus on genetic effects with a desire by groups such as the AEC "to include representation of the genetic viewpoint." (Whittemore 1986, see footnote 258). This concern of the AEC originated within its Advisory Committee for Biology and Medicine principally because of the fact that the workforce would now be engaged for the foreseeable future in numerous activities involving exposure to radiation and the size of this workforce would be likely to markedly increase.

In the prolonged period between the development of the new exposure standard and publication of the official NCRPM report the key intellectual challenge dealt with how to address reproductive genetic hazards induced by radiation. There was essentially no disagreement on the shape of the dose response; it was assumed however to be linear, especially at low doses. How to extrapolate the findings in insects and other models in a quantitative manner to humans was a major problem. Catcheside (1946, 1948) of Great Britain claimed an extrapolation breakthrough and a way out of this predicament. He proposed the existence of an interspecies mutational constant for the rate of induced mutation per roentgen per individual gene when adjusted for differences in lifespan as expressed in terms of the spontaneous mutation rate per generation rather than per year. In so doing, he claimed that he could predict the rate of human mutation due to radiation based on data from experimental animal studies.

Prior to WWII the key biological receptor for the radiation exposure standard was the occupationally exposed individual and the occurrence of non-genetic somatic damage. The concern with genetic damage would re-orient attention to the population gene pool as the receptor. If this were the case then it was important to know not only the dose response but also the size of the exposed population. One could also assess the impact of an occupational standard on both the individual for non-genetic somatic damage and on the population gene pool. Based on Catcheside's analysis, a 50 r lifetime exposure for the entire population

would increase the mutation rate by 2% per generation. If only a relatively small proportion (~1%) of the population would have a radiation exposure approaching the occupation standard the mutation rate would increase by only about 0.2% in the first generation, a rate that could barely, if at all, be detected, thereby making it sound acceptable. Such reasoning created a framework within which the population gene pool could be reasonably protected by the current occupational exposure standard. This perspective lead Taylor (1971) to indicate that the new standard of 0.3 r/week is one that is safe for the individual and will not reveal any discernable impact on the population for many generations.

Despite these insightful intellectual vignettes, Failla's subcommittee could still not find consensus on the matter. This led him to create a subcommittee to his subcommittee, which was composed of two eminent geneticists, Curt Stern at the University of Rochester and Hermann Muller at the University of Indiana and Nobel Prize recipient. While the two geneticists proposed an exposure value for the whole population of reproductive age (5 r for the first 30 years), Failla required them to provide a written justification (Whittemore 1986). In fact, the first draft of Failla's subcommittee had been approved by Dr. Donald Charles, a geneticist at the University of Rochester. Yet this wasn't good enough as the AEC wanted the perspective and support of Muller, not only for his prominence but also because of his publically expressed health concerns. This document was never provided by Stern and Muller, leaving the Failla justification of 1954 without the key genetics piece. Even though the genetics subcommittee failed to offer their report, the NCRPM standard contained two parts, one based on the occupation exposure and then 0.1 of that level to protect the population gene pool, that is, limiting the damage to a certain percentage increase in mutation rate over generations.

An insight into why Muller and Stern may not have completed their assignment to Failla is revealed in their separate letters to Sturtevant (Jolly 2003). Muller's letter clearly reflects his frustration with the NCRPM and its reluctance to incorporate elements of genetic risk assessment into the recommendations for their permissible exposure. Similar concerns were expressed by Stern who wrote: "In the U.S. Bureau of Standards report Muller was willing to permit 20 or 30 r total dose for a population. I was shocked and wanted it down to about 3 r if applied to millions. The outcome was that the whole section on this topic was dropped."

The NCRPM position was soon overshadowed by the NAS/NRC publication of the Biological Effects of Atomic Radiation (BEAR) Report in 1956 which affirmed that genetic mutation needed to be viewed as a public health hazard. It also introduced the concept of linearity at low dose which they applied to mutations of reproductive cells. The BEAR I report assessed mutation risk by employing the concept of doubling dose (i.e., dose of radiation that doubled the background or spontaneous rate, assuming a linear relationship at low doses). It proposed a population-based exposure level of 10 r above background to the reproductive glands. This exposure level was the geometric mean of a value proposed by Muller (20 r) and Curt Stern (5 r). In the end, the BEAR Committee report formed the basis for future radiation protection policies. Their report provided the intellectual basis that lead to the adoption of non-threshold cancer risk assessment policies for both ionizing radiation and chemical carcinogens.

The BEAR I committee was born out of the fall-out controversy and the need for an authoritative scientific assessment that was independent of the financial and political influence of the AEC. Despite this fact the committee's recommendations were broad, affecting medical as well as environmental exposures to radiation. In many respects the BEAR I Committee provided relief and opportunity for some in the genetics community who had come to believe that genetic hazards were being broadly marginalized. Jolly (2003) claimed that the genetics community saw this as their opportunity to finally get around roadblocks placed by the AEC, some in the medical community and the NCRPM, as these groups tried to down play the radiation-mutation hazard. The committee would take liberties with their charge, aggressively asserting the fundamental importance of mutation as a public health issue, its linear dose response and the need to establish population and worker exposure standards that would minimize harmful impacts on the present and future generations. The committee created an attitude that finally radiation induced damage would be seen as linear, cumulative and deleterious and that new medical practices and exposures standards would be established to protect the public.

Low dose linearity for radiation-induced cancer

Even though he was not a cancer researcher Muller was very supportive of the somatic mutation hypothesis for cancer starting with his 1927 landmark paper. This interest in the linkage of mutation and cancer continued unabated as seen in his presentation at a 1937 conference in Paris in which he advocated the study of the relationship between genetic mutation and carcinogenesis, saying that "it is but a logical step" to conclude that carcinomas, sarcomas and leukemias are causally related to radiation induced mutation (Carlson 1981).

By the late 1950s the scientific and political dynamic had changed significantly because of concern associated with radioactive fallout. The major emerging issue was no longer principally genetic mutation but somatic injury, such

as cancer, especially due to exposure to strontium-90 which could be concentrated in bone. The debate had shifted to the shape of the dose response for cancer with the underlying mechanism of somatic mutation. Interest was now focused on the current generation rather than a perspective of many generations into an unclear future. The fundamental question arising from the fall-out issue galvanized into whether or not there was a threshold for biological effects from low dose exposures. The public debate over the public health implications of radiation fall-out could probably be said to have publically can started when Sturtevant, a professor of genetics at the California Institute of Technology and President of the Pacific Division of the AAAS, gave a presidential address in 1954 challenging a recent statement of AEC Secretary Admiral Strauss (1954) that current levels of radioactive fallout would not have a public health impact.

The Strauss position was based on the 13th semiannual report to Congress in 1953 in which the AEC stated that "no person has been exposed to a harmful amount of radiation from fallout. In general, radioactivity resulting from fallout has been many times below levels which could cause any injury to human beings, animals or crops, etc. Fall-out radioactivity is far below the level which could cause a detectable increase in mutations or inheritable variations" (Jolly 2003). After his presentation at the conference Sturtevant (1954) published a paper in the journal *Science* on the topic. A key conclusion was that the frequency of mutations was believed to be directly proportional to the dosage of radiation. Thus, lacking a threshold, the implication was clear that there could be no safe exposure and that Strauss was seriously incorrect and misleading the public.

It is ironic that the AEC report which provided the basis of the Strauss statement actually supported the linearity at low dose concept but argued that the level of fallout was too low to be biologically detectable. Thus, in principle the AEC and Sturtevant were in agreement but it nonetheless lead to a major confrontation. Furthermore, in another 1953 report the AEC explicitly suggested the LNT model for Sr-^{90} induced cancer. In this report they stated that the bone-retention and radioactive properties of Sr-^{90} make it a high carcinogenic hazard; they further indicated that a given amount of exposure above the threshold (which may be zero) fixed in the bone will result in an increase in the incidence of bone cancer (AEC-World Wide Effect of Atomic Weapons: Project Sunshine 1953, p.4 as cited in Jolly 2003, p. 154). Again there was a strong basis for agreement on fundamental principles between the AEC and the genetics community.

This visible challenge to the Secretary of the AEC by Sturtevant soon raised the public health concerns of fallout to a heightened level. Of particular note was the paper of future Nobel Prize winner E. B. Lewis, a geneticist who had received his Ph.D. under the direction of Sturtevant, in the journal *Science* who made a case of radiation induced leukemias as being a linear (and not threshold) at low doses. It may be also relevant to note that Lewis may have been first introduced to the linearity at low dose concept by Clarence P. Oliver at the University of Minnesota who started him in the late 1930s on his university research with *Drosophila*. About 7 years prior to this time Oliver had been a student of Muller, demonstrating a linear dose response for X-rays as noted above. In December, 1956, Muller wrote to the NAS BEAR Genetics panel concerning a draft of the Lewis paper. Muller noted that Lewis estimated the number of new cases of leukemia induced by fall-out worldwide by the year 2000 would be 80,000 (Jolly 2003). The cancer risk assessment aspect was an important new direction since the prior debates on low dose linearity dealt principally with reproductive genetic damage. The low dose linearity concept was strongly endorsed in an accompanying editorial in *Science* by its editor-in-chief (DuShane 1957) as seen in a quote from his paper:

> "Ed Lewis shows that there is a direct linear relationship between the dose of radiation and the occurrence of leukemia. Thanks to Lewis it is now possible to calculate –within narrow limits– how many deaths from leukemia will result in any population from any increase in fallout or other source of radiation. And for the individual it is possible to calculate the probability of death from leukemia as a result of any particular dose of radiation. We are approaching the point at which it will be possible to make the phrase 'calculated risk' for radiation mean something a good deal more precise than the 'best guess'. It is apparent that the atomic dice are loaded. The percentages are against us and we ought not to play unless we must assure other victories" (DuShane 1957)

Such a statement from the editor in Chief of *Science* was as significant as it was inappropriate, being, at best, a gross overstatement of the capacity to predict risks from ionizing radiation at low doses, and even possibly wrong. Yet such comments from the editor in Chief of such a prestigious journal strengthened the position of Lewis, considerably enhancing its likelihood of being broadly accepted within scientific and governmental domains as well as by the legislature, media and general public.

