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Review article

The additive to background assumption in cancer risk assessment: A reappraisal

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ABSTRACT

The assumption that chemical and radiation induced cancers act in a manner that is additive to background was proposed in the mid-1970s. It was adopted by the U.S. Environmental Protection Agency (EPA) in 1986 and then subsequently by other regulatory agencies worldwide for cancer risk assessment. It ensured that cancer risks at low doses act in a linear fashion. The additive to background process assumes that the mechanism(s) resulting in induced (i.e., treatment related) and spontaneous (i.e., control group) cancers are identical. This assumption could not be properly evaluated due to inadequate mechanistic data when it was proposed in the 1970s. Using the findings of modern molecular toxicology, including oncogene activation/mutation, gene regulation, and molecular pathway analyses, the additive to background assumption was evaluated in the present paper. Based on published studies with 45 carcinogens over 13 diverse mammalian models and for a broad range of tumor types compelling evidence indicates that carcinogen-induced tumors are mediated in general via mechanisms that are not identical to those affecting the occurrence of the same type of spontaneous tumors in appropriate control groups. These findings, which challenge a fundamental assumption of the additive to background concept, have significant implications for cancer risk assessment policy, regulatory agency practices, as well as fundamental concepts of cancer biology.

1. Introduction

This paper assesses a critical, but overlooked area of cancer risk assessment (i.e., cancer dose-response assessment), the additive to background assumption, that essentially ensures low dose linearity in the estimates of carcinogen exposure risks. This assumption was proposed for application to cancer dose-response assessment by Crump et al. (1976). A decade later it was incorporated into governmental risk assessment policy and practices during 1986 (Anderson et al., 1983; Crump, 1984; U.S. EPA, 1986) and has continued to the present (U.S. EPA, 2005; EFSA, 2017). This assumption was proposed during the mid 1970s when it was not possible to assess its scientific validity with the oncogene revolution starting in the mid-1980s and the continued clarification of molecular mechanisms for spontaneous and induced tumors to the present. It is now possible to evaluate the scientific validity of the additive to background assumption. The present paper demonstrates that the additive to background assumption that spontaneous and induced tumors occur via identical mechanisms is not compatible with the vast body of modern molecular findings. Prior to assessing the additive to background hypothesis, a brief historical reconstruction of how linearity at low dose was adopted for cancer dose-response assessment by U.S. regulatory agencies during the 1970s is presented, providing the necessary scientific and regulatory contexts and introduction needed to assess the additive to background assumption.

2. Historical foundations of cancer risk assessment

2.1. The Thanksgiving Cranberry Scare of 1959

Within five years following the National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel report (NAS/NRC, 1956) recommending the use of linear dose response modeling in risk assessment, Nathan Mantel and Raymond Bryan (1961) would publish their landmark paper on cancer risk assessment. The modestly entitled paper, *Safety Testing of Carcinogenic Agents,* was based on the use of the tolerance distribution probit dose response model. The probit model was originally derived to assess non-carcinogenic responses (Zeise et al., 1987). However, Mantel and Bryan (1961) generalized its use, applying it to modeling responses of carcinogens. Their efforts followed by nearly two decades the earlier work of Bryan and Shimkin (1943) who applied the probit model to estimate cancer risks for several carcinogenic hydrocarbons based on chronic studies with male C3H mice, a study that suggested an hormetic dose response

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that was not addressed by the investigators.

What stimulated the reemergence of interest in quantitative estimates of cancer risks was U.S. presidential politics. Mantel was employed as a biostatistician for the U.S. National Cancer Institute (NCI) during the time of the 1960 presidential election, pitting John F. Kennedy against Richard M. Nixon. During the run up to the election, there was the so-called Thanksgiving Cranberry Scare of 1959. The event proved to be both a major chemical scare for the American public and a chance for the two presidential candidates to demonstrate that they were not afraid of a small dose of the cancer causing (i.e. thyroid cancer) herbicide in their cranberry sauce or juice (i.e. Nixon had four servings of cranberry sauce while Kennedy had two drinks of cranberry juice-of course on the same day.) (http://coldwarstudies.com/2017/11/15/the-cranberry-scare-of-1959). The agent, 3-amino-1,2,4-triazole, which had been approved in 1957 for use on Cranberry bogs only after harvest, had been found in several sources of cranberries in the weeks leading up the Thanksgiving holiday (note that the farmers did not follow the instructions properly; they were only supposed to apply the herbicide after harvesting but applied it before). It became a political story when the Secretary of Health, Education & Welfare (HEW), Arthur Sherman Flemming went public on November 9, 1959 with the recommendation to the public not to buy cranberry products that year. His actions resulted in what might be called a consumer panic, which then threatened the livelihood of the cranberry industry. In an effort to prevent a similar public backlash in the future, Secretary Flemming asked the NCI for guidance on which cancer causing agents could be considered "safe" and what may be a safe or acceptable dose. To the rescue would come Mantel and the laboratory animal model cancer researcher Bryan, who were asked by the Director of the NCI to provide the needed guidance, including issues such as how to design appropriate animal bioassays and how to estimate risks and establish a means to distinguish between safe and unsafe. Little did the Secretary of HEW and the NCI Director realize that they had just opened a scientific version of Pandora's Box, with issues that still confront politicians, scientists and the general public.

