

## THE VALUE AND USE OF HUMAN DATA FOR PESTICIDE REGULATION

Derek Gammon<sup>1</sup> of DPR, California EPA, reports on a lunchtime discussion session at the Society of Toxicology (SOT) meeting in Philadelphia in March 2000

A lunchtime Panel Discussion addressed issues related to human data collection for pesticides. The distinguished panelists described their own perspectives on the subject and then time allowed for a few comments from the audience.

### Viewpoints of distinguished panelists

*E. McConnell* (Consultant veterinary pathologist) provided the regulatory history of the issue. In December, 1998, USEPA's Science Advisory Board (SAB) and the FIFRA<sup>2</sup> Scientific Advisory Panel (SAP) held a joint meeting to determine whether human data were appropriate for pesticide registration purposes. The findings were to have been published during 1999 but in August, it was decided that the subject would be a suitable topic for a debate at the SOT conference in 2000.

*P. Fenner-Crisp* (USEPA, Senior Science Advisor, Pesticides) described the reasoning behind the request for an expert, objective opinion from outside USEPA and the types of data that were being gathered using humans. Fenner-Crisp pointed out that there was only one type of human study which the SAB/SAP wanted USEPA to discontinue using: those which simply attempted to increase the critical NOEL/RfD values. Studies designed to consider public health pesticides and dermal/eye irritation or pharmacokinetics would still be permissible in humans. It was specifically mentioned that hazard identification or NOEL studies in humans for neurotoxic pesticides, such as organophosphates, were being considered for discontinuation. Guidelines and protocols were needed for human studies because it remained possible that some of these types of experiment would be allowed, on a case-by-case basis.

*G. Ellis* (National Institutes of Health (NIH)) presented the guidelines under which chemicals (usually drugs) could be tested in humans. Prior informed consent rules applied, including a full description of the study and possible risks along with the benefits either to the individual or the population. Alternatives to human experimentation should have been exhausted, confidentiality guaranteed and compensation, including possible medical attention, agreed in advance. Details of whom to contact in the event of adverse effects should have been provided and finally, it was

The Reference Dose (RfD) is defined as the maximum daily dosage of a pesticide that can be safely consumed over a lifetime. It is calculated by dividing a NOEL value from a chronic study by an uncertainty factor of (usually) 100. However, if the NOEL is determined from a human study, the uncertainty factor would only be 10 (to account for differences among the human population) and the RfD would be correspondingly 10-fold higher. This issue could be critical under the Food Quality Protection Act (FQPA), 1996 because under this law, USEPA can now apply an extra 10x safety factor if it appears appropriate, based generally on non-human data.

stressed that participation must be voluntary with absolutely no coercion. Experiments with children should be avoided unless the potential benefit was large. A Bioethics Advisory Panel ensures an independent review of the risks and benefits before an experiment on humans is allowed. It was pointed out that the Helsinki Declaration should apply *i.e.* that concern for the individual (subject) should exceed the needs of science or society.

*D. Goldstein* (Monsanto) provided an industry perspective on experiments on humans. He stressed that such experiments were the most relevant for human health risk assessment and that the highest possible ethical standards must be adhered to. Worker exposure studies have been considered legitimate, as have skin allergy tests and attempts to define biomarkers of exposure. Goldstein therefore felt that there should not be a blanket ban on human experiments with pesticides provided they started with very low doses, did not induce symptoms, did not involve chronic exposure or exposure of children or during pregnancy.

*J. MacGregor* (Consultant) addressed the issue of whether experiments on humans were ethical. It was felt that industry should discuss its human data with EPA and design human studies only after all animal experiments had been completed and reviewed.

*B. Weiss* (University of Rochester) described some experiments on humans that have been conducted on non-pesticidal compounds. Examples included mercury vapor and other heavy metals along with experiments to assess the neurotoxicity of solvents. However, he had doubts about the validity of human experiments designed solely to change the critical NOEL/RfD. He also pointed out that, because it was clearly unethical to test pesticides on pregnant women, developmental toxicity in humans could not be addressed

<sup>1</sup> The views expressed in this report represent those of the author and not necessarily those of Cal EPA.

<sup>2</sup> Federal Insecticide, Fungicide and Rodenticide Act

although the protection of the fetus was one of the main issues in FQPA, 1996.