The Lewis paper was crucial in the public debate over low dose linearity as it quickly lead to a major story in *Life Magazine* (10 June 1957), becoming the object of an debate on the national TV program Meet The Press (May 26, 1957-interview of Admiral Lewis Strauss, Secretary of the Atomic Energy Commission) (Lipshitz 2005), and testifying at Congressional Hearings (3 June 1957) on the topic. It

Table 2 Criticisms of the Lewis (1957) key linearity paper concerning radiation and leukemia

Atomic bomb survivors and leukemia
The doses used by Lewis (1957) were believed to be very uncertain and likely highly biased. The survivors were placed into dosage groups based on distance from the hypocenter, with considerable possibility of misclassification (Court-Brown 1958a).
While Lewis (1957) reported a linear-dose response for leukemia, Mole (1958) reported that systemic errors in the estimation of dose are generally in the same direction, implying that the dose response is actually curvilinear rather than linear at low dose. In fact, such uncertainties in dose estimates at that time prevented most investigators from over-interpreting the findings.
The data used by Lewis was "grouped" together based on distance from the hypocenter as noted above. For example, all subjects greater than 1,500 m from the hypocenter were grouped together. However, later investigators broke this group up into three more groups—> 2,500, 2,000–2,500, and 1,500–2,000 m. Only the survivors in the higher exposure group (1,500–2,000 m) displayed leukemia. Yet by grouping all three together it supported his linearity at low dose relationship. Subsequent investigators raised the possibility of their being a threshold for the leukemia response. In fact, the data could have also fit an hormetic dose response model.
Ankylosing Spondylsis (AS)
Lewis (1957) presented evidence of a linear relationship for leukemia and X-ray treatment therapy in patients with AS and then extrapolated these findings to the general public. The doses used were all high especially as compared to diagnostic assessments. In fact, in only two patients were the doses to the bone marrow less than 470 r.
There were several criticisms of this approach. These include that an adequate control group was not available (Court-Brown 1958a). Thus, the spontaneous rate of AS patients to radiation-induced leukemia was assumed to be the same as healthy people. However, there are some reasons to think that this may not be the case and that their susceptibility to radiation induced leukemia may be different than the general population.
It is necessary to know whether the susceptibility of AS patients to radiation-induced leukemia is the same as healthy people. Inflamed connective tissue is generally viewed as being considerably more sensitive to radiation-induced sarcoma than is normal tissue (Glucksmann et al. 1957). It may also be true that the physiological state of the bone marrow of AS patients may affect the capacity of radiation to induce leukemia. While speculative, these concerns should have lead to more caution in the application of a dose response in AS to the healthy general population.
Court-Brown (1958a) made several key assumptions about the latent period and that dose fractionation would not affect the course of the disease. With these assumptions they derived a linear relationship of radiation exposure with leukemia. While Court-Brown (1958a) used this approach as a working model in their paper, a subsequent paper by Court-Brown (1958b), after reading criticisms of Picho (1958), amended their views indicating that while there was still a straight line relationship, it intercepted the dose axis not at the origin but it intercepted the dose axis at 100 r, supporting the threshold response (Lamerton 1958).
This was also the case concerning leukemia and thymic enlargement in which X-ray exposure enhanced the risk of the disease. For example, Lewis indicated that the average absorbed dose to the entire lymphatic system is estimated as 100–300 rad. Using these dose estimates, Lewis developed a dose response relationship for X-rays and leukemia that would be predictive of very low dose exposures. This attempted to extrapolate very high single exposures to low doses of a chronic nature. Lamerton (1958) indicated that such studies lacked a proper control group of untreated infants with enlarged thymus glands, seriously limiting the capacity to interpret the findings.
Other areas of evaluation
The Lewis paper presented data on leukemia amongst radiologists. While this was useful in helping to establish that X-rays may cause leukemia in this group of physicians, there was no application to the issue of dose response. Therefore the data were not directly related to the issue of linear or threshold dose response relationships.

also lead to Lewis being appointed to the NCRPM and NRC committees on ionizing radiation (Lipshitz 2005) where he effectively advocated for the acceptance of linearity at low dose.

The extent to which the Lewis perspective was accepted surprised his detractors who at first dismissed his paper as seriously technically flawed with a geneticist analyzing epidemiological data and being unaware of important sampling and statistical methodological nuances (Kimball 1958). According to Mole (1958) the publication of detailed criticisms of the Lewis paper would "hardly have been worthwhile if his conclusions had not gained a wide currency as a quantitatively accurate assessment." While these papers were correct in their principal criticisms of his flawed approach to exposure estimation related to the atomic bomb survivors and in extrapolating risks of cancer to the general public from persons with various pre-existing disease conditions (Mole 1958; Lamerton 1964), they misunderstood the power of the fear of cancer on the development of a cancer risk assessment paradigm (Table 2). These events helped to establish the linearity threshold concept and the somatic mutation theory mechanism as scientifically credible and of considerable importance for the public health of the country, even though there were a number of high level researchers who disagreed with Lewis (e.g. Brues 1958; Finkel 1958; Mole 1958; Kimball 1958; Lamerton 1964).

Shortly after the publication of the Lewis paper in *Science* U.S. Congressional Hearings were initiated on the effects of radioactive fallout on humans. In some ways it was a referendum on the question of what is the nature of the dose response for radiation-induced cancer (e.g. bone cancer and leukemia as the principal concerns). While the majority of the expert testimony did not support the linear non-threshold

theory for low level long term somatic effects, the Congressional Committee left unresolved the question of whether there was a threshold or "safe" level for exposure to these cancerous endpoints (JCAE 1957). Congress renewed the debate on the issue of low dose linearity in 1959 and once again was unable to resolve this issue. However, the final summary report, while still equivocating on which model was most correct, quoted the strikingly equivocal testimony of K. Z. Morgan that only certain types of effects such as genetic mutations, leukemogenesis and life shortening were without a threshold (JCAE 1959). However, Morgan would also state that "it would be ultraconservative and at least with respect to genetic mutation, it would be incorrect to assume a linear relationship between dose and effect all the way from high chronic dose rates of 400 rad/30 years to background dose rates of about 4 rad/30 years". More hearings in 1960 by Congress lead to additional testimony by E. B. Lewis who continued to make his case for a linear hypothesis as the foundation of protection standards. The Joint Committee on Atomic Energy (JCAE) continued to meet during the 1960s (JCAE 1960a) on various aspects on the low dose fall out issue, edging progressively closer to the linear non-threshold hypothesis for low level long term effects with each succeeding series of hearings (Kathren 1996).

Sandwiched in between these initial hearings were the efforts of the NCRPM to clarify the dose response question. In addressing this issue in December of 1958 the NCRPM committee stated that "it was not possible to establish the exact character of the dose response curve. Lacking sufficient unequivocal information, the committee believes it would be desirable to take a conservative position and to assume a non-threshold linear dose response relationship" (Whittemore 1986). This effort by the NCRPM was particularly significant for several reasons. First, it created a committee of those on opposing sides of the linearity at low dose question, best seen in the personalities of E. B. Lewis and Austin Brues. This committee found a way to create an acceptable compromise, while giving plausible face-saving deniability to each leading player. The Committee got Lewis to agree that his advocacy for linearity at low dose was scientifically unconvincing at best and seriously flawed at worse. On the other hand, Brues came to accept that there was also not enough data to make a convincing argument for the threshold model. An agreement was reached that no model was scientifically superior with the available data. Consequently, the NCRPM Committee decided that as a matter of protectionist public health philosophy that the conservative linearity at low dose model should be accepted. In essence, Lewis had lost a battle but won the important policy war. The position of the NCRPM with its now cooperating antagonists on the same page was published in the journal *Science* (NCRPM 1960), with subsequent and mutually supportive testimonies at the 1960 Congressional Hearings by Lewis (1960) (see JCAE 1960b) and Brues (1960) (see JCAE 1960c). It was this policy based compromise on linearity at low dose that would have a profound influence on the actions of subsequent expert committees and regulatory agencies for the remainder of the twentieth century and first decades of the twenty-first century.

Other influential groups were also very involved in the low dose linearity debate, including the UNSCEAR (1958) which gave its version of a confusing picture, providing partial support for both a threshold or linear relationship, which lead them to conclude that either model could fit the atom bomb leukemia data. This view was quickly challenged by the NAS Committee on Pathology who supported a threshold interpretation, in contrast to the genetics committee (NAS/NRC 1959). This was followed by a report by the U.S. Federal Radiation Council (FRC) (1960) which adopted the NCRPM position as lead by Lewis and Brues, that the linear at low dose model, while not validated, provided an upper bound of risk, and should be accepted as policy. This idea that would come to be insidiously adopted throughout the reminder of the twentieth century in many countries for both radiation and chemical carcinogen risk assessment. UNSCEAR continued to assess the dose response question with subsequent reports in 1962, 1964 and 1972 indicating that even though there was considerable uncertainty with the low dose extrapolated values of the linear model, the extrapolated linear curve provided the upper limit of the estimate risk, in line with the comments of the FRC (1960) and the ICRP (1966).

