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COSTS OF NEW MATERIALS: THE MANUFACTURER'S DILEMMA

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CHAIRMAN JACKSON: One area that has had a number of marginal comments directed at it during both days of our conference has been that of the problem of development of new materials. Perhaps Chemagro with Queletox has had as great a round of problems as any other company in this area of bird toxicants. I've asked Dan MacDougall, Director of the research area for Chema-gro, if he would bring us up to date on this material called Queletox and talk just a little bit about this whole area of concern in developing new materials for the market.

MACDOUGALL: Thank you very much, Bill. Gentlemen, I was interested in coming to this meeting particularly for my education rather than the fact that I could contribute anything to you people in regard to bird control. But I did think it was possible that some of you might not be acquainted with some of the frustrations which are involved in jousting with the bureaucracy in Washington. So I thought I would review that situation very briefly for you, particularly in regard to the compound Queletox.

We will confess that we had some real qualms about accepting this material for control as a bird toxicant initially. And the reasons we were concerned about this were because the compound was being used in other areas as an agricultural chemical. It was registered for mosquito control, and it was being used in other parts of the world as an agricultural chemical. We felt that with the tremendous number of bird lovers around the country, if the reputation got out that the material would kill birds or could be used to kill birds, even if in a different formulation, and in a very different method of application, then it was still possible that it would cause problems in the area in which we are concerned, primarily agriculture. I think some of the Fish and Wildlife people who are here will realize that it is possible to get into rather difficult problems by this cross-referencing business. So I think that concern about the reputation of the compound was warranted, originally.

However, in spite of this, Dr. Philip Spear came up to see us in the spring of 1963, and he did persuade us that this was a real problem and that the National Pest Control Association was interested in getting this material registered for control of birds. And so we, rather naively, took a crack at it.

Remember that this material was already used; we had the basic toxicology picture on it. We felt we had very strong arguments for getting the material registered as we had suggested for use in the paste for the control of birds without further work. We went to Washington and began to discuss this in the summer of 1963 after Dr. Spear's visit to us. In order to get a material registered you must demonstrate efficacy first, and the only way you can demonstrate efficacy for this kind of formulation is in actual practice. If you demonstrate it in caged experiments, results aren't applicable for registration purposes.

Then a lot of problems arose in regard to applying this material in the way in which it would be used in actual practice in order to determine the efficacy data. In the first place decontamination became a problem. These were the types of questions we were asked: How long will the material stay on a ledge or a roof? How rapidly does it deteriorate? What are the effects of a variety of different weather conditions, rainfall, sunshine, different temperatures, etc.? If there's runoff from areas, will there be enough material to get into streams to cause a problem? Can the material be tracked by birds, for instance, and get on hand railings or other places where birds might walk and people might afterwards come in contact? What was the problem with regard to secondary poisoning?

To answer these questions adequately is almost impossible. You have to do a variety of tests under a series of weather conditions varying each variant independently. This we had to do in spite of the fact that we could demonstrate on the basis of our toxicity data we had that the possibility was remote of any individual being exposed to amounts which could possibly cause a problem. It seemed to me that this kind of data were much more pertinent in evaluating this overall problem than the kind of data for which the USDA asked us.

Then we talked about formulations and they said, "Well, we'd like a formulation which is tacky enough so the birds can get into it and it will stick to their feet in sufficient amounts to kill them at temperatures that will range all the way from 0° up to 100°. And we'd like the consistency to stay the same through this temperature range, because if it gets too cold and gets hard it would lose its efficacy, and if it runs when it gets too hot then that could be a problem." Now it's obvious for anyone who knows any physical chemistry that this does pose some problems in making formulations which will match these exactly, because things do melt when they get hot and do get hard when cold. And with all due respect to the Wildlife people here, it's very easy to sit in Washington and develop all these specifications, but very difficult to devise experiments which can answer questions of this sort.

The problem of absorbency on building materials was raised. And then we discussed the idea of putting the material on tape, adding warning labels at various intervals so that window washers, etc., working on the building after it had been treated would be able to remove the tape. They would know there had been toxicant applied there, and be able to clean it up, or alternatively the pest control operator could come back and remove the material after a given length of time. Now after what I've heard today, there are probably some very good methods of applying materials to tape which we didn't explore; we did do a lot of work trying to find an adequate tape. We explored the possibility of marketing

a tape with paste, with labels, with all the things that had to be done, and there immediately arose some new problems and certain conditions. The tape didn't adhere very well to the roof surfaces; and you might have had some instances where a piece of tape would be blowing around with toxicant on it. This was a worse situation than if you had put it on without the tape. Then once you decontaminate it, how are you going to dispose of the material? Burn it and breathe the smoke? Well, that didn't seem like too good an idea. So you're faced with new problems.

