ty. On this knowledge can be based timely, well-considered corrective action on a national and, hopefully, international level.

I frankly admit that in our time, in which there is hardly a doubt left about the limitations of many of our material resources including the capacity of our environment to dilute and digest the refuse of nearly 5 billion humans, environmental laws are a necessity. They are, or should be the firm framework within which for instance the chemical industry can move in relative enterpreneurial liberty and with impunity, exactly as the behavior of the citizen is circumscribed by the rules, prohibitions and sanctions of the civil and penal legislation. But just as the individual is left with the legal and moral responsibility of leading his life within this framework and collides with it only in transgressing it, the chemical industry should be accorded the opportunity of responsible fulfilling the legal obligations by applying its own initiative, scientific, technical and business knowledge to arrive at economically optimal solutions. By this the best interests of society as a whole are served. The legal rules and norms should represent the best possible approximation of all interests of society, including economy and the industry. They should be of the nature of objectives rather than prescriptions, and their application should be possible with a minimum of bureaucracy.

All this is, of course, only possible when the two sides co-operate and have sufficient trust in each other. Although a part of the public seems to be convinced that the past record of our industry does not justify this confidence, there is abundant evidence that the overwhelming part of the chemical industry is conscious of its responsibility and ready for reasonable solutions of the common problems. Quite apart from ethical reasons such behavior is from a number of viewpoints, such as tight liability legislation, also clearly in the self-interest of industry.

Unfortunately the necessary constructive interaction between the chemical industry, the authorities and the public is constantly disturbed by the interminable rehashing (in an often distorted and scientifically incorrect manner) of the same old 'cases' of the past which from the state of knowledge of today appear as mistakes. They are well known indeed, and have been learnt from and dealt with as well as possible by technical measures and/or regulations. Many of the allegations moreover, concern matters outside the sphere of influence and responsibility of those accused. Future mistakes of course cannot be excluded and the learning process will have to continue. The chemical industry is prepared to carry its share of the responsibility of minimizing the hazards.

It is evident that our society will increasingly have enormous environmental problems, but I dare to say that, contrary to widespread belief, the chemical industry in the industrial countries of the West is not among the most prominent causes of them. On the contrary, it will have to play an important role in the vital endeavors to control the priority environmental problems in the fields of energy production and use, and land and soil use.

## How safe are pesticides?

by Hans Geissbühler

*Agricultural Division, Ciba-Geigy Ltd, CH-4002 Basel (Switzerland)*

*Summary.* Pesticide safety has not only been extensively assessed but also, as science has advanced, pesticide safety features have been continuously and significantly improved. Large scale industrial and government research can be expected to achieve further ameliorations. Academia is called upon to assist with relevant contributions.

When discussing chemicals in a recent publication, Ernst Otto Fischer, the Nobel Laureate, said: 'He who intimidates laymen by such things as newspaper articles without knowing anything about the dangerous dose, is, in my eyes, guilty. Seveso is not everywhere' (Fischer, 1982). When skimming our Swiss media one is indeed confronted with a continuing barrage of accusations (not by trained, but by self-made toxicologists) concerning the alleged hazards of chemicals, including pesticides. Personally, I believe that biologically active ingredients which are purposely brought into the environment are too important a matter to be the subject of ignorance, emotions, sloganism and ideologies. What is needed are scientific facts and assessments. With this in mind, I wish to submit four theses which I hope to defend with appropriate arguments and with some illustrative examples.

Thesis 1: Pesticides safety testing and evaluation is extensive.

By pesticide safety we mean safety for the consumer who is exposed to treated agricultural commodities, safety for the farmer and worker who apply or produce pesticides and safety for environmental non-target organisms as specified by our laws. The experimental testing program includes comprehensive studies in toxicology, biochemistry and residue analysis. In the major research-oriented companies this task currently absorbs 25% of the total R&D budget, which, in absolute terms, represents 10–20 Mio SFr. per registered product. The financial commitment is amplified by a continuing increase in the time elapsing between the discovery of a promising compound and its registration, which now covers up to 50% of its patent life.

