The 1970s were an exciting time for the development and attention given to estimating human health risk for environmental and occupational exposures. In the 1960s much attention and concern was given to the epidemiological studies by Richard Doll on cigarette smoking and lung cancer, Irving Selikoff’s studies of asbestos workers, Rachel Carson’s book *Silent Spring*, and the adverse health effects of ionizing radiation observed by the Atomic Bomb Causality Commission in Hiroshima. This all helped lead to the creation of the Environmental Protection Agency (EPA) as well as the National Institute of Environmental Health Sciences (NIEHS) in 1966 and its National Toxicology Program (NTP) in 1976. Also at the international level, the International Agency for Research on Cancer (IARC) of the World Health Organization began their monograph series of the evaluation of cancer risks to humans in 1972. There have been over 100 of these important monographs that include for each topic evaluations of sources of the material under study along with evaluations of the toxicology, epidemiology, and mechanistic evaluations. The monographs, however, do not attempt to quantify the cancer risk. The EPA’s Integrated Risk Information System (IRIS) reports do provide quantitative estimates of risk. There are now over 900 substances listed in the IRIS directory of reports. There are now about 600 NTP reports from NIEHS. These reports are the result of rodent tests of various chemicals. The typical study consists of 300 animals (150 mice, 150 rats) exposed to a maximum tolerated dose (MTD), 1/2 the MTD, and a control group exposed for 2 years with thus 50 animals per dose group.

What was of particular importance is how one analyzes the rodent data and how to translate any positive rodent effects to human risk particularly to low doses for setting environmental and occupational exposure limits. The major risk assessment challenges in the 1970s were high- to low-dose extrapolation and “mouse to man” extrapolation. The primary focus was on cancer effects since they were of greatest concern from a public health viewpoint.

Back in the 1950s the idea of a safety factor approach to set acceptable limits on exposures was developed. This was especially of importance for food additive policies. The use of a factor of 100 applied to the highest “no effect level” in a study was used. A factor of 500 was applied if instead one used the “lowest positive effect level.” The use of 100 was based on the idea that a factor of 10 when extrapolating from animals to humans and incorporated another factor of 10 to account for differential sensitivities within the human population. Weil proposed using a factor of 5000 from the lowest positive effect dose because of uncertainties in animal to man extrapolation. Instead of a simple safety factor approach, the log-probit method of Mantel and Bryan in 1961 attempted to fit a function (the probit) to the observed dose–response data and then to estimate effects at given low doses. This seemed appropriate for cancer since it was not accepted that thresholds exist for carcinogen exposures. This helped to set off a lot of varied activity in selecting appropriate dose–response functions for the purpose of estimating low-dose cancer effects for regulatory exposure limits. The logit function has provided similar fits; however, the choice of dose–response function can make a considerable difference at very low doses.

For extrapolation purposes, carcinogenesis data consisted of 2 types. The usual form gives lifetime incidences at various doses for estimation of a dose incidence curve and its associated error probabilities (eg, probit, logit, one-hit). The second type of dose–response modeling is time-to-occurrence as a function of exposed dose. The time-to-occurrence would typically be time of death due to the cancer of interest or time of first appearance of the particular tumor of interest. This brought forward competing distributions. Albert and Altschuler considered the lognormal distribution. The other popular choice was the Weibull distribution (Pike and Peto et al).

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What received the most attention has been the Armitage and Doll’s\(^6\) multistage model of cancer. Mathematical algorithms were developed at NIEHS by Guess and Crump.\(^7\) In 1976, Crump et al\(^8\) published a basic paper on the fundamental carcinogenic process and its effect on low-dose risk. Kenny Crump continued to develop programs for multistage analyses after returning from his year’s visit to NIEHS. These analyses have and continue to be applied in various EPA projects. A review and analysis of the mathematical models of risk was published in 1978 by Whittemore and Keller.\(^9\) It should also be mentioned that during these years there was excitement and hope that the salmonella microsome mutagenicity test could actually replace the animal experiments (see McCann and Ames\(^10\)). Since there is a reasonable correlation between animal cancer potency and degree of mutation in the Ames test, the test could help to be used for priority setting in animal bioassays. Also, an Ames positive assay adds to the strength of the animal bioassay results.

The question of extrapolating animal cancer results to man has been of considerable concern. For a given compound, there are likely to be species differences in absorption, metabolism, and excretion. Extrapolation of dose exposure from laboratory animal studies to man seems to be best when based upon dose per surface area or equivalently 2/3 power of body weight.

For an extensive and detailed review of risk assessment as has been briefly discussed here, one is referred to the study by Hoel et al.\(^11\) The article presents the position of the Public Health Service on risk assessment as of 1975.

### Personal Reflections

The years of the 1970s were very interesting and exciting for those in the statistical/mathematical areas. When I first came to NIEHS shortly after its establishment, it was especially invigorating due to its connections with National Institutes of Health (NIH) in Bethesda, NCI, and DCRT in particular, as well as interactions with faculty and students at University of North Carolina (UNC). By our close proximity to UNC, there was the opportunity to interact with their faculty and to supervise some of their PhD student’s dissertation work. For example, Chris Portier was a student of mine, and for his dissertation, we worked on the best bioassay design for low-dose extrapolation. Chris stayed on at NIEHS after his degree and much later became director of the National Center for Health Statistics. National Institute of Environmental Health Sciences had funds for visiting scientist who allowed me to invite Kenny Crump to visit for a year and introduce him to the multistage model of cancer for which he successfully developed very important statistical algorithms used by government agencies for cancer risk estimation. The 1970s were especially fulfilling by the number of committees working on cancer reports. This especially included the NIH, IARC, and EPA. Working on these committees provided the opportunity to make new friends and colleagues. This was personally very satisfying for me. Finally, the 1970s were a time of challenging research problems with rapid and interesting results in the area of quantitative human risk assessment.

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