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The 1980s—A Decade of Change[1]

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It is indeed a privilege and a pleasure for me to be with you for these 3 days of discussion on "Procedures and Methods for the Assessment of Environmental Quality." It has been great fun for me to visit with some of my old friends whom I have not seen for some time, but more importantly it provides me with an opportunity to share with you some of my thoughts on the changes which will be taking place in our SOPs, our standard operating procedures for assessment of safety. I believe it is extremely important that we proceed into this new decade of the eighties with an objective and open mind, so that we apply our resources to the right problems and in the most effective manner to give us the greatest return on our investment in terms of environmental quality. We cannot afford to squander inordinate amounts of our growing but still limited resources on emotional issues of low priority, as we did in the seventies.

It is becoming apparent that we, the scientific community, must speak out for science and technology. We must fight to remove the emotionalism and politics from decision making on matters of environmental quality. We must reverse some of the policies of the seventies. It is a challenge but I am optimistic that we can do this in the eighties. But, let me discuss some of the specific areas in which I believe we can effect change.

In the seventies we saw the burgeoning of the adversary process in the field of safety evaluation. There has always been a sense of competition between government and industry, but always a high degree of mutual respect. In the seventies that spirit changed from competition to an adversary posture and from respect to distrust. It will be interesting to see what others who analyze the seventies will say was the cause of this disastrous change, but in my opinion it was the "zero risk" concept which infiltrated the regulatory agencies—the Delaney philosophy. Certain sincerely motivated and dedicated individuals wanted to achieve a 100% safe en-

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vironment, free of any risk from chemicals which cause cancer, interfere with normal reproduction and genetics, or accelerate senilic or other changes in a single living human being or in any other creature on earth. There should be no provision for trace exposure to a carcinogen because that might permit a little bit of cancer.

This "zero risk" concept was thrust upon the regulatory agencies in the seventies by the involvement in the regulatory process of many individuals untrained in the scientific process, especially lawyers, who were called upon to help draft regulations for new laws passed by Congress.

Prior to the seventies we used such language as "safe beyond a reasonable doubt," the language of the food additives amendment to the Food, Drug, and Cosmetic Act. We knew that absolute safety was a fantasy, an unachievable goal, and we tried to reduce risks to an ever-diminishing level. Maybe we were somewhat cavalier, but if we had to resort to statistical analysis of tumor incidence at a maximum tolerated dose of a chemical in comparison with the control, we generally concluded that we did not have a toxicological effect worth pursuing. Rather than devote a great professional effort to repeating the study, or to reducing exposure to a minimum, we generally considered it more productive to move on to examining other chemicals for more significant health hazards.

This is the tragedy of the NCI bioassay program. Originally it was designed and intended to be a screening program to detect tumorigens, under the most extreme testing conditions. It was not intended to be a definitive safety evaluation. If a chemical gave a positive response under these extreme conditions, it was intended that more extensive and definitive studies be conducted, including lower doses, metabolic rates, other species, etc., to permit evaluation of the health hazard.

Unfortunately our hysteria over cancer and the Delaney philosophy—the "zero risk" philosophy—have prevented the regulatory agencies from this type of rational action. They are forced to act on the basis of preliminary, screening data from NCI or any organization. They find it politically unacceptable to wait for definitive research, or as the clichés go: "we cannot gamble with public health," "chemicals have no constitutional rights, they are guilty until proven innocent"—the "zero risk" philosophy.

Fortunately, there is now growing recognition of the fact that there is no such thing as absolute safety and that the demands for "zero risk," as per the Delaney philosophy, are incompatible with other needs of society. However, with this increased realization that the terms safe and hazardous are not white and black situations, but are judgments which were made previously by toxicologists, there is a growing sentiment that the public should play a role in deciding how safe is safe.