Table 1. Number and type of mammalian and ecotoxicity studies required for registering the fungicide metalaxyl with the U.S. government authorities

| Category | Objective | Number |
|---|---|---|
| Acute | Oral, dermal, inhalatory, irritation, sensibilisation | 12 |
| Subchronic | Rat, mouse, dog (oral, inhalatory) | 4 |
| Chronic | 2 rodents (lifetime), dog | 3 |
| Special studies | Mutagenicity, neurotoxicity, teratogenicity, reproduction | 5 |
| Ecotoxicity | Birds, fish, deer, crabs, microfauna/flora, etc. | 12 |

Table 2. Number and type of metabolism studies required to date for maintaining the worldwide registration of the herbicide atrazine

| Animals | | Plants | | Soil/water | |
|---|---|---|---|---|---|
| Rat | 6 | Corn | 5 | Hydrolysis | 2 |
| Sheep | 1 | Sorghum | 2 | Photolysis | 2 |
| Goat | 2 | Sugercane | 2 | Aerobic | 6 |
| Cow | 1 | Rotational crops | 6 | Anaerobic | 2 |
| Fish | 2 | Microflora | 1 | Pond | 1 |
| Microfauna | 1 | Selectivity | 2 | Sewage | 2 |

Standard *toxicity* testing for registering or maintaining the registration of one single pesticide comprises roughly 40 different studies as shown in table 1 for the recently introduced fungicide metalaxyl. The program covers a series of acute, subchronic, chronic, special and ecotoxicity investigations. The emphasis is on the life-time, i.e. up to 3-year feeding experiments on rodents, and on the appropriate substance-related selection of special studies which, together, project a fair picture regarding potential mutagenic, carcinogenic and reproductive effects of a compound and its metabolites.

*Biochemical* investigations are designed to define the behaviour and fate of a pesticide in animals, plants and pertinent ecosystems. Table 2 demonstrates the scope and volume of these investigations for the herbicide atrazine which has been subjected to almost 50 different studies involving 4 mammalian species, 10 target and rotational crop plants and a number of components of the terrestrial and aquatic food chains. A summary of the composite metabolic pathways of another herbicide, chlortoluron, is shown in figure 1. These metabolites and conjugates have not only been characterized but also quantified in terms of their distribution in specific organs and compartments, their persistence, and their respective rates of dispersal and elimination, etc. Therefore, it is sheer ignorance or bad faith when Swiss scientists continue to perpetuate in public the statement that (and I quote) 'environmental problems of less persistent pesticides have simply been moved to their degradation products' (Schweizer, 1981).

The third component in evaluating the safety of a pesticide is *residue analysis*. Atrazine is again a good example of the efforts invested. The assessment of

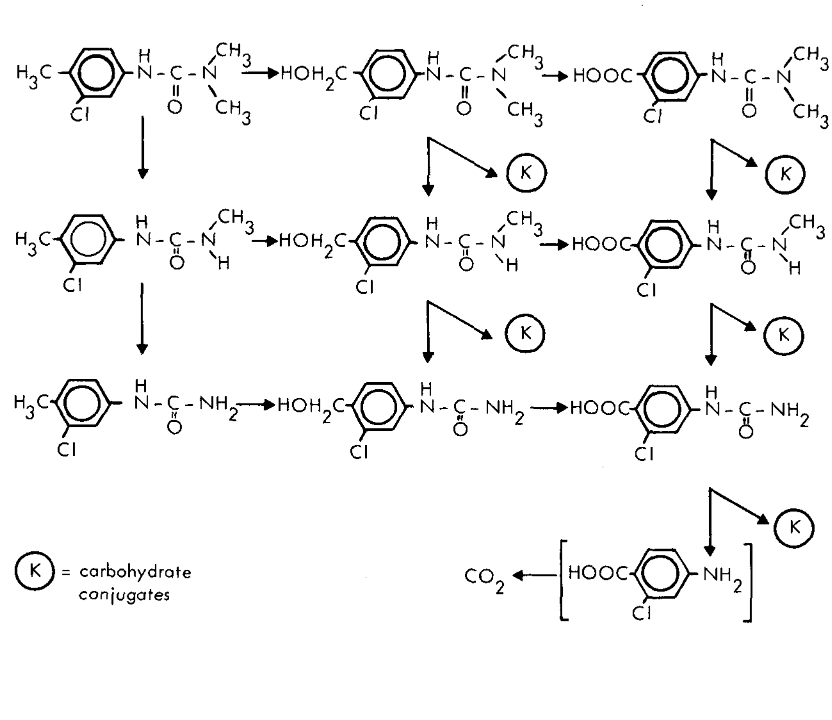


Figure 1. Composite metabolic pathways of the herbicide chlortoluron.

residues under practical use or field conditions required no less than 25 different analytical methods to cope with the active ingredient and its major metabolites, conjugates and impurities. The 11,000 samples analyzed by the company to date cover the agricultural conditions of 18 different crops in 27 countries. ⅔ of the total effort, i.e. 7200 samples were devoted to tracing and characterizing residues in soil and water. Monitoring for atrazine residues continues and the amount spent so far for these analyses has reached 5 Mio SFr.