While regulatory agencies and advisory groups were weighing in on the nature of the dose response in the low dose area so to were some individuals who offered views that were counter to those of linear at low dose leaders such as E. B. Lewis. For example, in the years following the Lewis paper, Lamerton (1964), in the presidential address of the British Institute of Radiology, stated that "an approach which I hope will not be taken is to extrapolate from available data at high doses on the most pessimistic assumptions possible, that is, the assumption of no threshold and linear relationship between incidence and dose, not only for genetic effects where the assumptions may well be correct, but all the possible hazards envisaged for the individual. This, for instance, was the approach of Lewis (1957) in consideration of the leukaemogenic hazard of environmental contamination arising from fall out. In this way a figure is obtained for numbers of leukaemias, bone tumors, a shortening of life span and as many other effects as one chooses, relating to a given type of radiation exposure and one would say "this is the maximum possible cost of such a procedure."

> "Such an approach is, I believe, quite wrong. The figures derived may have no relation to reality, and if

we adopted the criterion of "maximizing pessimism" as Mole has called it, for the other possible hazards of life on which our information is incomplete, such as chemical contamination of the atmosphere, tobacco smoke, consumption of saturation fats, food additives, even the effects of social changes, we should all have died many deaths by the now."

This period was characterized as one of dueling experts (Table 3), individuals of considerably high stature within the scientific community. These included the likes of multiple Nobel Prize winners on opposing sides of the question, and others with considerable experience on the topic of mutation, cancer and dose response. A limited sampling of such experts reflects a broad spectrum of perspectives. However, in general, it appears that the data to support the linearity at low dose perspective was generally viewed as lacking but the fear that it may be true was a motivating factor. It was a situation in which the science could only take one so far, allowing intuition and fear into the policy equation. This was also a time which preceded the discovery of DNA repair in the early 1960s (Setlow 1964) and the later insights into the concept of adaptive response (Samson and Cairns 1977; Olivieri et al. 1984) and how they might affect the predictions of the dose response in the low dose zone.

The issue of linearity at low dose for radiation induced cancer was occurring during the later part of the 1950s. Ironically, the Delaney "Amendment" to the 1958 Food Additives Amendment in the U.S. became law on 26 April 1958. It stated that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals". This Delaney clause was later inserted into the Color Additives Amendment of 1960, following the cranberry crisis of 1959 (White 1994). Despite their parallelism in time there was no apparent interaction between the development of a linearity at low dose methodology for radiation induced cancer and the science underpinning the decision to prevent adding carcinogens to food.

Table 3 Dueling experts—quotations

George Beadle (1957) Nobel Prize for Biology and Medicine	Are gene mutations in body cells responsible for some or all malignancies? The answer is not known. This question is important, for if gene mutation is indeed responsible, one might well expect a direct linear relation between exposure of the cells of an individual to ionizing radiation and the chance of developing a malignancy such as leukemia. A linear relation at all levels of exposure would mean that there is a real hazard seen at levels as low as those of background. Present radioactive fallout from testing of nuclear weapons is perhaps only one-tenth of background, but if the relation is linear at all levels, this would increase the incidence of malignancy by a small but real amount. On the other hand, if there is a threshold below which no effect is produced and if that threshold level is higher than background plus medical radiation plus fallout, there maybe little to worry about in their regard. Presently available data for man are insufficient to answer the question of linearity at all levels. The data are consistent with a linear relationship but are also consistent with the hypothesis that there is a threshold at low levels. (source: Caron 2003, page 30, see ref. 37; Beadle 1957)
Jacob Furth, President of the American Association for Cancer Research, and longtime researcher on leukemia	"The statement that there is no threshold injurious dose to somatic cells, and every irradiation, no matter how small will cause cancer and leukemia, as is stated by some geneticists, is mere speculation. This applies to the statement that even background irradiation is leukemogenic. The available facts allow argumentation on both sides. In my opinion, the statements that background irradiations will induce leukemia are contrary to observations and the reverse is more likely." (source: Caron 2003, page 47, see ref. 29; Furth 1957)
Dr. L. H. Hampelmann, University of Rochester	Stated that while there is a definite relationship between leukemia and radiation at high dosages, but that "the data at hand is insufficient to allow one to conclude that this relationship also holds for low-dose levels." (source: Caron 2003, page 47, see ref. 29)
Walter Selove, Chairman of the Federation of American Scientists' committee on radiation hazards and associate professor of physics at the University of Penn	He noted that the linear relationship had been demonstrated at high doses of radiation for leukemia. However, it was not certain what the nature of the dose response would be at low doses. (source: Caron 2003, page 45, see ref. 29)
EB Lewis, Cal Tech Professor, Nobel Prize Winner in 1995	"This is presumptive evidence that the relationship between incidence of induced leukemia and dose of radiation is either linear or approximately linear….these data provide no evidence for a threshold dose for the induction of leukemia." (source: Caron 2003, page 27; Lewis 1957)
AW. Kimball (1958) JNCI paper	Lewis failed to prove the linearity hypothesis because there were insufficient data "to support any conclusion about the shape of the dose-response curve, particularly in the low-dose region." (source: Caron 2003, page 56 and 57, see ref. 58; Kimball 1958)

During this period Delaney began to interact with Dr. Wilhelm Hueper, an NCI scientist, and leading expert on environmental and industrial carcinogens. Hueper offered a very strong protectionist philosophy to Delaney along with powerful credentials, thereby allowing Delaney to proceed. Since scientists were unable to define what a safe level of exposure to carcinogens may be along with not understanding their mechanisms of action, Delaney asserted that there was no risk worth taking with respect to chemical carcinogens, and that chemicals "did not have rights". In the case of radiation, there was a different concept of risk evolving which related to permissible risk that could now be estimated with the linear model. The Delaney amendment, inspired by the strong views of Hueper, were to lead to the prevention of possible exposures. The FDA would later modify the Delaney amendment to address the concept of a de mininus risk, so that carcinogens could be added to the food supply if they were estimated to have a risk less than a certain value (e.g. one in a million/lifetime), following a linearity at low dose model. Thus, in time the radiation and food additive risk perspectives converged. It should be noted that Committee 17 of the Environmental Mutagen Society (EMS) attempted to have the Delaney Amendment generalized to include chemical mutagens in the early 1970 s but failed to achieve this goal, falling back to the earlier guidance of the 1956 BEAR I committee that assessed genetic risks within the context of a doubling dose framework that was still consistent with the linearity at low dose model (Drake et al. 1975; Drake 1978).

Part 1: Conclusion

The acceptance of linearity at low dose has had a long history that is rooted in radiation-induced mutation. This article showed that in the 1930s–1950s geneticists strongly believed that the shape of the dose response for mutagens was linear, that mutagenic damage was cumulative and that it was harmful. While the evidence supporting linearity for radiation was limited and not based on low doses, the genetics community nonetheless asserted their beliefs and concerns into high level governmental deliberations, especially those sponsored by the U.S. NAS, but not limited to them. Their cause received a tremendous boost when H. J. Muller received the Nobel Prize in 1946 for his discovery of radiation induced mutations. Muller used the acclaim associated with the award to highlight his concerns about genetic damage caused by radioactive fall-out.

The concept of low dose linearity of reproductive cell mutation was endorsed by the BEAR I committee, leading to its further acceptance within the scientific and regulatory communities. The concept of low dose linearity was eventually generalized to encompass somatic genetic endpoints within the context of the somatic mutation theory based on a public health protectionist philosophy rather than a scientifically acceptable predictive dose response model. This lead to linearity at low dose becoming the framework for assessing radiation induced cancer risks.

PART 2: How EPA came to adopt linearity at low dose for chemical carcinogens

Introduction

Perhaps the most significant risk assessment decision that has been made occurred when the U.S. EPA decided that chemical carcinogens should be assumed to act in a linear at low dose manner. This critical judgment added huge costs to society via a wide range of regulations and exposure standards and created the basis for innumerable legal disputes between government, industry and other parties, all without the scientific capacity of validating whether this decision was correct or not. As far as the U.S. EPA was concerned, they took their signal on how to estimate risks following exposures to chemical carcinogens from the 1977 U.S. National Academy of Sciences (NAS) Safe Drinking Water Committee (SDWC) report, Drinking Water and Health. This NAS SDWC was established by federal legislation (i.e. Safe Drinking Water Act of 1974) in order to provide guidance to the U.S. EPA on the public health implications of contaminants in community drinking water. On the question of carcinogen risk assessment, this committee recommended a linearity at low dose approach which was adopted by the Agency, became policy, and has, for most practical considerations, remained such to the present, affecting how carcinogens were to be assessed by other U.S. federal agencies, state regulatory agencies, the legal system and many other countries.

It will be shown that the NAS SDWC report which recommended the adoption of linearity at low dose for carcinogen risk assessment was poorly documented on this most critical point, with the decision on the choice of risk assessment model being principally based on a protectionist precautionary philosophy. The suite of unifying principles supporting the decision of linearity at low dose included a mixture of testable and non-testable assumptions. In the more than 30 years since the publication of this far-reaching report each of the testable assumptions has been generally discredited and/or severely weakened. Yet there has been little regulatory response to this profoundly altered scientific landscape. This analysis suggests that while science is an inherently self-correcting discipline, that government regulatory actions, based in large part on scientific evidence, does not follow a similar self correcting process.

SDWC attitudes about the shape of the dose-response in the low dose zone

The following section represents a series of quotes taken from the 1977 Drinking Water and Health book. These quotes are intended to be representative of the position of the Committee on the critical question of how low dose extrapolation would be guided. In this 1975–1977 time period, the decision broke down to two options: the threshold dose response model or linearity at low dose approaches (EPA 1976). As will be seen below, the committee unequivocally supported the linear at low dose perspective.