This public participation is welcome and I believe beneficial for all involved. However, it necessarily involves education and understanding, which slow the process of decision making and the ability to act. It sometimes is reduced to a standstill if the public is represented by individuals who have antiestablishment motives. But realistically, the question usually evolves from "how safe is safe?" to "how safe can we afford?" The cost of removing an ever-diminishing doubt of safety increases geometrically; and by cost, I refer not only to financial commitments, but to social benefits which are delayed or denied. At some point with every decision a degree of risk must be accepted.

Now this brings us to what is going to be the fad of the eighties—risk assessment.

This is an attempt to quantify the probability of injury or illness which may be associated with a decision to permit a specific exposure to a chemical. It is predicated on the assumption that society generally accepts certain degrees of risk associated with natural phenomena—lightning, tornadoes, tidal waves, sun radiation, etc.—and that risks from chemical exposures which are no greater than these background risks are generally acceptable to the public. No effort has been made to obtain a public vote on this concept and I am not at all certain how such a vote would turn out. In reality, risk assessment is merely a device for regulators to communicate to the public in a reassuring manner—so they can say that the risk of injury from exposure to a specific chemical is no greater than being struck by lightning. Everyone can relate to this analogy and it seems to have a reassuring effect.

Whether or not the assessment of risk is correct is another matter. How do you arrive at such an estimate of the probability of injury? In the case of chemicals for which we cannot establish a threshold, like some direct carcinogens, there is no biological method for predicting or extrapolating the potential effect from a dosage several orders of magnitude below a dosage level already demonstrated to produce "no measurable effects." A small fraction of a dose which causes "no measurable effect" also should cause "no measurable effect." But maybe biology fails us, because it is theoretically possible that an effect may exist and biology cannot measure it. In desperation we turn to the experts on probabilities and find a solution because statisticians rush in where biologists fear to tread. In statistical analysis, numbers are impersonal and are treated the same whether they are probabilities for winning at roulette or for developing a liver tumor. Fortunately, statistics can extrapolate from a "no measurable effect" level to a "less than no measurable effect" level, even though it has no biological basis and is indeed contrary to biological concepts. This is the current fad and it appears that we will spend the first several years of the eighties not debating the concept, but trying to decide which of many statistical methods is the best for extrapolation.

I am pessimistic that we will ever find any way to make this type of risk assessment a useful procedure. At the same time, I am optimistic that we will return to the positive approach of *safety* evaluation, in which we accept, for most toxic responses, the concept of a threshold below which no risk is involved. I believe that biological rather than statistical evaluation of the significance of effects needs to be restored, but I also believe that the public should share in this process. That sharing should not be a public debate or even public involvement in each and every decision, but participation in establishing the principles which guide the decision maker, principles based on biological observations rather than hypothetical risks.

This movement toward risk assessment and hopefully beyond it will be one of the major changes for the eighties and will affect not only the evaluation of our laboratory data, but also the type of data which we collect and the way we perform our experiments.

Again, let me return to our "zero risk" concept which has caused so many changes and apply it more directly to the laboratory. There are several things which can be done to reduce the risk of obtaining a false-negative response—of failing to detect a toxicologic response in our laboratory animals. The easiest is to increase the number of animals we use per group. We experienced two such increases mandated by the regulatory agencies for chronic rodent studies in the seventies and we can anticipate pressure for additional increases in the eighties. There is no com-

pletely effective argument against the statistician's claim that 200 rats are better than 100 rats.

As consumers, our pocketbooks seem to be at the mercy of OPEC, who can raise the price of oil anytime they want. As toxicologists, our budgets seem to be at the mercy of the regulatory agencies who can raise the price of our experiments anytime they want by doubling the number of animals. We must ask ourselves if the increment of additional risk reduction is worth the cost, especially when part of that cost is a diversion of effort from other health and environmental activities. As a profession, we must accept the principle of diminishing return and resist further erosion of our productivity.