In their publication, Mantel and Bryan (1961) would emphasize the generality of their dose response model approach for other agents and tumor endpoints. They introduced the concepts of no threshold and acceptable risk within a public health policy framework. In a manner to illustrate its practical utility they expressed the outcome of their model estimate in public health terms suggesting an acceptable risk with a value sufficiently low that few would have concerns over, that is, one cancer per 100 million people per lifetime. While this effort in 1961 by Mantel and Bryan was thought to have put a lid on concerns with chemical carcinogens, it was only the beginning, as Rachael Carson would publish her *Silent Spring* book a year later (Carson, 1962). The Carson publication, which was partially inspired by the efforts of radiation geneticist Hermann J. Muller, would galvanize the fledging environmental movement, lead to the creation of the National Environmental Protection Act (NEPA) (1969) and the EPA (1970) and help spark efforts to address the issue of cancer dose-response assessment about a decade later.

2.2. U.S. EPA, Cancer risk assessment, and low dose linearity

It would take about 12 years but the U.S. FDA would eventually restart its cancer risk assessment agenda by formally proposing the Mantel-Bryan (1961) model while still retaining the 1/100 million acceptable risk level in their July 19, 1973 (U.S. FDA, 1973) cancer risk assessment announcement in the *Federal Register*. As the regulatory stakes had changed since the Cranberry scare of 1959, this proposal was taken seriously, and became stalled in the U.S. regulatory apparatus. It finally emerged following what could only be seen as a rather elephantine-like gestational period in 1977 (U.S. FDA, 1977), having survived a presidential election and new political leadership. The Mantel-Bryan probit model approach had been largely retained, although with a number of alterations, including the adoption of a new acceptable risk value of one in a million.[1]

The practical significance of such actions was that it became the risk estimate below which no further governmental regulatory actions would be initiated. This recommendation was placed within the framework of a public health safety response to carcinogen residues in food products. Even though it had taken a long time to get an approved cancer risk assessment process through the regulatory system, the FDA-approved Mantel-Bryan model became the first cancer dose-response assessment model officially adopted by a U.S. federal regulatory agency. The next change would not take so long. About two years later, the U.S. FDA (1979) would alter its approach by dropping the tolerance distribution Mantel-Bryan model approach, replacing it with a linear dose response model. The rationale for such a decision was due to the more conservative risk estimates of the linear model along with its conceptual simplicity and ease of risk calculation (Anonymous, 1979). In the low dose zone, the one hit model as initially proposed by Timofeef-Ressovsky et al. (1935) yields very similar risk estimates as a simplified linear model. Getting a federal agency to change its cancer dose-response assessment model only two years after a long incubation period should raise the proverbial "why"? In fact, the FDA's actions were the direct offshoot of the recommendations of a multi-governmental agency panel with FDA technical representation (biostatistician David Gaylor) that published their linear dose response recommendation (Hoel et al., 1975). It was simply a matter of being more conservative, simplifying the process and timing.

While the U.S. FDA was pursuing its cancer risk assessment methods and issues, so to was the U.S. EPA. The posturing and approaches that emerged from this fledgling environmental regulatory agency seemed somewhat confusing to the outside reader and the regulated community. Much of the initial conceptualizing on the issue of regulation of cancer causing agents emerged from the Rachael Carson-inspired need to address the issue of risks from pesticides. Thus, during major pesticide hearings EPA staff attorneys presented an intellectual blueprint of what amounted to a set of Agency "cancer principles". The new "Principles" reflected the Agency view that carcinogen exposures should not be permitted…..that is, prevented from occurring in the first place. While the goal of this Principle was to ban carcinogenic agents from the market place, it was quickly seen as simply unrealistic, though it could remain a goal (Albert, 1994; Calabrese, 2009, 2013).

What emerged from this process was EPA adopting a set of non-regulatory guidelines that could be applied to a generic cancer risk assessment process (U.S. EPA, 1976). This system would have considerable practical importance, as it would employ quantitative risk assessment on chemicals and engineering-based processes. This conceptual framework would be the functional lead-in for a critical paper by the EPA's Carcinogen Assessment Group (CAG) (Albert et al., 1977), which reaffirmed the LNT concept and justified it based on

[1] During this regulatory "incubation" period within the FDA, Mantel et al. (1975) would update the original (Mantel and Bryan, 1961) application of the probit model with an "improved Mantel-Bryan procedure". The original Mantel and Bryan (1961) procedure incorporated Abbott's (1925) correction to adjust for spontaneous tumor background. This new procedure would account for background/spontaneous tumors via the introduction of a new estimated parameter "C", the expected (spontaneous) incidence in untreated animals, with the subsequent application of Abbott's correction (Abbott, 1925; Zeise et al., 1987). It is likely that the adoption of the independent of background approach using Abbott's formula by Mantel et al. (1975) lead to EPA accepting this approach several years later when it was incorporated into the single-hit model (Costle, 1979) and later into the multi-stage model (Anderson, 1983). Mantel et al. (1975) noted the possibility of an alternative to the independent of background model, by proposing a scheme similar to the additive to background concept. In this scheme, the spontaneous tumor rate "represents the response to the load of the test agents and its equivalent ALREADY in the environment. The total load for an individual or animal is then the sum of its administered dose and its environmental load. This was similar to that proposed earlier by Albert and Altshuler (1973) and later by Crump et al. (1976), except that Crump et al. (1976) tied the background and induced tumors via an identical mutation mechanism as discussed later in the text.