AEIC Spring Meeting
DowElanco
Indianapolis, IN

4/11/94

The meeting was called to order at 8:05 am by Chuck Mihaliak (President). Perry Gerhing, VP of Research and Development at DowElanco gave the opening remarks. He gave a brief history of DowElanco as a joint venture. Perry also discussed how important immunoassay is to DowElanco.

Agenda and Goals: Chuck Mihaliak reviewed the "to do" list that was generated after the September 1993 meeting. He commented on how much we completed since the last meedng. (See attachment) We will need more activity by all the members to complete the next list. Jim Rittenburg (Past President), who had responsibility for organizing the agenda, reviewed the agenda and noted any changes in the order of presentations.

Pat Nugent (Secretary): The minutes from the fall meedng were approved. Jim Rittenburg moved for approval and Bertold Hoch seconded the modon. The minutes from the January board meedng were approved. Joe Dautlick moved for approval and Jim Rittenburg seconded the motion. We reviewed the notes from the board meeting held at Chuck Mihaliak's house on April 10, 1994. We discussed the nonpayment of dues. After this meeting we will send a second notice. Payment is due 30 days from receipt of the second notice. Members should contact the board in writing if they can't meet this deadline. By company, Pat read off the names of all the members of the AE1C. Copies of the trifold were handed out to everyone present and the mechanics of the AEIC mailing address were explained. We reviewed the proposed changes to the bylaws. The suggested mod)fications will be added for voting at tomorrow's session.

Jim Rittenburg asked all tbe attendees to introduce themselves and state what organization or company they represent.

Sharon Berberich reviewed the history of the guideline document and why we are developing it. She handed out the manuscript from the talk at the ACS and asked for comments from the membership before the document has to be submitted for publication. In her talk, Sharon reviewed current OPP (Office of Pesticide Programs) policy. Many documents have been developed for traditional methods. Many times they just need to be changed to fit immunoassay (IA) methods. OPP will review case by case each registrant who wants to submit an IA method. Members of OPP believe that a registrant with an 1A method needs to be given the flexibility to choose the best method. They must also show how it compares to traditional methods when possible. Dave Rothman brought up data quality objectives. If an IA method will allow one to meet those objectives then it should be able to be used. IA methods should be used when they can add value, there are low limits of detection, the compound being analyzed is labile or polar, and for environmental fate methods. How are IA methods implemented? One must evaluate appropriateness, performance/validation and develop a confirmatory analysis strategy when tradition method is already in place.

Appropriate uses of immunochemical based methods include screening, methods with low detection levels, economic reasons, and for field use. Inappropriate uses include a small study, poor matrix and inadequate specificity.

Sharon outlined the necessary information to be included in an analytical method using immunochemistry. This included a summary, the principle, the procedure to include the materials the, method, results and discussion, and conclusions and references. Results and discussion include accuracy, precision, detection limit, LOQ, sensitivity/specificity, correlation, ruggedness, and limitations. One table gave examples of a confirmatory strategy and she discussed questions to ask when developing the strategy

Sharon showed example confirmadon strategy i.e. the number of confirmations to do both positive and negative. In concluding, the EPA is now encouraging the use of IA methods. Industry must submit correlation data for IA.

In the following discussion, Dave Rothman asked about how to convince analytical chemists. DQO (data quality objectives) is a means of communicating for all chemists. If IA methods were also formatted to meet DQO, they would be closer to the method development that traditional analytical chemists follow. The need to include correlation data in some of the talks was also emphasized. Steve Cohen said that the New Jersey EPA was putting out a guidance manual for using IA screening methods. EPA OPP (Elizabeth Leovey) now wants all raw data so that they can do their own statistical analysis. The need to validate computer software that is used to do data manipulations was discussed. The manufacturer of the software should offer that with the software. The method should be validated in every lab that runs the method. What is a kit and what is a method? A kit is usually used in the procedure part of a method. The argument was made that as long as you met the methods' specs you shouldn't have to revalidate. Jim Brady commented that in order to comply with GLP, you would have to revalidate.

Break

Jim Rittenburg reviewed the talk on kit inserts he gave at the ACS in San Diego. The AEIC mission statement includes the establishment of performance standards for manufacture of IA test kits Included in performance standards are sources of quality standards, consistent terminology, a standardized package insert, and guidelines for user QC. The AEIC devdoped a set of definidons for key terms used in IA. Discussion followed including definidon of LOD and LOC. The different offices of the EPA define these terms differently and the defioitions are based on written regulations. Maybe it would be better if we included how we do that calculation with our definidon.

Other definitions discussed included stabiliy, both kit and sample, bias(absolute and relative), and method verses kit verses assay. There is a list of items to be included in a kit package insert Brinton will cover the insert in more depth. Discussion followed concerning exactly what the kit inserts should tell you. The insert is a global standard for the test not specific for that lot. It should include certain minimum specifications that the kit will have. Barry Lesnik suggested adding an action limit in the beginning related to the particular matrix the kit was developed for. That action limit can be used for only the matrix that is specified by the kit manufacturer.