Initial *registration* and the continuing registration of a pesticide is dependent upon its safety and risks which are assessed by national authorities according to internationally established and formalized procedures which rely on extensive experimental data, as described before. The starting point is the no-effect level (expressed in mg/kg b.wt) observed in the most sensitive mammalian species or system upon chronic exposure. By using an appropriate safety factor (of at least 100) an 'acceptable daily intake' (ADI, mg/kg/day) for the entire life span of human beings is established which, in turn, is the base for calculating permissible residues for the proposed raw agricultural commodities. Since for the majority of compounds and uses, good agricultural practice leaves residues which are below the permissible level, the legal maximum residue limits provide an additional margin of safety and are not, as is often implied, the threshold above which detrimental health effects are imminent.

At the international level the United Nations Codex Alimentarius Organisation provides a frame which gives any country the opportunity to ask for recommendations or reviews concerning acceptable daily intake values and maximum residue limits for those agricultural commodities which move in international trade. These recommendations are made and regularly reviewed by a joint committee of experts of FAO and WHO. The tight, formalized and scientific regulatory process just summarized is hardly ever mentioned in public criticism of pesticides.

I accept that risks must not only be properly assessed, but, whenever possible, be reduced. This leads me to my second thesis.

Thesis 2: As science has advanced, safety features of pesticides have been continuously and significantly improved.

In following the time-scale of introduction of new pesticides I shall concentrate on three aspects: rate of application, fate in the environment and dietary residue intakes (Geissbühler, 1980).

The rate of application of insecticides has steadily declined and has dropped to the 100 g and even 20 g/ha range with the recent introduction of synthetic pyrethroids (fig. 2). Exactly the same qualitative and quantitative development can be demonstrated for herbicides and fungicides. As these decreases have not been accompanied by corresponding increases in chronic toxicity to non-target organisms, including humans, they represent a significant reduction of what is often referred to as the 'indiscriminate loading' of our environment with hazardous chemicals.

The potential of a pesticide to be distributed and accumulated in the environment is determined by a number of factors which are now well recognized and defined. The potential is enhanced by the volatility of a compound and by its susceptibility to being partitioned into living organisms and tissues. On the other hand the potential is reduced by a decreased rate of application, by the degradability of a compound and by its ability to be adsorbed on soil particles. Water solubility has a neutral position, as depending on conditions, it increases or decreases dispersal. Figure 3 presents the mentioned properties for a number of major insecticides which have been arranged according to time of introduction. The steady decline of dispersal and accumulation potential is demonstrated by a steady reduction of bar size and by a shift of these bars towards the bottom half of the graph. This figure shows that it is not justifiable to generalize on pesticide properties by continuous reference to chlorinated hydrocarbons, including DDT.

When looking briefly at the evolving pesticide residue situation, I rely on official data which were submitted to a recent Codex Alimentarius Meeting. Figure 4 summarizes average actual daily dietary intakes of some pesticide residues expressed in µg/person/day, as presented by the Canadian Government, which is conducting one of the most extensive and systematic residue monitoring programs in the world. The curves show a steady decline of residues during the last 10-year period for most of the compounds analyzed. But, what is even more important, the recent data demonstrate that the average daily intake of pesticide residues by Canadians is between 800 to more than

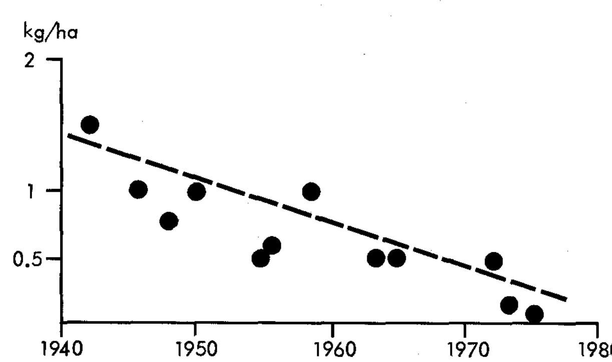


Figure 2. Evolution of rate of application of insecticides (Geissbühler, 1980). Graph based on: DDT (1942), parathion (1946), dieldrin (1948), diazinon (1951), azinphosmethyl (1955), dimethoate (1956), carbaryl (1958), chlordimeform (1963), monocrotophos (1965), diflubenzuron (1972), permethrin (1973), decamethrin (1975).