### Points raised by the audience

How would human data affect the RfD in practice? P. Feather-Crisp responded that USEPA had recently conducted a risk assessment for a pesticide using a human NOEL and had subsequently re-calculated the RfD by replacing this NOEL with an animal NOEL. Another audience member pointed out that an extensive databank is available for humans as well as for laboratory animals. Using "reverse toxicology" it was found that the closest animal equivalent to humans for the insecticide Kepone (chlordecone) was the

gerbil. Nevertheless, the critical data used for human risk assessment was proteinuria in the rat, although this effect had never been observed in humans! Someone else thought that the issue should not be *whether* we conduct human pesticide studies but *how* we conduct them. Finally, Jay Goodman (SOT President) spoke out firmly in favor of pesticide studies using humans, because if we don't conduct such studies under carefully controlled conditions, then the general population (especially workers) become experimental subjects. Goodman thought that a proportion of people did not want to see pesticides used and that they have created a barrier specifically for pesticides that could be difficult to overcome.

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## SUSTAINABLE WEED MANAGEMENT DISCUSSED AT GHENT

Brian Hicks reports on a recent conference

Over 400 delegates from some 25 countries attended the *52nd International Symposium on Crop Protection* at Ghent University, Belgium, on 9 May. The opening plenary lecture was delivered by Dr Bert Lotz, a senior scientist at Plant Research International (PRI), Wageningen, the recently formed organisation that has amalgamated three different research institutes based at the site.

Dr Lotz spoke on the theme of *Towards a More Sustainable Weed Management in the Netherlands*, an area he works closely on with collaborators from the Dutch Ministry of Agriculture. Whilst the Dutch government's pesticide reduction plan has reached its target of a 50% reduction of pesticide use by 2000 (largely due to the removal from use of two key soil sterilants), it has failed to reach the other target of a 40% reduction in herbicide use. Although there was a reduction in Dutch herbicide consumption over the period 1987-1982, usage was constant or rose slightly over the period from 1992 to 2000. The Dutch government now acknowledges that the herbicide target cannot be achieved. PRI and other organisations are making progress with developing weed science programmes to reduce usage, in close co-operation with farmers and the Ministry of Agriculture.

A variety of approaches are being tested, including stale seedbed techniques and weed suppressive cultivars. Another technique is to cover the soil with fibre in a matrix, *Azofill*, using a special applicator. Effective weed suppression has been achieved in leek crops and Dr Lotz sees good prospects with this novel technology over the next few years. Another approach has been to harrow or hoe in maize during the pre-emergence period, thereby reducing the number of herbicide applications. This has been rarely used in the past, but is expected to be used on over 60% of the Dutch maize acreage this year. In vegetables, sugar beet and onions, hoeing is being used on 25-75% of the crop area.

A "finger weeding" device, using spinning wheels, is proving increasingly popular in weed control in chicory in the Netherlands. It has angle adjusters and sold out last year

Many have been sold this year as well. New methods for intra-row weed control are also progressing, with a promising new device currently being tested in a laboratory set-up. It detects plants and weeds and has a fast mechanical device to remove the weeds.

The Dutch are also examining the use of fungal spores for control of *Chenopodium album*, part of a European Union programme involving Novartis. When the spores are used in combination with sulfonylurea herbicides, some synergistic effects on weed control have been found.

Another methodology is the "minimum lethal herbicide dose", which is being tried out first with Photosystem II inhibitors. A check is made 1-3 days after treatment to check that the herbicide has been effective, using chlorophyll fluorescence with a device costing about 1500 euros. On trials over two years on 30 farms, most farmers have found it very useful. Herbicide doses were cut by up to 50% (even 70% in a few cases). Re-treatments were required in only 10% of cases. The methodology is also going to be extended to other herbicide groups.

Dutch farmers are keen to be included in a GAP (good agricultural practice) or similar certification scheme. Financial support will be extended this year by the Dutch government for approved programmes. In maize, growers will have to use one mechanical treatment (hoeing or harrowing) followed by application of less than 1 kg/ha of a herbicide in order to qualify for this support. There is also a programme for starch potatoes. By 2010, the authorities are aiming for 10% of the arable crop area in the Netherlands to be farmed organically. Dutch farmers realise that there is no room for complacency with respect to their herbicide practices and Dr Lotz commented that the leading Dutch supermarket group has disclosed that it is aiming to have all its potatoes and vegetable crops produced without herbicides by 2005.

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