Jim also discussed sources of standards and calibrators and the type of materials that one might need such as metabolites and degradation products. He listed data quality indicators that kit manufactures could provide for kit users and discussed the dose response curve and what should be explained to increase the understanding of the user. Future work includes protocols for evaluadng kits, insights into troubleshooting and help to establish operating standards. Dave Rothman suggested prepasted inserts that could be included for archiving required information.

Brinton Miller went through the package insert document in more detail. Under "Intended Use" a manufacturer should state the material to be tested and in what matrix. Test Principles include the type of IA. Material required refers to what is in the kit and what else you might need to run the test. "Preparation for Testing" includes kit preparation such as bringing reagents to room temperature, sample preparation and precautions and limitations. Steve Cohen.suggested adding the addition of a MSDS to a first time user. "Test Procedure" includes step-wise procedure and includes diagrams if helpful. Results could include a standard curve, selectivity, specificity and dose response. "Technical Service" includes ways to contact the vendor. Also should be included is a list of reference materials and a way to obtain the references. Chuck Mihaliak mentioned including a comment about a confirmatory method. It could be included in the intended use section. Specificity could include a table of cross reactivity.

Discussion followed as to how extensive the insert has to be. FDA requires cross reacdvity data on the inserts instead of being offered as a technical bulletin.

The AEIC would like a review to take place a year from the annual meeting this fall. We would review package inserts from all the kit manufactures against our guideline.

Lunch

EPA Speaker Elizabeth Louvey, Office of Pesticide Programs(OPP): When registering a pesticide label they look at risk versus benefits for a pesticide. The risk is the hazard times the exposure and is related to calculated environmental concentratdon.

Lab studies are done first with C14 and field studies are done next. Her branch deals with environmental fate and ground water. Field studies, modding and incident reports for an area are other techniques used to study a pesticide. Methods in OPP are performance based (PBM). Approved methods must be used to enforce tolerances. Acceptability criteria are the same for methods used to set tolerances and enforcement methods. OPP will be publishing a Federal Registradon nodce in May for comments on a protocol for data reporting guidelines. The types of studies impacted fall largely in Subdivision N.

A recent EPA agreement required an immunoassay (IA) for registration. IA is beneficial for ground water studies because they are cheaper and allow for more sampling. With the greater emphasis on water monitoring, there will probably be more IA methods usod. Several IA methods have been sent to Don Marlow for validadon. Hc will accept IA methods for screening in large scale monitoring studies. Negatives must be confirmed with a sign)ficantly representadve subset. Primary IA methods can be used for very low levds, microbials and bioradonals if it is not feasible to devdop a tradidonal method. Feasible means doesn't mean using 3 or 4 liter water samples. Always come in and ask first with protocols.

Immunochemical methods should have 20% precision and accuracy ranging from 70-120%. They need to be quandtadve, specific(low cross-reacdvity rates) and have a confirmadon scheme. On site methods mean the method can be used at the well and can determine whether the pesdcide is present and at what level. IA is also needed for worker reentry on site.

EPA Speaker Ivan DeLoatch Office of Ground Water and Drinking Water In 1993 the office was charged with piloting Performance Based Methods (PBM). The first draft was completed in January of 1994 and is currently being reviewed by an EMMC steering committee. Hopefully this document will be ready for comment in thc next year. A PBM was defined by EMMC as "an analytical procedure containing the necessary method performance specifications to assure the desired quality of results." Method performance specifications include sensitivity, specificity, accuracy, precision and performance range. The OWDW has been looking at AOAC's test kit validation program and stated that the AOAC will evaluate test kits/immunochemical methods based on USEPA compliance criteria.

Ivan reviewed what reference methods include now. Using their decision tree requires knowledge of the following: specific details of the method to be evaluated, performance testing results, and regulatory status of analyses in question. Ivan went through the decision tree and explained how it works.

EPA Speaker Bill Telliard, Office of Waste Water, Analytical Methods Staff: Their department has used performance based methods since 1976 and believes some analysis will never be performance based. The direct discharger has already treated its water and IA usually works well. The real need is for the indirect discharger (smaller companies). Their office is currently involved with studying TPA in oil and grease. If you had a test kit working in hexane or cyclohexane there would be a large use for indirect dischargers. Future needs include dioxin testing to include 2,3,7,8 TCDD in waste water at ppt levels and also furans. Trace metals are also of a concern at the 100 1000 ppt levels. Their office will split samples and will be glad to work with you but all is public knowledge. They can't live with false negatives but can live with false positives. There is also a demand for IA for use in salt water from the bay area.

