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ISSUES IN ENVIRONMENTAL TOXICOLOGY AND CHEMICAL ANALYSIS

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Presented before the
Association of Official Analytical Chemists
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I. Introduction

It is a pleasure for me to come before you this afternoon on the occasion of the centennial meeting of the Association of Official Analytical Chemists (AOAC). In the annals of professional organizations there are few which are so venerable in terms of age and accomplishment, and yet so unknown and unheralded by the general public.

The AOAC serves several vital functions. First, I would like to note the development of AOAC methods of analysis, which in many ways become the "coin of the realm". If a procedure merits the title of "an AOAC method", you know that it has proven itself. Second, the organization is of such a quality that it attracts accomplished scientists from industry, government and academe. In this way, AOAC provides a mechanism for substantive scientific dialogue on a professional plane, even when regulatory and judicial activity may encumber other levels of communication.

I have been asked to give the Introductory presentation in an analytical chemistry symposium dealing with environmental toxicology. The fact that you have avoided the temptation, on the occasion of your centennial, to essentially show home movies of your first 100 meetings bespeaks your vitality and youthful perspective about the future. You are to be commended in selecting "environmental toxicology" as the theme for the conference. This topic might be viewed by some as a sometime brash, error prone, over exuberant but well-meaning "new kid on the block". Impartial observers might question whether your sympathetic view might not be evidence of some degree of paternity by analytical chemists. (Such observers are probably correct!) Whatever its ancestry I believe that Environmental Toxicology merits some pride. However, even a proud parent must acknowledge that this kid is often clumsy, needs a fair degree of supervision and, on occasion, lacks discipline.

Today, I would like to share my views on environmental toxicology, the role analytical chemistry plays in the field, and the practical implications of your work in my work as a regulator sworn to protect public health and the environment.

First, to set the stage in a somewhat facetious way, I want to provide some background on the risk assessment/risk management process so much in vogue in the regulatory arena these days.

It has become quite fashionable lately to refer to the rite of regulatory decisionmaking in matters of chemicals and health as "risk management". Further, it is current dogma, that risk management can only proceed after the art of "risk assessment" has been practiced by those priests steeped in the knowledge of science and other arcane technical matters. Further, it has recently been revealed to the general public that chemical risk is only realized when one understands the concepts of "hazard and exposure". The means by which the technical wizards interact hazard and exposure data is still viewed as mysterious by most spectators (also many practitioners), perhaps because the one true, enlightened way has yet to be revealed in an area where false prophets may abound.

Hazard identification is generally held to be the domain of the biologist and biochemist. Significant progress has been made in using basic scientific knowledge to develop laboratory procedures that identify

a broad spectrum of toxicological effects. We are also becoming more sophisticated. Only 15 years ago, it was routine practice to equate a toxic effect observed in laboratory studies to a clear human risk. Today, the process is much more deliberate. One first determines in a qualitative sense that a laboratory toxic effect may reasonably predict plausible human hazard. For example, in determining the relevance of an immunosuppressive effect observed in animals to a possible human hazard, one currently attempts to determine if the effect is direct or mediated through systemic toxicity. In assessing the implication of an animal teratology study to the question of human hazard, one discriminates between a frank teratogenic effect and one that may be secondary to maternal toxicity. One also strives to differentiate between morphological changes that represent maturation delay and structural changes that represent frank fetal toxicity. In cancer studies, attempts are made to distinguish between primary and secondary effects, for example, rat mammary tumors may represent a response secondary to altered prolactin levels; bladder tumors may be secondary to bladder stone formation which in turn is dependent on chemical dose.

Since we now venture to state that a laboratory result in animals does not a priori equate to human risk, the general public is being asked to unlearn the simplistic dogma that science fostered less than a generation ago. Many in the scientific community are also slow to change. Some scientists are reluctant to accept the fact that they may no longer be able to play the role of instant risk predictors and have refuted the correctness of the change. In this situation, the media does not know who to believe and reports all sides of the issue. The public, who is the dubious beneficiary of this news, certainly is not well served by this plethora of conflicting views and becomes more cynical than sanguine. Youthful environmental toxicology is learning that growing up isn't painless!

Analytical chemistry plays a vital role in hazard determinations. This role ranges from straightforward characterization of test chemicals to stability of test solutions. More recently, advances in analytical chemistry have permitted the identification and quantification of the chemical form(s) at the target site. The accuracy and precision of these methods needs the dispassionate scrutiny traditionally associated with the AOAC.

If hazard is the fiefdom of the biological scientist where the analytical chemist serves as a serf in the fields, the analytical chemist is the czar of the realm of exposure. If recent advances in hazard prediction can be described as sure and deliberate, the analytical chemist's progress is appropriately described as "lapping the field." The exploitation of computers and electronics have given them the gas chromatograph/mass spectrometry interface that provides exquisite sensitivity and specificity. Curve fitting, computer generated graphics, machine massaging of data and the like have resulted in a limits of detection that could only have been imagined a generation ago. Not infrequently have I heard a middled-aged colleague ruefully state that the equivalent of his postdoctoral research, the true flowering of the intellect, is now processed overnight!