Quotes from chapter 2 of drinking water and health

> "Those who argue that safety factors are inadequate and that almost no thresholds can be determined, or theoretically developed, suggest that even one or a very few molecular events have a finite probability of initiating a successful malignant or neoplastic transformation in a cell, and that this can lead to a lethal cancer. Although one malignant cell can lead to death by cancer, many liver or kidney cells can be killed or damaged (but not malignantly transformed), without causing any detectable disease. Furthermore, man is never exposed to one carcinogen at a time, but is exposed to low concentrations of many at the same time. Accordingly, we have adopted a "non-threshold" approach for estimating risks from pollutants that have been shown to be carcinogenic in laboratory animals." page 21

> "But, because evidence of the correlation between mutagenicity and carcinogenicity continues to accumulate, we suggest that a conservative safety factor be provisionally applied to the mutagenicity data and that, if new information (such as the results of a reliable carcinogenicity study) is lacking 4 years from the time a mutagenicity study is completed, non-threshold methods be used to establish risk." page 22

> "Many scientists now distinguish between injuries produced by chemicals for which there is likely to be a threshold dose and effects (e.g. carcinogenesis and mutagenesis) for which there is likely to be either no threshold dose or no way presently known to estimate one for large, heterogeneous populations." Page 25

Quoting Weil (1972) it was stated that "No matter how small the dose, however, one, or a few, of millions of subjects may exhibit the critical response." Page 25

> "It is more prudent to treat some kinds of toxic effects that may be self-propagating or strictly cumulative, or both, as if there were no threshold and to estimate the upper limits of risks for any given exposure. Included amongst these are effects that result from an initial, chemically induced alteration in cellular genetics that is transmitted by cell propagation. Carcinogenesis and mutagenesis are examples in which a single cell transformation has the theoretical potential for irreversibility, which might involve self-propagation, even in the absence of further exposure." Page 25

For self-propagating effects, "assume no threshold, assume a linear dose-response at low doses, and estimate risk." Page 26

> "If the mechanism involves somatic mutation or alteration, there is no threshold dose for long-term exposure; if the mechanism is unknown, it is prudent to assume that DNA damage is involved……..Every dose would be regarded as carrying some risk." Pages 27, 28

> "We would expect that mutation can be caused by a single molecule or perhaps a group of molecules in proximity to the DNA. The necessary conclusion from this result is that the dose-response relationship for radiation and chemical carcinogenesis cannot have a threshold and must be linear, at least at low doses." Pages 37, 38

> "We therefore conclude that, if there is evidence that a particular carcinogen acts by directly causing a mutation in the DNA, it is likely that the dose-response curve for carcinogenesis will not show a threshold and will be linear at low doses." Page 38

> "Thus, it is likely that any carcinogenic agent added to the environment will act by a particular mechanism on a particular cell population that is already being acted on by the same mechanism to induce cancers. This reasoning implies that only if it acted by a mechanism entirely different from that already operating on the tissue could a newly added carcinogen show a threshold in its dose-response curve." Page 38

> "In view of the common finding –for example of a linear dose-response relationship (unaffected by dose-rate)-for cancer induction in animals by high LET radiation, it is unlikely that such thresholds exist." Page 38

> "Recent reviews by Barendsen (1975) and Brown (1976) suggest that the dose-response curve for mutation induction, the production of chromosome aberrations, and the induction of tumors in mammals is linear with low-LET radiation up to about 50–100 rads. Brown (1976) concluded from the available

human data that this also applies to man. Such findings argue against a threshold for ionizing radiation. Because many carcinogenic agents act like radiation in producing mutations, chromosome aberrations, and cell killing, we see this as an additional argument against the likelihood of thresholds in the dose-response curves of these agents." Pages 38, 39

"It seems, therefore, that even if we were to postulate an average threshold for a particular cancer induced by a particular agent, we would in practice need a series of thresholds for different individuals. It would be extremely difficult to establish a single threshold." Page 39

Assessment of the NAS SDWC position on the nature of the dose response for mutagenicity and carcinogenicity

After reading Chapter 2 of the 1977 book, *Drinking Water and Health* by the SDWC of the NAS, a report that was mandated by the U.S. Congress, one is struck by the fact that the Committee did not simply recommend consideration of linearity at low dose after further detailed evaluation. No, the Committee did their best to place its recommendation on as firm and unalterable ground as possible and to ensure that what they were saying was clear. This critical chapter reveals that the Committee repeated their desire that linearity at low dose be followed for carcinogen risk assessment, at least a dozen times, all with subtle nuances but all unmistakably clear. The forceful clarity of the Committee was transmitted to the EPA and this recommendation became their guiding principle on cancer risk assessment. For all practical purposes, the NAS SDWC provided the needed scientific credibility for the U.S. EPA to adopt as policy the assumption of linearity at low dose modeling for chemical carcinogen risk assessment. This very authoritative recommendation by the NAS SDWC provided the Agency with the needed framework in order to move aggressively in this area. In fact, this was soon implemented (1979) in EPA regulations for total trihalomethanes (THMs) in drinking water, based on the carcinogenicity of chloroform in animal models (Larson 1989).

A distillation of the Committee support for linearity at low dose for chemical carcinogen risk assessment identifies eight different supportive arguments (Table 4). At the time of the publication of Drinking Water and Health the arguments were powerful, layered and integrated. In the arrangement of the conceptual perspective on chemical carcinogen assessment there appears to have been a strategic plan to construct arguments in a fail-safe manner such that if one or several were shown to be incorrect or needed significant modification then others were still sufficient for the linearity position to be sustained. For example, there was the assumption that only one or two changes in a cell were needed to transform the cell and propel it along an irreversible course to cancer. This irreversible genetic change was simply only adding to an already identifiable background cancer burden, assumed by the Committee to most likely be acting by the same mechanism. In addition, even though some people are somewhat resistant to the development of certain types of cancers, others are at greater risk, some at considerable greater risk. Given the profound level of human heterogeneity, even assuming that all people may have different personal thresholds, the Committee believed that there would be no population based threshold, thereby again asserting linearity at low dose. Finally, the Committee saw evidence of low dose linearity for radiation induced mutation in the published literature and then appealed to a previous authority, that is, the BEIR II committee of 1972 (NAS/NRC 1972), and asserted that chemical carcinogens must act in a linear at low dose fashion just as radiation was asserted earlier by the BEIR II committee.

The evidence that the Committee provided to support their case was very limited and inappropriate given the significance attached to document, one that was at the core of

Table 4 NAS SDWC (1977) low dose linearity guiding principles: no longer tenable 3 decades later

Only one or two changes in a cell could transform it and this could lead to cancer	Not tenable
Human population heterogeneity was a factor, and some people may be at greater risk. Such heterogeneity leads to the conclusion that there was no population-based threshold.	Impossible to practically study
A transformed cell will be irreversibly propagated.	Not tenable
If the mechanism involved mutation, there would be no threshold; in fact, if there were no information on mechanism and cancer occurred, mutation should be assumed.	Not tenable
It is necessary to assume that a single molecule or a few molecules can cause a mutation. Therefore, linearity at low dose can be assumed.	Not tenable
There is also the assumption that the exposure would be directly additive to background, if acting via the same mechanism. This would also support the linearity conclusion.	Generally not shown
Available mutagenicity data with radiation indicated that it was linear at relatively "low" doses.	Not tenable
Since chemical carcinogens act like ionizing radiation, low dose linearity should also be assumed to be the case for such chemicals.	Not tenable

the Safe Drinking Water Act requirements of 1974. Chapter 2 (see "Introduction") to the Drinking Water and Health book provides what may be characterized as an assertion of basic beliefs, for the most part unproven, and certainly not reasonably supported with documentation from the peer-reviewed literature. It was an early assertion of an overall precautionary principle framework.

Now more than three decades later, how have these basic beliefs held up? In some cases the belief can not be tested, so they can remain unthreatened by new data. For example, the assertion that very susceptible subjects may be at risk and this "may affect but one or two of millions" can not be practically tested with epidemiological methods. Even in the most controlled and extensive experimental study with animal models using 24,000 animals risk was only determined to the 1 in 100 level (Bruce et al. 1981). Assertions that low doses could affect but one person in a million can remain a safely protected, untested and unproven assumption.

Another very general and vague statement that is difficult, if not impossible to test and prove, is the assumption that chemically induced cancers occur via the same mechanisms as similar cancers that occur as background cancers in the population. There have been investigations that have indicated that genes that are subject to carcinogen attack with different mutagenic endpoints occurring, depending on the agent, dose and other experimental factors (Houle et al. 2006; Valadez and Guengerich 2004; Loechler 1996; Solomon et al. 1996). Such observations invalidate a key assertion of the Committee. Further, it seems that the Committee had little idea what the exact mechanisms of the cancer formation may be as this is a multi-staged process, possibly involving numerous sequence mechanistic processes, thereby making this particular guiding principle of questionable value.

The idea that a single alteration in DNA is sufficient to lead to cancer and that the process, once started, is irreversible, has been shown repeatedly not to be the case. This has been demonstrated in experimental studies leading to conclusions that there are likely multiple processes involved in the process of carcinogenesis (e.g. Driver et al. 1987). Thus, this central feature of the 1977 set of beliefs can not be broadly sustained.