EPA Speaker Office Barry Lesnik of Solid Waste: The biggest advantages of IA in solid waste is fast turn around time and selectivity. The primary use they see for IA is for quantitative screening purposes, setting a quantitative

action level. General guidelines for development of a screening method include set a quantitative action level, target no false negatives and up to 10% false positives, determine interferences and demonstrate performance data at action level. Validation criteria for IA include: cross reactivity with similar analyses, with dissimilar analyses, false positive/ false negative rates, extraction efficiency for soils, performance data on spiked samples validated with SW 846 methods and performance data on actual samples. They can live with a 40% recovery as long as it is consistent. The regulatory approval process consists of: 1) Technical work group review, 2) proposed regulation for public comment through a Federal register notice, 3) response to public comment and 4) final approval. Method 4010 is the official method for PCP in water and soils and 4020 is for PCB in soil. Each kit is treated as a separate method. Method 4015 for 2,4-D is in progress and 4031 for BTEX Seven more methods arc in various stages of approval.

Other needs include dioxin and furans, haloginated compounds, phenols, benzidines and other analines. Enviromental applications include: mapping of waste sites, monitoring for compliance to corrective action, monitoring for permit compliance, monitoring for wood surface treatment and monitoring underground storage tanks. Future uses include: quantitative determinations of RCRA analyses. Perceived barriers include: lack of technical knowledge, use of inappropriate methods in sampling and inaccurate knowledge of the regulations. OSW has initiated a major effort to train EPA pemit writers and enforcement people in thc regulatory aspects of using RCRA methods.

In conclusion, OSW has validated 4 methods in 4 months. IA has become more accepted for site mapping and screening which is its biggest emphasis in OSW. They are looking for quantitative methods now.

Panel Discussion
To Barry: If an IA method is compared to traditional method and is better than the traditional can you use it? Response: If it meets the DQO, it will be accepted.
To Ivan: Jim Brady commented on the negative aspects of a closed end relationship with AOAC i.e. high costs and residue methods do not have to go through AOAC Response: So far there is just a preliminary investigation, no decision.
To Barry: Will each kit for a specific analyte get a separate number? Response: No, but each will get a separate validation.
To Elizabeth: Rosie Wong asked for her to expand on the registration for acetochlor. Is this a precedent setting agreement? Response: It is an indication of what to expect in the future. What do you use for a confirmatory scheme when primary method is IA? Response: Use another IA method.
To Bill: Is 2.3,7,8 TCDD the one you are most interested in? Response: Yes, but are interested in others including the pentas.
To Barry: Will TNT be a candidate? Response: Yes, but not immediately.
To Barry: When you pick a target action level what is the gray zone? Response: At the action level you will get 80% positives. One half of the tolerance level should come up negative all the time.
To Elizabeth: What do I do first if I have a method? OPP needs to review a protocol. Call your product manager to get a protocol review at the agency.
To Ivan: Comment on the lack of speed of the AOAC kit review. Could AEIC help with review of PBM document. Response: It is possible but they are not at that stage yet. California has started a certification program that has a significant cost, any comment? Response: EPA can set regulated methods and it will void that What is thc role of EMMC to thc divisions? Response: EMMC was created to address issues of new methods across agencies. The new administrator hasn't set path of EMMC yet. PBM were formed out of frustration of trying to get integrated methods for all.
To Bill: How do you find the list of EMMC methods? Rcsponse: This year they will be adding field methods and next year will bc adding IA. There is a big push on lab accreditation now and a biological group is being organized which will deal with risk assessment techniques.

To all: What can AElC do? Response: Ivan wants thc EMMC to from an IA group and AEIC could work with that group. What is good for OSW is not always good for Waste Water but what is good for Waste Water can be used for OSW.

Responsc: (Elizabeth) The AEIC will give seminar at the ACS in Washington. Reviewers want to see data success stories.
To Elizabeth: Is more publication of correlation data valuable for EPA? Response: Yes. They are following the work of the US Geological ground water survey and have become believers.
To Elizabeth: Are accuracy and precision numbers hard or application driven? Response: It depends on the use.
To Barry: Can a manufacturer run their own assay for a field study? Response: Yes, except in the state of Georgia
To Elizabeth: How do GC and LC methods go through OPP? The procedure is identical, they use the same performance criteria They can interact with the registrant any time during thc review.

The meedng was adjourned at 4:30 p.m.

4/12/94

The meeting opened at 8:35 am. by Jim Rittenburg. An attendance sheet was passed around and will be distributed before the end of the meeting with attendees and addresses.