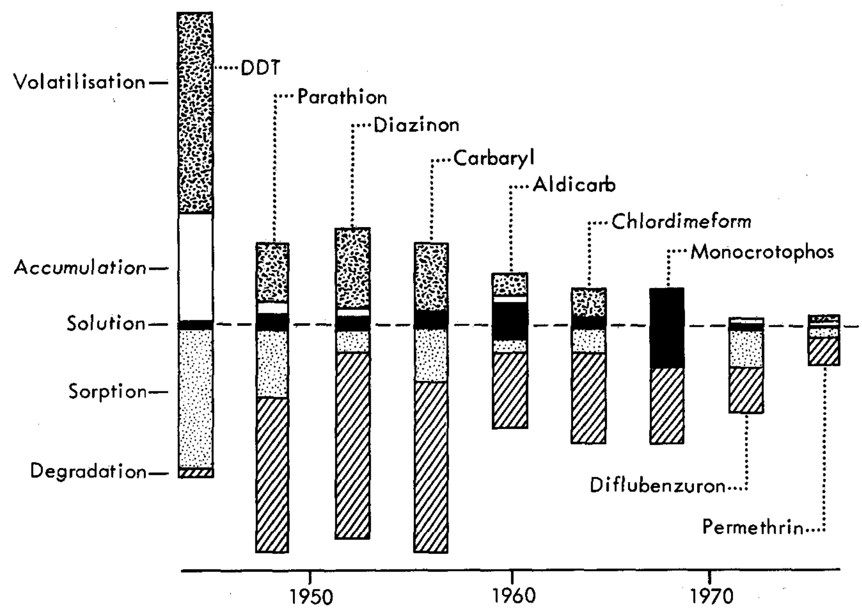


Figure 3. Evolution of the potential of insecticides for being distributed and accumulated in the environment. Compounds arranged according to time of introduction (Geissbühler, 1980).

1000 times lower than the 'acceptable daily intakes' determined by WHO (table 3). Comparable Swiss data are less recent, much less extensive and mainly limited to chlorinated hydrocarbons (Zimmerli et al., 1973). However, according to the authors 'they indicate that exposure to pesticide residues does not significantly deviate from that in other industrialized countries'.

Thesis 3: The responsible parties involved recognize that there is sufficient scope for improving the safety in the use of pesticides further.

Industrial and also government research continues on a large scale for ameliorating further the inherent undesirable properties and the use of plant protection agents. In the following I shall briefly touch on 4 areas:

- efforts to improve the biological selectivity of compounds by exploiting systematically natural regulatory and defense mechanisms ('biorational approach/design');
- progress being made in integrated pest management or control (IPM);
- efforts to improve pesticide targeting by better formulation and application;
- opportunities for suppressing or retarding the development of resistance to pesticides.

When looking at the area of *insect control* one can identify systematic efforts in several directions to improve biological selectivity (fig. 5). The development of diflubenzuron, an insecticide which inhibits chitin synthesis at low concentrations and which is non-toxic to a number of beneficial insects, has initiated extensive synthesis programs and we can hopefully expect additional derivatives which are active against economically important pests. Research on endogenous insect juvenile hormones, their synthetic mimics (such as methoprene) and especially their antagonists (exemplified by precocene II) continues at a high rate, and appears to offer specific insect control solutions

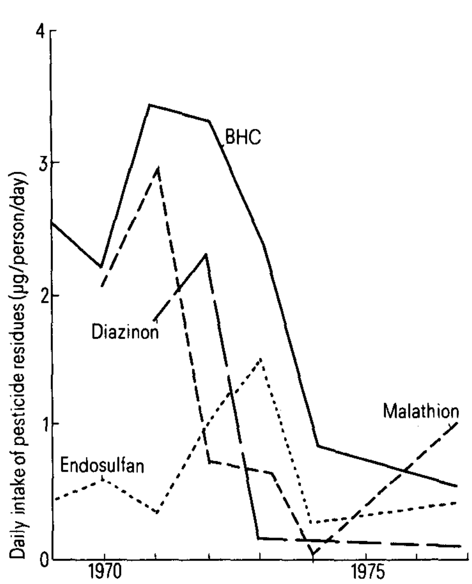


Figure 4. Changes in average daily dietary intake of pesticide residues. Drawn from official Canadian data submitted to the Codex Committee on Pesticide Residues (Geissbühler, 1980).