This retrospective consideration of the underlying rationale for the linearity at low dose guidance provided by the 1977 Drinking Water and Health report to EPA by the NAS SDWC shows that the original rationale has been considerably eroded over the intervening years. Every testable assumption upon which its principles were based has been shown to be either invalid in light of new knowledge or only of limited value and certainly not the scientific foundation upon which to base a major national risk assessment program for carcinogens. The only basic principles that have withstood the test of three decades of scientific research are those assumptions which do not lend themselves to experimental or epidemiological validation. In such cases, there is no value to continue to rely on un-testable assumptions as foundational principles for national public health programs.

If the past thirty years of research has essentially undermined the "firmly" and often asserted principles of that historic first NAS SDWC, then the question must be posed as to what was the basis of these strongly held beliefs. Did they have a strong scientific foundation or were they more philosophically based? What was known about the dose response in general, about mutagens in particular, and how this endpoint was related to the process of carcinogenesis?

Attitudes and beliefs of low dose linearity by scientific leaders in the early 1970s

Some highly visible leaders in the government and academic mutagenicity communities were very firm in support of the linearity at low dose concept by the early 1970s. This conclusion is unequivocally supported by published comments during a high level scientific conference chaired by Alexander Hollaender with the proceedings published in Environmental Health Perspectives in 1973.

Ernst Freese (Johns Hopkins University)

> "Unless one has experimental evidence at low doses, one has to extrapolate from the data obtained at high dose. To do that one certainly should not accept a threshold dose. There is a basic difference between a mutagenic effect and a toxic effect. A mutagenic effect alters single cells which then multiply; in a toxic effect a large number of cells must be affected, inhibition or cell killing before significant toxicity is observed." P. 176 (Freese 1973)

> "You may decide that you want to extrapolate the experimental curve down to that dose which will give you a no-effect point or you may decide to take the lowest experimental value and extrapolate it linearly down to zero concentration, which will give a dose effect at any dose." P. 176 (Freese 1973)
> "I think that what we are trying to do is to put the burden of proof upon those who argue that there may be a threshold." P. 177 (Freese 1973)

R. B. Cummings (Oakridge National Laboratories)

> "I don't know of any data that would suggest that there is any real threshold." P. 176 (Freese 1973)

Jim Crow, University of Wisconsin

> "I wanted to reiterate Dr. Freese"s point. When we say linear extrapolation we don't really mean to fit a least-squared line to the existing points and carry that back as far as it goes. What we really mean is to connect the existing point with the zero effect and regard that as linear. P. 176 (Freese 1973)

B. Bridges (University of Sussex)

> "I think that I would very much agree with what you say, that you cannot assume that for genetic effects in a cell there is a no-effect threshold." P. 176 (Freese 1973)

Samuel Epstein (Case Western Reserve)

> "The fact that we have a background of environmental mutagens I presume has some relationship to mutagenesis in man and the adverse mutations and the high incidence of cancers that man has suffered since time immemorial. To suggest that the existence of a natural background of environmental carcinogens and mutagens therefore brings the concept of threshold in the relationship of new synthetic agents into the environment is a non-sequitor." P. 177 (Freese 1973)

There was one "apparent" alternative, but non-dissenting, perspective offered during this discussion, that of L. Friedman of the FDA. His argument was not so much that the above speakers were wrong but that their opinion was based not on data but on a theory or a belief. He emphasized that the field was incapable of even measuring doubling rates of mutagenic endpoints let alone even talking about increases of one percent or lower. He did not know whether a threshold or linear perspective prevailed and was not willing to extrapolate to that conclusion without the studies to prove it. However, he believed that the human population had already exceeded their threshold and was experiencing adverse mutagenic effects and this needed to be addressed.

Several years later Committee 17 of the Environmental Mutagenesis Society (EMS) (Drake et al. 1975) was more cautious in addressing the scientific underpinnings of the nature of the dose response for mutagens. They asserted that:

> "no information exists proving or disproving the existence of a threshold response to a mutagen in any system; when a mutagen active at a high concentration produced no detectable effect at a low concentration, it is generally impossible to determine with confidence that sufficient statistical accuracy has been achieved to conclude that an effect is truly absent. It therefore seems to us that the best practice, when extrapolating from curvilinear dose-response curves, consists of interpolating linearly between the spontaneous rate at zero dose and the response from the lowest dose tested for which reliable data exist. It is unlikely that this procedure will underestimate the risk. If there is a threshold, or a deviation from linearity in that direction, this procedure will overestimate the risk, which we assume to be the prudent policy to follow in a matter of this importance. As more data on low doses accumulate, the extrapolation line can be regularly revised."

This quotation from Drake et al. (1975) in Science represents a significant change in the "scientific" belief in linearity at low doses for radiation as seen in the BEAR I committee in 1956 as well as the series of personal perspectives summarized in the 1973 *Environmental Health Perspective* issue as presented above. With respect to chemical mutations the consensus position was that the shape of the dose response in the low dose zone was not resolved. The committee indicated that decisions on how risk would be assessed should be made on policy rather than a scientific determination.

The above comments represent principally beliefs and/or concerns about public health issues of mutation and cancer. The key elements to the scientific underpinnings were factors that indicated that mutation and cancer were causally linked and that mutation was linear at low dose. With respect to the first question, what was known or believed about the relationship of mutagenicity and carcinogenicity in the pre-1977 time period?

Scientific understandings on low dose linearity preceding the 1977 SDWC report

The somatic mutation hypothesis

The hypothesis that carcinogens are mutagens and that the process of carcinogenesis was dependent on the occurrence of one or more mutagenic effects is known as the somatic mutation hypothesis (SMH). This hypothesis has been a core historical assumption underpinning approaches by regulatory agencies that assess risk to carcinogens from the 1970s to the present. As successful as the SMH has become within the environmental health and regulatory communities, the SMH was not readily accepted by the scientific community during the mid decades of the twentieth century. However, the political and regulatory acceptance of this concept was extremely rapid during initial years of the 1970s despite important and lingering scientific uncertainties.

It has not been easy to demonstrate that mutagens are carcinogens and carcinogens are mutagens in a direct causal sense. From an historical perspective, chemicals, radiation and viral-induced tumors were discovered well before these treatments were found to induce mutations. In the case of radiation, X-ray induced sarcoma in the rat was first experimentally demonstrated in 1910 (Mustacchi and Shimkin 1956) whereas X-ray induced mutations were only later reported by Muller (1927). The linkage of X-ray induced mutation and cancer lagged for more than two decades, until Muller (1951) focused on a mechanism of radiation induced cancer. According to Lawley (1994) this delay in the development of radiation induced cancer assessment based on mutagenicity set the stage for the emergence of chemical carcinogenesis as the principal foundation for a comprehensive theory of carcinogenesis from the mid 1950s to the present.

While chemically induced tumors were first experimentally achieved in 1918 by Yamagiwa using coal tars (see Henschen 1968) and expanded rapidly in the area of specific PAHs (see Kennaway 1955 for a review), it was not until after World War II that Auerbach and Robson (1946) reported that chemicals could induce mutations, noting that mustard gas could induce mutations in the fruit fly. While this was confirmed and extended in the years soon thereafter, the link between mutation and cancer was problematic. This was because mustard gas, the prototypic mutagen, was initially shown not to induce tumors in several experimental protocols both with and without promoting agents (Berenblum and Shubik 1949) as well as inhibiting the occurrence of PAH induced skin cancer in the standard mouse model (Lawley 1994). A further major limitation was that the vast amount of research on PAH and skin cancer involving several hundred agents was not particularly supportive of the SMH. Attempts to demonstrate PAH induced mutagenicity were generally weak, in contrast to the capacity of such PAHs to act as carcinogens in standard rodent bioassays (Lawley 1994). Other researchers, such as Latarject (1948), failed to find any correlation between mutagenic and carcinogenic potencies, further challenging the SMH. Such observations lead significant leaders in the field such as Hieger to express doubts about the SMH into the 1960s (Lawley 1994). This was also the case with Rous, who, nearly 50 years after his seminal discovery of viral induced tumors (Rous 1910), remained skeptical of the SMH stating that carcinogens had not yet been shown to act as mutagens (Rous 1959).

As DNA became known as the hereditary material in the mid 1940s (Avery et al. 1944) with its structural basis being revealed in the helical model of Watson and Crick (1953) considerable research explored whether carcinogens acted via altering DNA. The initial general consensus revealed that physiological complexing between carcinogens and chromosomes, including DNA, was largely irrelevant to its biological actions and that covalent binding to protein was more likely the critical factor in tumor initiation and development (Lawley 1994). Such a perspective was reaffirmed by observations that the well known liver carcinogen, butter yellow, was principally bound to liver proteins (Lawley 1940).

During this period Burdette published numerous papers (Burdette 1950, 1951a, b, 1952a, b, 1953) that demonstrated a continuing lack of consistency in the capacity of carcinogens to act as mutagens culminating in a comprehensive review on the topic in 1955. According to researchers such as Burdette (1955), it was possible that this association was fortuitous. He was quick to point out a number of discrepancies in the data that precluded a convincing conclusion. For example, there was a general lack of mutational effects in *Drosophila* with well known polycyclic aromatic hydrocarbon carcinogens (Auerbach 1939–1940; Bhattacharya 1949; Burdette 1950, 1952a, b; Demerec et al. 1948). In addition, formaldehyde increased the mutation frequency in males but did not alter the incidence of tumors for either males or females (Burdette 1952a, b). Likewise, he noted that 20-methylcholanthrene is tumorigenic but not mutagenic within *Drosophila*. These findings and others summarized by Blum (1953) and later by Burdette (1955) asserted that a causal relationship between mutagenicity and carcinogenicity should not be assumed true until such discrepancies were resolved. This position placed the burden of proof on those asserting the validity of the relationship. As late as the early 1970s Malling (2004a; b) challenged the position of Burdette (1955) on the proof between mutagencity and cancer. In fact, Malling incorrectly indicated that Burdette staked his case principally on PAHs and nitrosoamines, failing to point out the wide range of other agents marshaled to support Burdette's perspective. The point here is not that Malling actually discredited the position of Burdette but rather it illustrates the importance of this basic assumption in the mantra of linearity at low dose. The lack of broad acceptance continued for the SMH during the 1960s as seen in a subsequent major review by Foulds (1969) in which he was unenthusiastic about the role of mutagenesis in neoplastic development.