However, we did go ahead with this type of approach. It took about eighteen months to get to that point, and we did not really feel we'd gotten off dead center. So I had a meeting in Washington with a Wildlife representative, a Department of Agriculture representative, Phil Spear, Jim Steckel, and several of our people. We decided to meet and decide once and for all, if we really could get a registration of this type. After a four-hour harangue, USDA suggested that we apply for an experimental permit with the material on tape in order to get the necessary efficacy data. If I remember correctly, Phil, that was in October or November when we had that meeting, and in March, 1965, I happened to be in the director's office with the president of our company and inquired as to how this experimental permit application, which we had pending, was progressing. One of the officers of the USDA pesticide regulation branch said, "I'm amazed that you even had any idea that an experimental label of this sort would ever be granted." I said, "Well, for good heavens, you suggested it." His reply was that they had not suggested it. Luckily my conferer was able to produce a letter from the division, written the day after our meeting, in which they did admit that they had suggested it.

So in another six months, and this took us up to August, 1965, we got an experimental label. Of course it was too late to do anything that year really, so we didn't get started doing things until 1966.

The problem that arose after we got the experimental product ready was that our marketing people came back and said, "Pest control operators say using tape and doing this sort of thing is just not practical." The USDA said that if we didn't use it, they wouldn't register it. And there's the dilemma we're in in a nutshell.

Now if you sit back and think about, how much does it cost us to put a chemical on the market? Of course I'm more familiar with pesticide chemicals really. We developed veterinary medical drugs but not human drugs, but I think the data which I have in the first slide would give you some picture of development. Now remember with a material that is going to be used for bird control will probably be a basic material that has been developed for some other purpose, and a lot of the development expense born by the other purpose. Could I have the first slide now?

These data I'm sure many of you have seen before. They appeared in 1964 in an article in *Farm Chemicals* by John Field; but I still think they're reasonably accurate, because there's a lot of variation in the cost of an individual chemical. The way these are calculated is simply this: suppose it costs us $200 to synthesize a new compound in the laboratory, and only one compound out

of a hundred gets through the initial screening stage (now this will be true probably whether we're screening for bird control or screening as a pesticide). The chemical that proceeds to the next step has cost us $20,000. It has to bear the cost of all the others that were screened in order to get to that point. Then you go to the advanced screening stage, and suppose one in nine survives. Now if one in nine survives, all nine of these that get to this point are going to cost us $20,000, so we've got to add that on and then we have nine times three, so the one that survives the seconds screening costs $207,000. I don't see any way of getting around this type of additive process no matter what you're screening for. That's what you've got to do before you've got a biologically active material.

The big cost in developing pesticide chemicals of course comes after that. These costs are relatively lower than many people have quoted. But as I said there's a lot of variation from material to material. We do initial feed field screening, and here we may have a survival of one in two; but the expense is relatively high. We obviously go up twice this, plus 2 times that, and then maybe a survival of one in two for these final development problems. If you're only developing a chemical for bird control and there is no possibility of the material becoming a problem as far as human feed or animal food is concerned, then the last stage could drop out to a large extent, not completely, but partially. The work which we have to do on detailed metabolism and residues and that sort of thing would not be required. So you can see that if we were going to screen, this represents a very considerable investment.

Now what other costs would we have? Suppose we picked out a chemical for bird control. We'd have the development costs of a special formulation to do the job. We'd have the packaging development costs. We'd have analytical costs, because we have to develop satisfactory analytical methods. We'd have to determine what the shelf life is, storage stability, and that sort of thing. And we'd have to do rather extensive toxicological investigations.

I want to spend just a few minutes talking about toxicology for two reasons. Some of you may not be aware of the scope of the toxicological investigations that are required for development of a pesticide chemical, and these same things in my opinion would be required for a chemical for control of pest birds. On the next slide I simply wrote the three basic reasons why we do toxicological studies. The first thing that USDA would be concerned with is protection for people who are handling the material; what is the toxicity hazard to the handler? The second one; is there any possible exposure to the public or hazard to the public from accidental exposure? And third: what are the hazards to wildlife species other than the target species?

Let's think about how the data we normally get fits those criteria. To accomplish this we have acute toxicity studies and sub-acute toxicity studies. The chronic toxicity studies would only be required when and if we were going to obtain a tolerance or there was some food or feed use involved. Let me think with you for just a minute about these acute toxicity studies. In the first place they have to be conducted on a number of species. The rationale is that if the toxicity is relatively similar on a number of mammalian species, then it presumably will be in the same range for humans. So there would have to be a number of

rodent species and a number of non-rodent species as well on which you have acute toxicity data.