Table 3. Comparison of daily dietary intake of pesticide residues in Canada with the acceptable daily intake (ADI) as determined by joint WHO/FAO meeting on pesticide residues (Geissbühler, 1980)

| Pesticide | Daily intake 1976-78 (µg/person) | WHO-ADI (µg/person) |
|---|---|---|
| BHC | 0.60 | 500 |
| Endosulfan | 0.50 | 375 |
| Diazinon | 0.10 | 100 |
| Malathion | 1.09 | 1000 |
| Captan | 0.27 | 5000 |

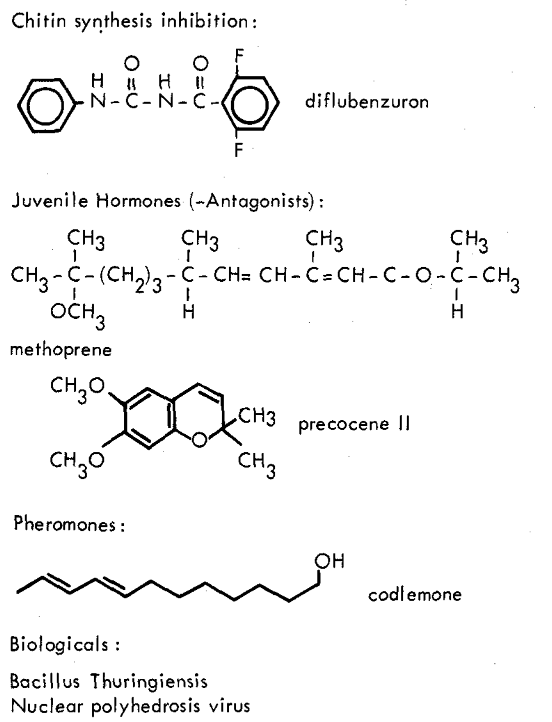


Figure 5. Structures of recent selective insect control agents derived from exploiting natural regulatory and control mechnisms.

by causing precocious metamorphosis and sterilisation. Progress in the chemistry and biology of pheromones (such as codlemone) which, as attractants, repellents or disruptants, affect insect behaviour is on its way to a number of practical applications in the monitoring and mass-trapping of specific pest populations. Some biological insect control agents, including *Bacillus thuringiensis* and nuclear polyhedrosis virus have been introduced into the market. The economy of production and the spectra of activity of such biologicals are likely to be improved by modern biotechnology, including genetic engineering. *Integrated pest management* (IPM), the systems approach to insect, plant disease and weed control attempts (according to the FAO-definition, FAO, 1979) 'to utilize all suitable techniques and methods (i.e. cultural, chemical, biological, genetic and plant breeding, etc.) in as compatible a manner as possible to maintain pest populations at levels below those causing economic injury' (fig. 6). The perfection and extension of this approach will depend on the continued systematic acquisition of agronomic and biological knowledge on the components of the crop ecosystems involved (i.e. crop and pest dynamics and their interactions, etc.) and on the further development of pest monitoring and forecasting devices.

In spite of considerable progress made in the formulation and application of pesticides the present techniques are still rather inefficient in terms of the quantity of active ingredient which actually reaches the target organisms to be controlled. Although it will never be

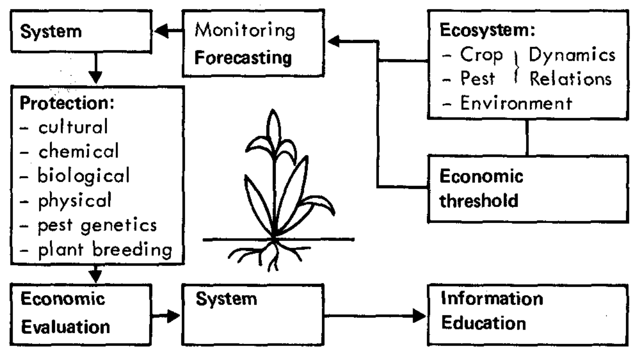


Figure 6. Major components of integrated pest management (IPM) system and their sequential interlinkage (Geissbühler, 1981). Systems analysis and modelling can be performed at different stages of the IPM-scheme.

possible to confine the entire quantity of an applied pesticide to its targets, there is considerable room for improvement. To reduce unnecessary dispersal and drift the corresponding scientific and engineering efforts include the design of more efficient equipment (such as electrodynamic spraying) the development of controlled release devices and increased application of compounds via the seed or seed coatings.