Support was gathered for the SMH in the mid 1960s by Brooks and Lawley (1964) who reported that DNA was a more significant target of PAHs than RNA and protein. Such findings lead Lawley (1994), in a retrospective review, to conclude that DNA was the key molecular target of carcinogens, thereby removing any obstacle to recognition that the concept of cancer should be equated with mutagenesis. However, even the findings of Brooks and Lawley (1964) were far from conclusive as they were based on associational relationships, rather than a clear mechanism.

By the late 1960s, a mechanistic breakthrough occurred when Loveless and Hampton (1969) reported that alkylating agents caused GC to AT transitions thereby providing a possible means by which mutagens specifically altered DNA, possibly accounting for how a mutagen might specifically alter the product of DNA mediated protein formation. However, despite this advance there was still a substantial lack of evidence supporting the SMH.

During this period Ames developed and refined the Salmonella bacterial test for screening mutagenic responses. This activity culminated in the publication of a significant paper within PNAS with now over 1,800 citations (Ames et al. 1973b). This article supported the SMH, as illustrated by the initial words of its title: Carcinogens are mutations", a title that was repeated in that same year (1973a) in articles by Ames et al. within Environmental Health Perspectives (Ames 1973) and Mutation Research (Ames et al. 1973c). With the acceptance of the view that "Carcinogens are Mutagens", this concept became the mantra for the risk assessment community for the rest of the 1970s, leaving the Burdette challenge and those of other critics as marginal historical footnotes.

In order for the Ames claim to support the SMH, a claim that was impressive but still associational in nature, however, he had to markedly alter the biology of his test bacteria, removing the lipid coating of the bacterium, remove its DNA repair capacity and add a plasmid to enhance the mutagenic response. In many ways, this was an organism that was stripped of its defenses and made far more sensitive than the wild-type bacterial strain. It was not a fair test of the SMH under any circumstances. The optimal test of the SMH would involve the induction of mutations in an animal model which directly lead in a step by step casual mechanistic manner to the development of cancer, something that has been very elusive (Trosko and Upham 2005). The SMH perspective should not have been strongly associated with the findings of a predictive model (i.e. bacteria) that would not develop cancer. Nonetheless, the field embraced the assumption of a causal relationship and with that a key element of the linearity at low dose belief was in place. One clearly sees the impact of the Ames findings on the thinking of the NAS SDWC in the earlier quoted material that highlighted the high correlation between mutagenicity and carcinogenicity and how that would support the use of non-threshold models for risk assessment.

From many hits to few hits to linearity

While acceptance of the SMH was a key feature in the development of low dose linearity there was more required for this concept to be accepted. The question that emerged once the SMH was proposed was how many mutations were needed to produce a cancer. In fact, as early as 1951 Hermann Muller indicated that many or most cancerous tumors would need a series of inter-related mutations in order for cells to deviate from apparently normalcy. This would require that the frequency of such growths depend upon an exponent of the dose higher than one, rather than upon the dose itself, an observation likely to be at odds with some approaches to model a linear at low dose response. Picking up on this theme, Nordling (1952, 1953) related cancer deaths as a function of age, coming to the conclusion that as many as six or seven sequentially related mutations were needed for cancer development. In the ensuing years numerous models of mutation related cancer development have been presented. In general, they agree with the perspective of Nordling in which multiple mutations or hits are needed to account for the frequency of cancers within the population with some exceptions as in the case with retinoblastoma which supports two genetic alterations. The key point was that human population based cancer frequencies adjusted for age supported a complex and multi-hit framework that was necessary to account for the occurrence and distribution of tumors within the population.

This being the case, the carcinogenesis process required multiple hits over time in order to result in the development of many different types of cancers. This epidemiological perspective, which was not generally supportive of low dose linearity, was ignored by the NAS SDWC and the U.S. EPA which supported a linear perspective based on a 2 decades earlier recommendation of the BEIR II (1972) committee in response to public health concerns with respect to ionizing radiation and in part by the highly repeated intellectual mantra of Ames (Ames 1973; Ames et al. 1973a, 1973b, 1973c) that "carcinogens are mutagens".

This second critical line of argument was also dependent on the assumption that mutagens displayed responses that were linear at low dose and that this perspective was sufficient to validate the belief that carcinogens would act similarly. The key element is what is a low dose. Up to the time of the acceptance of the linearity at low dose for cancer risk assessment by the NAS SDWC (1977) there was no comprehensive scientific assessment of the nature of the dose response in the low dose zone for mutagens, but there were policy-oriented statements. As noted earlier, of particular significance was the report of the Environmental Mutagen Society (EMS), which concluded that it was not yet possible to scientifically resolve the question of the shape of the dose response in the low dose zone for mutagens (Drake et al. 1975). However, it is curious that EPA (1980) adopted a position that was inconsistent with the highly visible position of the EMS (Drake et al. 1975) when it stated that "there is substantial evidence from mutagenesis studies with both ionizing radiation and with a wide variety of chemicals that this type of modeling (i.e. LNT dose

response model) is the appropriate one to use". This position by EPA however was needed to provide a mechanistic basis to support linearity at low dose modeling for cancer risks. Thus, it appears that the EPA was compelled by policy rather than science to disagree with the position of the key professional society with the most relevant experience in assessing mutagenicity.

Part 2: Conclusion

The present paper has framed the mutagenicity, carcinogenicity and risk assessment debate that would carry the environmental health and risk assessment fields from the 1970s to the present. In the end, the decision on how to proceed, that is, what risk assessment model would be the default, would be based on a set of beliefs that could not be verified, with a precautionary perspective philosophy at its core, based on a direct causal linkage of mutagenicity and carcinogenicity serving as the guiding hand for carcinogen risk assessment. This was the prevailing view, the perspective that infiltrated the thinking of that first NAS SDWC (1977) where the linearity at low dose recommendation for cancer risk assessment emerged and which became the philosophical mantra of the EPA (1979, 1980) and many other regulatory agencies in the U.S. and elsewhere. The philosophical mantra became of overriding importance when EPA went the next step and implemented it within a broad set of multi-media environmental standards starting with the trihalomethanes (THM) drinking water standard in 1979 (Larsen 1989) and setting the course for a broad series of initiatives affecting standards, clean up procedures and technology requirements down to the present. It also set the direction that many aspects of environmental litigation would follow. In the end, society accepted a view of science that was based on philosophical, social and scientific beliefs of some leaders in the field and country. As science is a discipline that is inherently self-correcting, it is hoped that the present assessment of the flawed acceptance of linearity at low dose by the NAS SDWC (1977) and EPA will be recognized, broadly discussed and may lead to an improved self-correcting process that follows data rather than philosophy within the domain of regulatory "science".

Acknowledgments Effort sponsored by the Air Force Office of Scientific Research, Air Force Material Command, USAF, under grant number FA9550-07-1-0248. The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official policies or endorsement, either expressed or implied, of the Air Force Office of Scientific Research or the U.S. Government. Even though their work is copiously cited in this paper, I wanted to highlight the important contributions of Whittemore (1986) and Jolly (2003) in their dissertations on critical assessment of the history of the dose response as seen through the eyes of historians of science.

References

Ames BN (1973) Carcinogens are mutagens: their detection and classification. Environ Health Perspect 6:115–118. doi:10.2307/3428066

Ames BN, Lee FD, Durston WE (1973a) An improved bacterial test system for the detection and classification of mutagens and carcinogens. Proc Natl Acad Sci USA 70:782–786. doi:10.1073/pnas.70.3.782

Ames BN, Durston WE, Yamasaki E, Lee FD (1973b) Carcinogens are mutagens—simple test system combining liver homogenates for activation and bacteria for detection. Proc Natl Acad Sci USA 70:2281–2285. doi:10.1073/pnas.70.8.2281

Ames BN, Durston WE, Yamasaki E, Lee FD (1973c) Carcinogens are mutagens—simple test system. Mutat Res 21:209–210

Atomic Energy Commission (1950) Thirteenth Semiannual Report, July 1930, Control of Radiation Hazards in the Atomic Energy Program. Government Printing Office, Washington

Auerbach C (1939–1940) Tests of carcinogenic substances in relation to the production of mutations in *Drosophila melanogaster*. Proc Roy Soc Edin 60:164–173

Auerbach C, Robson JM (1946) Chemical production of mutations. Nature 157:302. doi:10.1038/157302a0

Avery OT, MacLeod CM, McCarty M (1944) Studies on chemical natures of substance inducing transformation by desoxyribonucleic acid fraction isolated from pneumococcus type III. J Exp Med 79:137–158. doi:10.1084/jem.79.2.137

Barclay AE, Cox S (1928) Radiation risks of the roentgenologist. Am J Roentgenol Rad Ther 19:551–561

Barendsen GW (1975) The effectiveness of small doses of ionizing radiations for the induction of cell reproductive death, chromosomal change and malignant transformation. In: Presented at 5th symposium on microdosimetry, Verbania Pallanza, Italy, September 22

Beadle G (1957) Biology division, C., Biology 1957 at the California Institute of Technology: a report for the year 1956–1957 on the research and other activities of the Division of Biology, pp 126