Chuck opened a planning session for the next meeting and asked how the AEIC can be of the most benefit to the technology. Jim Brady commented that the chemists that have to review and use the methods would appreciate help. Paul Schudas' reviewers could also benefit from training sessions. The idea of a video was discussed and cost was a concern. Jim Brady had been asked to train EPA chemists by CIBA, his employer. If we develop a training program we would emphasize the applications not the differences between the different kits. We would develop a master list of the kits available. What would be a canned program? Could we also give them a program that would be taken to the regional areas? We could target OPP and the Office of Water. Chuck asked for volunteers for a committee for putting together a program for the September meeting. The following people volunteered to develop training program for the OPP: Rosie Wong, Chuck Mihaliak, Jim Brady, Cristina Rankin and Allen Iske. This can include videotapes from test kit companies or an AEIC video and should stress applications instead of specific kits. It would also include travel to the EPA.

The committee for a training program for the Office of Drinking Water included Barbara Young, Jim Rittenburg, Tom Grace, Bruce Crane and Bonnie Copeland. Included in the training would be data cerrelation from IA verses traditional methods. We would give these presentations to the group at the September meeting for review.

For OSW, Joe Dautlick agreed to offer assistance in developing an IA training program.

Brinton Miller will do a master list of all the kits

Pat Nugent will type the letter to all the EPA representatives for specifics on what they would like help with.

The next meeting will be September 22 and 23. Penny Hunst and Mark Platshon will responsible for the facility and Chris Rankin and Dave Grothaus volunteered to work on the agenda Chris Rankin volunteered to have the Spring AEIC meeting in 1995 in Wilmington, Delaware.

Dr. Bertold Hock: Dr. Hock started off his talk with a review of pesticide use in Europe. Europe is very populated with a small amount of land to sustain its population. He reviewed the amount of pesticides used in Europe over the last 8 years. The EU (European Unity) requires surface water analysis once per year. Drinking water must not be more than 0.1 ppb for single pesticide and no more than 0.5 ppb total pesticides. Only once per year is required but in practice water is analyzed once per week at water companies. Water surveillance programs by government have been increasing and there is a rising need for soil analysis. BASF has used an immunoassay method as a primary method for registration in Germany.

DIN (German Standards Institute) in cooperation with the German Chemical Society formed a standing committee of 29 experts, mainly chemists, which equally represent state authorities, universities and industries. Members include individuals from BASF, Bayer, and water treatment facilities. The group has developed a flow chart application for a standard or method. The procedure includes round robin tests which add interferring compounds

to test specificity. They use at least 10 labs and no more than 30. He gave an example of the criteria needed for the German standard methods for the examination of water, waste water-and sludge. A similar such group exists in England.

The immunoassays that either detect a broad family of compounds or are very specific have the most uses. Bertold believes a significant need in the technology is to speed up antibody development.

Joe Dautlick, Ethics: Joe discussed the promotion of IA as members of AEIC. As AEIC members, we have to be conscious of the two roles that we play. We belong to a company and the AEIC. We shouldn't use the AEIC as a means to introduce our own products. An AEIC member needs to let the Board know if they will be visiting a regulatory agency or company on behalf of the AEIC. When individuals from companies are selling products, remember to try and have immunoassay always look good.

Treasurers Report. Larry Miller. Larry showed a copy of a travel expense form we could use and the logo we developed. We decided to do a trademark search for which Brinton Miller will be responsible for doing. Dave Nardone wondered how a company could use the logo in company literature. Dave will also help Brinton with the search. Larry also put up the list of paid and non-paid members. The unpaid members will get a letter reminding them of their dues obligation and will serve as an official reminder.

Larry went through the balance sheet and discussed the option of incorporation. Larry reviewed the rules we must follow as a nonprofit organization. No taxes need to be paid for 1993 but will be for 1994. The checking account was set up as a joint account (president and treasurer) and there will be a charge for checks.

Voting: Pat Nugent Both bylaw modifications were passed. Out of the 24 members, 16 were present which was a two-thirds majority. Section 33(c) now reads: Staff or faculty of academic institutions having an interest in the use of immunoassays for enviromental applications may qualify as Associate members. Section 3.5 now reads: All members shall pay initial and annual dues or assessments, or both, insuch amounts and payable at such times and by such methods of collections as the board of directors may by resolution prescribe, including provisions for pro-rata payments for members joining during the fiscal year. Persons may attend a regular meeting of the AEIC without joining. They will be charged a registration fee which would be applicable toward full membership dues if application acceptance is completed within twelve months from the time of the meeting attended. A registration fee would also entitle the individual to receive AEIC mailings not intended for members only (i.e., ballots).

The following companies had merhbers present for the voting: Biocode, American Cyanamid, Battelle, CIBA, Dow, DowElanco, EM Science, General Electric, Monsanto, Neogen, Novo Nordisk Entotech, Pioneer, Strategic Diagnostics, Quantix, Bio-Tek, Ohmicron, DuPont, Ensys, and Millipore.

The meeting was adjourned at 12:10 p.m. by Chuck Mihaliak