Attempts to delay or prevent *resistance* of insect pests and crop diseases to synthetic pesticides have so far, in practice, not been very successful. However research in the physiology and biochemistry of resistance mechanisms has accelerated and will allow more rational approaches to controlling resistance phenomena. The tactics initiated or envisaged include, among others, the mixed or alternating application of compounds with distinctly different modes of action (fig. 7) and the addition of chemicals which antagonize the induction of resistance.

Thesis 4: Industry welcomes cooperation with any responsible scientist for achieving improved pesticide safety.

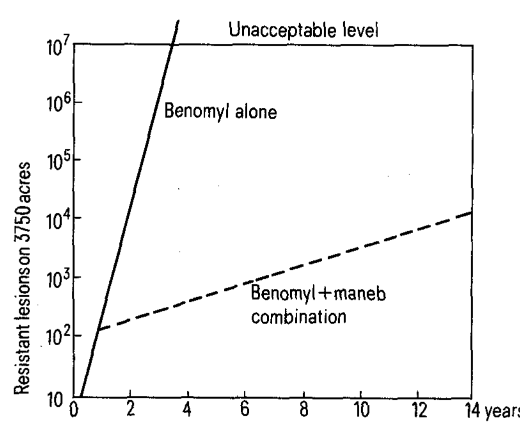


Figure 7. Delay of resistance of a fungal pathogen to the fungicide benomyl by mixing it with a toxicant (maneb) that exhibits a different mode of action. Graph prepared from Delp (1981).

As in all areas of applied biological research, straightforward and unbiased cooperation among industrial, government and academic scientists is necessary to achieve progress in the use of chemicals in plant protection. In many ways I regret that this tripartite cooperative effort is not more extensive in Switzerland. However, to achieve useful results, this research must be relevant to practice and will therefore be tedious and time-consuming. The often-chosen way of model laboratory experiments, rapid publication and speculation can and does cause confusion and unnecessary alarm, as I shall demonstrate with a recent example.

It is an established fact that a number of N-nitroso-compounds, i.e. derivatives formed by the reaction of nitrite with secondary amines and amides are carcinogenic in various mammalian systems. The assumption that many pesticides and their degradation products can potentially be nitrosated and the observation that some pesticide active ingredients and formulations indeed contained detectable amounts of N-nitroso-contaminants, caused a flood of academic laboratory investigations all over the world. Among the countless compounds which were described in publications as having been nitrosated at high concentrations under artificial test tube conditions was the herbicide atrazine. Though the various authors inferred that N-nitroso-atrazine was likely to pose a contamination and health problem, none of them cared to substantiate the relevance of their findings to practical use conditions. To answer pertinent inquiries by regulatory authorities, the company had to embark on an extended and scientifically demanding program by investigating all aspects of the potential formation of N-nitroso-atrazine from nitrite and atrazine in such diverse organisms and media as rats, goats, soil, corn and fish. Even when using the most advanced instrumentation, which was sensitive to 1-10 ppb, no N-nitroso-atrazine was detected in any of the systems mentioned. The effort required to answer N-nitroso-atrazine questions amounted to 15 man-years and more than 1 million SFr. As a consequence of this example I plead for a more differentiated and more factual discussion among those scientists who are able or feel entitled to evaluate and solve potential pesticide problems.

### *Conclusions*

I have attempted to demonstrate that pesticide safety testing is extensive, that the safety in use of pesticides has continuously been improved and that further improvements are being vigorously pursued. As with all science-based technologies, the risks associated with pesticides can and will never be zero. They must be carefully balanced against the benefits (which I have purposely omitted from my presentation) and they must be found to be acceptable. I recognize that misuses, errors and misjudgements cannot entirely be excluded. In addition, as scientific knowledge expands, we are likely to be confronted with new potential risk phenomena. These will need to be evaluated thoroughly and, if it is deemed necessary, appropriate action must be taken.

And a final, personal statement: The professional scientists involved in plant protection research and regulation (be it in industry or government) need not to be lectured by ideologists or journalists concerning the ethics of their approaches and activities. The consciousness of these scientists and their sense of responsibility vis-à-vis the public and society are as developed as anybody else's.

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