Berenblum I, Shubik P (1949) An experimental study of the initiating stage of carcinogenesis, and a re-examination of the somatic cell mutation theory of cancer. Br J Cancer 3:109–117

Bhattacharya S (1949) A study of the inability of methylcholanthrene to produce mutations in *Drosophila melanogaster*. Proc Zool Sox Bengal 2:187–193

Blum HF (1953) Regarding the somatic mutation hypothesis of cancer. Science 118:197–198. doi:10.1126/science.118.3059.197

Brooks P, Lawley PD (1964) Evidence for the binding of polynuclear aromatic hydrocarbons to the nucleic acids of mouse skin. Relation between carcinogenic power of hydrocarbons and their binding to deoxyribonucleic acid. Nature 202:781–784. doi:10.1038/202781a0

Brown JM (1976) Linearity versus nonlinearity of dose-response for radiation carcinogenesis. Health Phys 31:231–245

Bruce RD, Carlton WW, Ferber KH, Hughes DH, Quast JF, Salsburg DS, Smith JM, (Members of the Society of Toxicology ED01 Task Force), Brown WR, Cranmer MF, Sielken JR, Van Ryzin J, Barnard RC (1981) Re-examination of the ED_{01} study why the society of toxicology became involved. Fundam Appl Toxicol 1:26–128

Brues AM (1958) Critique of linear theory of carcinogenesis. Science 128:693–699. doi:10.1126/science.128.3326.693

Burdette WJ (1950) Lethal mutation rate in *Drosophila* treated with methylcholanthrene. Science 112:303–306. doi:10.1126/science.112.2907.303

Burdette WJ (1951a) Administration of diethylstilbestrol to the *tu-36a* strain of *Drosophila melanogaster*. Rec Genet Soc Am 20:93–94
Burdette WJ (1951b) Tumor incidence and lethal mutation rate in a tumor strain of *Drosophila* treated with formaldehyde. Cancer Res 11:555–558
Burdette WJ (1952a) Tumor incidence and lethal mutation rate in *Drosophila* treated with 20-methylcholanthrene. Cancer Res 12:201–205
Burdette WJ (1952b) Effect of nitrogen mustard on tumor incidence and lethal mutation rate in *Drosophila*. Cancer Res 12:366–368
Burdette WJ (1953) The somatic mutation hypothesis of cancer genesis. Science 118:196–197. doi:10.1126/science.118.3059.196
Burdette WJ (1955) The significance of mutation in relation to the origin of tumors: a review. Cancer Res 15:201–226
Calabrese EJ (2004) Hormesis: from marginalization to mainstream. A case for hormesis as the default dose-response model in risk assessment. Toxicol Appl Pharmacol 197:125–136. doi:10.1016/j.taap.2004.02.007
Calabrese EJ (2005a) Toxicological awakenings: the rebirth of hormesis as a central pillar of toxicology. Toxicol Appl Pharmacol 204:1–8. doi:10.1016/j.taap.2004.11.015
Calabrese EJ (2005b) Historical blunders: how toxicology got the dose-response relationship half right. Cell Mol Biol 51:643–654
Calabrese EJ (2008) Hormesis: why it is important to toxicology and toxicologists. Environ Toxicol Chem 27:1451–1474. doi:10.1897/07-541.1
Calabrese EJ, Baldwin LA (2000a) Chemical hormesis: its historical foundations as a biological hypothesis. Hum Exp Toxicol 19:2–31. doi:10.1191/096032700678815585
Calabrese EJ, Baldwin LA (2000b) The marginalization of hormesis. Hum Exp Toxicol 19:32–40. doi:10.1191/096032700678815594
Calabrese EJ, Baldwin LA (2000c) Radiation hormesis: its historical foundations as a biological hypothesis. Hum Exp Toxicol 19:41–75. doi:10.1191/096032700678815602
Calabrese EJ, Baldwin LA (2000d) Radiation hormesis: the demise of a legitimate hypothesis. Hum Exp Toxicol 19:76–84. doi:10.1191/096032700678815611
Calabrese EJ, Baldwin LA (2000e) Tales of two similar hypotheses: the rise and fall of chemical and radiation hormesis. Hum Exp Toxicol 19:85–97. doi:10.1191/096032700678815620
Carlson EA (1981) Genes, radiation and society: the life and work of H.J. Muller. Cornell University Press, Ithaca
Caron J (2003) Edward Lewis and radioactive fallout—the impact of Caltech biologists on the debate over nuclear weapons testing in the 1950s and 1960s. Thesis, Bachelor of Science. California Institute of Technology, Pasadena
Catcheside DG (1946) Genetic effects of radiations. Br Med Bull 4:18–24
Catcheside DG (1948) Genetic effects of radiations. Adv Genet Incorp Mol Genet Med 2:271–358
Court-Brown WM (1958a) Nuclear and allied radiations and the incidence of leukaemia in man. Br Med Bull 14:168–173
Court-Brown WM (1958b) Radiation-inducted leukemia in man, with particular references to the dose-response relationship. J Chronic Dis 8:113–122
Cowie DB, Scheele LA (1941) A survey of radiation protection in hospitals. J Natl Cancer Inst 1:767
Demerec M (1948) Induction of mutations in *Drosophila* by dibenzanthracene. Genetics 33:337–348
Drake JW (1978) Some guidelines for determining maximum permissible levels of chemical mutagens. In: Flamm WG, Mehlman MA (eds) Advances in modern toxicology, Volume 5-Mutagenesis. Hemisphere Publishing Corporation, New York, p 926
Drake JW, Abrahamson S, Crow JF, Hollaender A, Lederberg S, Legator MS, Neel JV, Shaw MW, Sutton EE, von Borstel RC, Zimmering S, de Serres FJ (1975) Environmental mutagenic hazards. Science 187:503–514. doi:10.1126/science.163482
Driver HE, White INH, Butler WH (1987) Dose-response relationships in chemical carcinogenesis: Renal mesenchymal tumors induced in the rat by single dose dimethylnitrosamine. Br J Exp Pathol 68:133–143
DuShane G (1957) Loaded dice. Science 125:964
Environmental Protection Agency (EPA) (1976) Health risk and economic impact assessments of suspected carcinogens. Fed Regist 41:21402–21405
Environmental Protection Agency (EPA) (1979) Water quality criteria. Fed Regist 44:15926–15931
Environmental Protection Agency (EPA) (1980) Water quality criteria documents; availability. Fed Regist 45:79318–79356
Evans RD (1949) Quantitative inferences concerning the genetic effects of radiation on human beings. Science 109:299–304. doi:10.1126/science.109.2830.299
Federal Radiation Council (FRC) (1960) Background material for the development of radiation protection standards. Report No. 1. Federal Radiation Council, Washington, DC
Finkel MP (1958) Mice, men, and fallout. Science 128:637–641. doi:10.1126/science.128.3325.637
Foulds L (1969) Neoplastic development, vol I. Academic Press, New York
Freese E (1973) Thresholds in toxic, teratogenic, mutagenic, and carcinogenic effects. Environ Health Perspect. doi:10.2307/3428074
Furth J (1957) Hearings on the nature of radioactive fallout and its effects on man, in joint committee on atomic energy. United States Government Printing Office, Washington, DC, p 2000
Glucksmann A, Lamerton LF, Maynford WV (1957) Cancer, Chapter 12. In: Raven RW (ed), Butterworths, London
Hanson FB (1928) The effect of X-rays in producing return gene mutations. Science LXVII:562–563. doi:10.1126/science.67.1744.562
Hanson FB, Heys F (1929) An analysis of the effect of the different rays of radium in producing lethal mutations in *Drosophila*. Am Nat 63:201–213. doi:10.1086/280254
Hanson FB, Heys F (1932) Radium and lethal mutations in *Drosophila* further evidence of the proportionality rule from a study of the effects of equivalent doses differently applied. Am Nat 66:335–345. doi:10.1086/280441
Hanson FB, Heys F, Stanton E (1931) The effect of increasing X-ray voltages on the production of lethal mutations in *Drosphila melanogaster*. Am Nat 65:134–143. doi:10.1086/280355
Henschen F (1968) Yamagiwas tar cancer and its historical significance—from Percival Pott to Katsusaburo Yamagiwa. Gann 59:447–451
Henshaw PS (1941) The biological significance of the tolerance dose in X-ray and radium protection. J Natl Cancer Inst 1:789–805
Houle CD, Ton TT, Clayton C, Huff J, Hong HL, Sills RC (2006) Frequent p53 and H-ras mutations in benzene- and ethylene oxide-induced mammary gland carcinomas from B6C3F1 mice. Toxicol Pathol 34:752–762. doi:10.1080/01926230600935912
International Commission on Radiological Protection (ICRP) (1966) The evaluation of risks from radiation, ICRP Publication 8. Pergamon Press, Oxford
Joint Committee on Atomic Energy (JCAE) of the Congress of the United States (1957) Hearings on the nature of radioactive fallout and its effects on man. 2 vols. plus summary. Government Printing Office, Washington
Joint Committee on Atomic Energy (JCAE) of the Congress of the United States (1959) Hearings on fallout from nuclear weapons tests. 3 vols. plus summary. Government Printing Office, Washington
Joint Committee on Atomic Energy (JCAE) of the Congress of the United States (1960a) Selected materials on radiation protection criteria and standards: Their basis and use. Government Printing Office, Washington
Joint Committee on Atomic Energy (JCAE) of the Congress of the United States (1960b) Statement of Dr. E.B. Lewis, Division of