I recently had cause to refresh my memory on the state of the art in residue chemistry in the early 1960s. Detection limits for pesticides were commonly expressed as parts per hundred thousand. Parts per million levels were a real accomplishment. By now, I am sure that you have all been regaled about the "vanishing zero." The application of this exploding analytical chemistry capability to environmental toxicology is in most

circumstances a real boon. However, I believe we sometimes approach the acme of inanity. For example, within the past two years reports have appeared that cite levels of detection for 2,3,7,8-tetrachlorodibenzo-p-dioxin in water in the range of parts per quadrillion. That is one part in 10 to the fifteenth power! Consistent with the importance of this number from an environmental toxicology point of view is the observation that 10^{-15} is equivalent to one hamburger out of all the hamburgers McDonald's will make in the next 1,000,000 years! Both numbers are beyond our ability to comprehend; some might suggest they both are irrelevant to practical issues.

Given that these analytical results are for the most part "real" (keep them honest, AOAC) we must frankly acknowledge that the exactitude of such results surpasses the ability of toxicologists to assess their significance.

From my current perspective as a risk manager there may be value to be realized from this state of affairs. It may provide an opportunity to set aside the widely held perception that absolute safety or zero risk is attainable. The concept that any dose of a carcinogen

poses inherent risk can no longer be translated to a practice that states that no level of the substance is permissible in food, water, or air. Rather, the concept must logically evolve toward a practice that encompasses a level that represents no practical risk. Tacit acceptance of such a concept may alleviate some of the regulatory quicksand that sometimes bedevils us.

In some respects the rigorous drill the country experienced with ethylene dibromide (EDB) exemplifies the often painful process of learning to live with our knowledge. EDB at the time of its introduction as a fumigant had no hazard data base as we know it today -- the test procedures simply had not yet been invented or were not required of pesticides seeking registration. The compound is volatile at temperatures that foster insect infestation. Therefore, low or no residual levels were anticipated, and, sure enough, the analytical methods of the day generally detected no residues in treated grain. The operating assumption became that residue levels were "zero" and grain, therefore, was exempt from an EDB tolerance level.

Perceptions change with time -- the knowledge of the 1960s suggested a need to assess the toxic effects

associated with chronic exposure to chemicals. The development of early test procedures evolved in the 1970s and EDB, in its turn, was tested. Tests for carcinogenicity in laboratory animals showed the chemical was associated with the development of multiple tumors, in multiple sites, of multiple species, in multiple tests, by multiple routes in both sexes, with a high degree of malignancy in a relatively short period of time. Even the skeptic might reasonably conclude that a hazard had been identified. Analytical chemists trained newer techniques on an old target and found that "zero" levels of EDB in grain were not zero any more. Thus, the cases for hazard and exposure -- the essential ingredients in risk assessment -- were now on the table. The weight-of-the-evidence in the hazard case was overwhelming. Despite questionable utility of the data for deriving quantitative dose-response estimates, such estimates were evolved. Coupling these data with information on exposures, the risk characterization was generated which compared the risk information with the non-risk information on benefits, alternatives, etc. On the basis of this balancing the risk management decision was made to suspend or cancel EDB use as a fumigant on soil, citrus and stored grain.

In retrospect, we see that analytical chemistry can be "risky business". The presence of EDB revealed by the sensitive analytical methodology, in a sense, was responsible for the risk since, according to current cancer dogma, the presence of a carcinogen implies a cancer risk. Hence, everyone suddenly became excited. Lost in the following hubbub, was the fact that the Agency had already taken action to eliminate use of EDB as a fumigant some six months earlier! The effect of the great public concern was simply to move the action up a bit.

Perhaps one of the lessons to be learned from the EDB/84 saga is the need for the field of environmental toxicology to come to realistic terms with the significance of data at hand. More specifically: is there value associated with the routine collection of data at a level of sensitivity that transcends the practical limits for which it can be utilized? I leave it for each of us to answer.

EDB is but one simple example of the issues that emerge from the application of high-powered analytical chemistry to the field of environmental toxicology. Earlier I suggested that the detection of 2,3,7,8-TCDD

in 10^{-15} range might be a possible misuse of capability. You are not in a unique class in this regard, however. Toxicologists have demonstrated 2,3,7,8-TCDD is perverse enough to be associated with reproductive and carcinogenic effect at very low levels. In alliance with our biostatistician brethren, using extant methodology, it is possible to project an upper bound limit of excess cancer risk of one in a million resulting from the consumption of water containing 2,3,7,8-TCDD in the parts per quintillion range (ppqt). For you smug chemists who can detect 1 part in 10 to the 15th power, a part per quintillion is not merely one-upmanship -- it is 3 orders of magnitude beyond your current capability. Really!! Someone is slacking off! The worst of it is that some people read these numbers, accept them, and expect a course of action to be developed appropriate to the "challenge". The next goal may be to extend this logic to the rest of the chemical class and the dibenzofurans.

In all candor, I must protest these acts. They ignore reality. The best surrogate for man is man. While I strongly preach the utility and predictive power of animal tests, they are not infallible. We have had the opportunity to observe various population heavily exposed to TCDD.

Acknowledging the inherent limitations of each of these studies, the data are aggregating toward a working conclusion that any disease associated with exposure of 2,3,7,8-TCDD in man is significantly less than those which might be projected quantitatively. The time is rapidly approaching when these data, in a weight-of-the-evidence analysis need to temper risk management decisions. Such practical reality needs to be the norm in all aspects of environmental toxicology.

Issues such as this must be the challenge for Environmental Toxicology if the field is to progress. The analytical successes that have been attained to date represent that which can be called "technical cleverness". It is time to leaven this process with a perspective that will allow WISDOM to prevail in dealing with these challenging social issues.