Another approach to reducing risk to zero as it applies to the laboratory is to challenge the validity of all negative data, because these data may be falsified. This has been our latest technique which has resulted from the extreme adversary process between industry and the regulatory agencies—the shift from mutual respect to distrust. Many of you will immediately recognize that I am now referring to the most onerous development of the seventies in the field of toxicology—GLPs, or good laboratory practices. These innocuous sounding words are very deceiving. For the regulatory agency, GLPs merely refer to proof that there was no cheating in the experiment. We should not delude ourselves into thinking that GLPs contribute anything to the precision of our investigations. They merely verify that a given study was performed as stated by the investigator. Only a few years ago, we were willing to take this for granted. We had mutual trust in each other, scientist to scientist; and even if a colleague was tempted, the penalty of loss of reputation if caught was considered to be enough to deter falsification of data. I think it is a sad commentary that the signatures and reputations of all of us in this room are not sufficient in the judgment of the regulatory agencies to validate a study. A reputation, built on a career of integrity, is worth nothing today. Peer review has been replaced by peer intimidation. Every piece of data we report is assumed to be falsified or fictitious unless a third party verifies that we derived it in an honest way. Without this verification the data are discarded and a data gap exists. "Zero risk" is inconsistent with any assumption, other than that of a possible risk.

I find this to be a tragic state of affairs for the profession of toxicology. It is pretty obvious that we have thrown common sense out of the window when a short-term toxicity report is as thick as the New York City telephone directory; when 90% of that report contains raw data and verification reports which contribute nothing to the conclusion, but merely permit a complete audit trail and assure compliance with GLPs, "form" has become more important than "substance."

I know of no other profession, no other occupation, no other business that has allowed itself to become so dominated by government and stripped of its integrity and pride. We are guilty until proven innocent, which is merely an extension of the same philosophy that has been adopted for years concerning chemicals. I have heard some people complacently say that the auditing/validation of toxicological studies is really not different from an outside accounting firm auditing of a company financial report. Yes, it is quite different. An accounting firm will come into a corporation or university periodically to inspect accounting procedures and practices and spot-check specific items. If these are being performed in accordance with good accounting principles, they will so certify. They do not audit and validate every contract, every bank transaction, every purchase order, every small transaction.

No, only the toxicologist and the toxicology laboratory are subject to this type of in-depth scrutiny, distrust, and regulatory overkill. More "zero risk."

The only hope I see of reversing this trend is through many of you, especially our European colleagues. Obviously, GLPs can be used as artificial trade barriers, by any country. Consequently harmonization is an objective being pursued through the Organization for Economic and Cooperative Development (OECD). The members of the Common Market countries are pressing for reasonable GLPs, which recognize a degree of dignity among professionals. Hopefully, the United States will agree to adopt these GLPs, rather than invite continued criticism from abroad and possible retaliation with further disruption to our balance of trade.

This brings us to the very practical and critical area of decision making which I think will describe the eighties—How will we spend our resources in the toxicology laboratory? We have reached the point when technology assessment is essential. We must apply greater selectivity to our choice of investigations or we will lose ground in our quest for lower risk. We cannot afford to spend a half-million dollars and two years of time to determine whether or not a chemical is a carcinogen, mutagen, or teratogen. We cannot afford to double and redouble the number of animals we use in our studies, merely to reduce the chance of a false-negative assay. We cannot afford to devote more time on the "form" rather than the "substance" of our toxicological studies. We cannot afford the distrust and the adversary atmosphere that have divided the profession. We cannot continue to divert an unreasonable amount of our resources trying to reduce risk to zero for one chemical at the expense of needed investigations on other chemicals. We must reduce to a minimum those studies which can be predicted to contribute nothing to a safety decision, regardless of the experimental outcome.

That is, I think, our challenge for the eighties: To effect change so that our resources are dedicated to significant health and environmental problems. We must assess our technology, select the best procedures and methods, and apply them with the wisdom of Job to the most rewarding problems.