Biology, California Institute of Technology. Radiation protection and somatic effects. In: Selected materials on radiation protection criteria and standards: their basis and use. Government Printing Office, Washington, pp 404–407
Joint Committee on Atomic Energy (JCAE) of the Congress of the United States (1960c) Statement of Dr. Austin M. Brues, Director, Division of Biological and Medical Research, Argonne National Laboratory, Argonne, IL. Radiation protection and somatic effects. In: Selected materials on radiation protection criteria and standards: their basis and use. Government Printing Office, Washington, pp 408–437
Jolly JC (2003) Thresholds of uncertainty: radiation and responsibility in the fallout controversy. Dissertation, Oregon State University, p 591
Kathren RL (1996) Pathway to a paradigm: the linear nonthreshold dose-response model in historical context: the American Academy of Health Physics 1995 radiology centennial Hartman oration. Health Phys 70:621–635. doi:10.1097/00004032-199605000-00002
Kennaway EL (1955) The identification of a carcinogenic compound in coal-tar. BMJ 2:749–752
Kimball AW (1958) Evaluation of data relating human leukemia and ionizing radiation. J Natl Cancer Inst 21:383–391
Lamerton LF (1958) An examination of the clinical and experimental data relating to the possible hazard to the individual of small doses of radiation. Br J Radiol 31:229–239
Lamerton LF (1964) Radiation carcinogenesis. Br Med Bull 20:134
Larson CD (1989) Historical development of the national primary drinking water regulations. In: safe drinking water act: amendments, regulations and standards. Lewis Publishers, Chelsa, pp 3–15
Latarject R (1948) Production dune mutation bacterienne par des substances cancerigenes ou non. Comp Ren Des Seances Soc Biol Filiales 142:453–455
Lawley PD (1994) Historical origins of current concepts of carcinogenesis. Adv Cancer Res 65:18–111
Lewis EB (1957) Leukemia and ionizing radiation. Science 125:965–972. doi:10.1126/science.125.3255.965
Lipshitz HD (2005) From fruit flies to fallout: Ed Lewis and his science. Dev Dyn 232:529–546. doi:10.1002/dvdy.20332
Loechler EL (1996) The role of adduct site-specific mutagenesis in understanding how carcinogen-DNA adducts cause mutations: perspective, prospects and problems. Carcinogenesis 17:895–902. doi:10.1093/carcin/17.5.895
Loveless A, Hampton CL (1969) Inactivation and mutation of coliphage T2 by *N*-methyl-*N*-nitrosourea and *N*-ethyl-*N*-nitrosourea. Mutat Res 7:1–12. doi:10.1016/0027-5107(69)90043-8
Malling HV (2004a) Incorporation of mammalian metabolism into mutagenicity testing. Mutat Res 566:183–189. doi:10.1016/j.mrrev.2003.11.003
Malling HV (2004b) History of the science of mutagenesis from a personal perspective. Environ Health Perspect 44:372–386
Mole RH (1958) The dose-response relationship in radiation carcinogenesis. Br Med Bull 14:184–189
Muller HJ (1927) Artificial transmutation of the gene. Science 66:84–87. doi:10.1126/science.66.1699.84
Muller HJ (1928) The problem of genic modification. Verhandlungen des V. Internationalen Kongresses fur Vererbungswissenschaft (Berlin, 1927) in Zeitschrift fur inductive abstammungs- und Vererbungslehre. Suppl Band 1:234–260
Muller HJ (1930) Radiation and Genetics. Am Nat 64:220–257. doi:10.1086/280313
Muller HJ (1951) In: Baitsell GA (ed) Science in progress, 7th series. Yale University Press, New Haven, pp 95–165
Mustacchi PO, Shimkin MB (1956) Radiation cancer and Clunet. J Cancer 9:1073–1074. doi:10.1002/1097-0142(195611/12)9:6<1073::AID-CNCR2820090602>3.0.CO;2-9
Mutscheller A (1925) Physical standards of protection against roentgen ray dangers. Am J Roentgenol Rad Ther 13:65–70
Mutscheller A (1928) Safety standards of protection against X-ray dangers. Radiology 10:468–476
National Academy of Sciences (NAS)/National Research Council (NRC) (1956) The biological effects of atomic radiation: a report to the public. NAS/NRC, Washington
National Academy of Sciences (NAS)/National Research Council (NRC) (1959) A commentary on the report of the United Nations scientific committee on the effect of atomic radiation. NAS Publication 647. NAS/NRC, Washington
National Academy of Sciences (NAS)/National Research Council (NRC) (1972) The effects on populations of exposure to low levels of ionizing radiation. National Academy, Washington
National Committee on Radiation Protection, Measurements (NCRPM) (1960) Somatic radiation dose for the general population. Science 131:482–486. doi:10.1126/science.131.3399.482
Nordling CO (1952) Theories and statistics of cancer. Nord Med 47:817–820
Nordling CO (1953) A new theory of the cancer-inducing mechanism. Br J Cancer 7:68–72
Oliver CP (1930) The effect of varying the duration of X-ray treatment upon the frequency of mutation. Science 71:44–46. doi:10.1126/science.71.1828.44
Oliver CP (1931) An analysis of the effect of varying the duration of x-ray treatment upon the frequency of mutations. Doctor of Philosophy Thesis, University of Texas, Austin
Olivieri G, Bodycote J, Wolff S (1984) Adaptive response of human-lymphocytes to low concentrations of radioactive thymidine. Science 223:594–597. doi:10.1126/science.6695170
Pochin EE (1958) Radiation and leukaemia. Lancet 1:51–52
Richter A, Singleton WR (1955) The effects of chronic gamma radiation on the production of somatic mutations in carnations. Genetics 41:295–300
Rous P (1910) A transmissible avian neoplasm (Sarcoma of the common fowl). J Exp Med 12:696–705. doi:10.1084/jem.12.5.696
Rous P (1959) Surmise and fact on the nature of cancer. Nature 183:1357–1361. doi:10.1038/1831357a0
Safe Drinking Water Committee (1977) Drinking water and health. National Academy of Sciences, Washington
Samson L, Cairns J (1977) New pathway for DNA-repair in *Escherichia coli*. Nature 267:281–283. doi:10.1038/267281a0
Serebrovsky AS, Dubinin NP (1930) X-ray experiments with *Drosophila*. J Hered 21:259–265
Setlow JK (1964) Effects of UV on DNA-correlations among biological changes, physical changes and repair mechanisms. Photochem Photobiol 3:405–413. doi:10.1111/j.1751-1097.1964.tb08163.x
Sievert R (1925) Einige untersuchungen uber vorricht ungen zum schutz gegen roentgenstrahlen. Acta Radiol 4:61. doi:10.3109/00016922509133488
Singleton WR (1954a) The effect of chronic gamma radiation on endosperm mutations in maize. Genetics 39:587–603
Singleton WR (1954b) Radiation effects on living systems. J Heredity 45:58–64
Solomon MS, Morgenthaler P-ML, Turesky RJ, Essigmann JM (1996) Mutational and DNA binding specificity of the carcinogen 2-amino-3, 8-dimethylimidazo[4, 5-f]quinoxaline. J Biol Chem 271:18368–18374. doi:10.1074/jbc.271.41.25240
Stadler LJ (1930) Some genetic effects of X-rays in plants. J Hered 21:3–19
Sturtevant AH (1954) Social implications of the genetics of man. Science 120:405–407. doi:10.1126/science.120.3115.405
Sturtevant AH (1965) A history of genetics. Harper and Row Publishers, New York, pp 71–72
Taylor LS (1971) Radiation protection standards. CRC monotopics series. Chemical Rubber Company Press, Cleveland

Timofeeff-Ressovsky NW, Zimmer KG, Delbruck M (1935) Nachrichten von der gesellschaft der wissenschaften zu Gottingen. Uber die nature der genmutation und der genstruktur Biologie Band 1, Nr. 13

Trosko JE, Upham BL (2005) The emperor wears no clothes in the field of carcinogen risk assessment: ignored concepts in cancer risk assessment. Mutagenesis 20:81–92. doi:10.1093/mutage/gei017

United Nations Scientific Committee on the effects of atomic radiation (1958) Report of the United Nations Scientific Committee on the effects of atomic radiation. New York, United Nations. General Assembly Official Records, Thirteenth Session, Supplement No. 17 (A/3838)

United Nations Scientific Committee on the effects of atomic radiation (1962) Report of the United Nations Scientific Committee on the effects of atomic radiation. New York, United Nations. General Assembly Official Records, Seventeenth Session, Supplement No. 16 (A/5216)

United Nations Scientific Committee on the effects of atomic radiation (1964) Report of the United Nations Scientific Committee on the effects of atomic radiation. New York, United Nations. General Assembly Official Records, Nineteenth Session, Supplement No. 14 (A/5814)

Uphoff DE, Stern C (1949) The genetic effects of low intensity irradiation. Science 109:609–610. doi:10.1126/science.109.2842.609

Valadez JG, Guengerich FP (2004) *S*-(2-Chloroethyl)glutathione-generated p53 mutation spectra are influenced by differential repair rates more than sites of initial DNA damage. J Biol Chem 279:13435–13446. doi:10.1074/jbc.M312358200

Watson JD, Crick FHC (1953) Molecular structure of nucleic acids—a structure for deoxyribose nucleic acid. Nature 171:737–738. doi:10.1038/171737a0

Weil CS (1972) Statistics vs. safety factors and scientific judgment in the evaluation of safety for man. Toxicol Appl Pharmacol 21:454-463

Weinstein A (1928) The production of mutations and rearrangements of genes by X-rays. Science LXVII:376–377. doi:10.1126/science.67.1736.376

Whittemore GF Jr (1986) The National Committee on Radiation Protection, 1928–1960: from professional guidelines to government regulation. Thesis. Department of History of Science. Harvard University, Cambridge