We determine the toxicity by a number of routes of administration: intraperitoneally, orally, dermally, by inhalation, and so on, because the rates at which different chemicals are absorbed by different routes vary, and you cannot assume a constant ratio between oral toxicity and dermal toxicity. I have lots of data to show this to you. I have a big bone of contention with a lot of entomologists in that they have one figure for an acute oral LD_{50} value to rats (which sex they don't know, which methods of determining they don't know), and that figure sticks in their minds and is regarded as the profile of the toxicology of a compound. It just can't be that way; you need data on different methods of application, and you must know exactly how the material was applied, if you're going to evaluate toxicological data.

I mentioned the way in which the material was administered. Obviously if it's in solution it's absorbed much more effectively in many cases that if it's applied as a solid. Now if the hazard to the public is going to be with the material as a solid, then the toxicity should be determined on a solid. If you're ever concerned with toxicological data, you should insist on obtaining data which were determined directly on the formulation to which the person is being exposed. This is the only way you really get a measure of hazard. I submit that as far as the hazard to the operator is concerned, it's not toxicity with which we're concerned, it's hazard. Hazard is a function of both toxicity and the possibility of exposure, and both must be taken into consideration if you're going to evaluate this properly.

With organophosphorous compounds we consider potentiation, that is, possible increase in toxicity over the amount expected when different materials are administered together. We consider the effectiveness of various types of antidotes, and here again I would emphasize the necessity of doing the studies on the formulation which is being investigated.

In the next slide I've listed some of the things we do for sub-acute toxicity studies. We do sub-acute toxicity studies on rats intraperitoneally and orally always, usually dermally as well (the USDA requires that for pesticides); and occasionally we do sub-acute inhalation studies. The point of these is primarily to show what the cumulative effects of the material are. Materials, even of the same type, are not metabolized at the same rate by mammals. There are some chemicals which when administered will be absorbed and metabolized very quickly, and the animal can stand a relatively high proportion of an acute LD_{50} dose day after day with relatively little effect. The one which is metabolized more slowly obviously can stand only a smaller fraction of an acute LD_{50} dose each day, and you may observe some cumulative toxic effect in that way.

Sub-acute toxicity studies are very important, and I submit they're the most critical studies with regard to wildlife hazards, because the exposure which the non-target species gets is by and large a sub-acute exposure. And you cannot extrapolate directly from acute toxicity data to sub-acute toxicity data. This is just out of the question.

We do the same sort of things on dogs; we do oral studies on hounds for demyelination with the organophosphorous compounds. Where there is any possibility of the material being skin sensitizer, we do human studies for skin sensitization. All studies on humans are also a possibility with some compounds, and there have been some very good studies published with low rates. The FDA is interested in investigations of materials, like an organophosphorous compound, where you have an excellent method of detecting incipient toxicity, namely the lowering of blood colinesterase. They like to do studies on humans to determine whether the "no-effect levels" on colinesterase are the same for humans as for experimental animals.

I pointed out that chronic toxicity studies would only be required where there's a possibility of having a problem of feed or food. Here we do 2-year studies on rats and dogs, 3 generation breeding studies on rats, and sometimes we've done breeding studies on hens, although I could tell you stories about that. The FDA has now decided that the hen is not a satisfactory second species on which to do breeding studies after we did several.

These are time consuming and very expensive. I sat down and tried to make an estimate on what it would cost us if we were doing different toxicological investigations. It seems to me that the acute toxicity profile of which I've described would cost us about $20,000. Toxicity to other wildlife species if we got everything everybody wanted, could easily cost us $50,000, and sub-acute toxicity studies about $100,000. These are just rough approximations. Chronic toxicity studies, if necessary, cost us another $200,000.

That brings me more of less to the end. Could I have the lights? Most chemical manufacturers don't have a primary screen for bird control, because we're obviously in business to make money or we don't stay in business. And the estimated value of the market, in the opinion of our marketing people, wouldn't warrant a primary screen to develop a chemical solely for this purpose. The problems involved in getting one of these registered are first psychological and secondly economic, as far as we're concerned. And really when you boil the whole thing down, I think there just aren't enough people in the government and the public at large convinced that this is a problem which has to be solved. Thank you very much.

JACKSON: Dan, do you want to mention one final word about the status of Queletox?

MACDOUGALL: Yes, I forgot to mention it when talking. We are back on the label again, working with the USDA with the view of getting a better description (which they asked us for) for the areas where tape would not have to be used and areas where it would have to be. There are two points though. If you people feel that the use of tape is feasible, we'd like to know it. And secondly, is that while this experimental permit was in effect, and I told someone in error that it still was in effect, we had to get the performance reports from the tests that we were conducting in order to get a final registration. The purpose of the experimental label is simply to go out on a limited basis and obtain performance data.

And of course we have to get the performance reports. A testimonial type of report is not a very satisfactory sort of thing. They want to know how many birds were there before and how many birds were there after, this sort of thing. We want all the reports we can get.